The Innsbruck Colloquium on Status Epilepticus

Final Programme

The Innsbruck Colloquium on Status Epilepticus 2009

Congress Innsbruck
April 2-4, 2009

www.innsbruck-se2009.eu
Besonders hohe Wirksamkeit bei Sturzanfällen
1) Signifikante Reduktion der Anfallsfrequenz
1) Reduktion der Anfallsschwere
1) Kognitive/psychiatrische unerwünschte Ereignisse auf Placebòniveau
1) Für alle Altersgruppen ab dem 4. Lebensjahr

* mit LGS assoziierte Anfälle


2) Fachinformation INOVELON®, Stand April 2008, Eisai Ltd.

Leben leichter machen
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So frisch und schon so erwachsen.

Auszgereifte Leistung...

- Überzeugende Reduktion der Anfallshäufigkeit\(^1\)
- Gute Kombinierbarkeit durch geringes Interaktionspotential\(^2\)
- Anhaltende Wirksamkeit in der Langzeittherapie\(^3\)

...in der Kombinations-Therapie der fokalen Epilepsie

1) Brodie MJ et al., Epilepsia 2005; 46(1):31-41
2) nach Sills GJ et Brodie MJ, Epilepsia 2007; 48(3):435-441
3) nach Faught, Seizure 2004;13: 59-65

Fokale Anfälle stark im Griff.

\(^*\) Zusatzbehandlung von therapierefraktären partiellen Anfällen mit oder ohne sekundäre Generalisierung bei erwachsenen Patienten mit Epilepsie
\(^*\) Diagnosestellung, Erstverordnung und regelmäßige Kontrollen durch den Facharzt
\(^*\) „L 12“ → Langzeitbewilligung für 12 Monate möglich (100 mg Hartkapseln)
Dear colleagues and friends,

We are very pleased to welcome you at the Innsbruck Colloquium on Status epilepticus 2009. The conference was made possible by an enormous effort of many people, and we are grateful to the Scientific Committee and the distinguished faculty for participating actively in the conference. The Innsbruck Colloquium on Status Epilepticus is held under the patronage of the CEA of the ILAE, the Austrian Chapter of the ILAE, the Medical University Innsbruck and the University College of London.

Status epilepticus is one of the most common neurological emergencies and even today, tonic-clonic status epilepticus carries a mortality of approximately 20% and a serious risk of cerebral damage amongst survivors. Although tonic-clonic status has been recognised as early as 2,500 years ago, it was 1825, when Calmeil introduced the term "état de mal", which was the expression of the patients at the Salpêtrière in Paris, for this complication of epilepsy. The first documented case of an absence status seems to be described on an ex voto table in 1501 in Austria (Wolf et al., Epilepsia 2007).

We hope that stimulating new ideas will come out of the vivid discussions on controversial topics. The conference is intended to give a state of the art-overview on current basic research in status epilepticus, new treatment options and to give a health science perspective in order to improve treatment and outcome of patients with this devastating condition. This conference follows in direct lineage the London Colloquium on Status epilepticus, and both these recent colloquia build on the traditions of the Marseilles Colloquium held in 1962 and the two Santa Monica meetings on this topic held in 1980 und 1997.

We wish you a stimulating and interesting conference in this wonderful city in the heart of the Alps and hope that you enjoy not only the scientific content of the conference, but also the very scenic and cultural and historically interesting places in and around Innsbruck.

We wish you a pleasant stay during these days, a successful and stimulating conference, and last, but not least, an enjoyable and unforgettable experience in Innsbruck.

Eugen Trinka            Iris Unterberger            Simon D. Shorvon
Chair of the Conference Local Organising Committee Chair of the Conference
**GENERAL INFORMATION**

**Congress Venue**
The meeting venue is "Congress Innsbruck", a state-of-the-art convention centre that has won the worldwide AIPC Apex Award "best congress centre 2001". It is located adjacent to the Old Town, i.e. in walking distance to most attractions, museums, and hotels.

Congress Innsbruck  
Rennweg 3  
A-6020 Innsbruck  
www.come-innsbruck.at

**Registration desk at the Congress Innsbruck**
The registration desk will be located on the ground floor of the Congress Innsbruck. Opening hours are as follows:

- **Wednesday, 1 April** 16:00 – 18:00
- **Thursday, 2 April** 08:00 – 18:00
- **Friday, 3 April** 07:45 – 18:00
- **Saturday, 4 April** 08:30 – 18:00
- **Sunday, 5 April** 08:30 – 13:00

**On site registration fees**
- Regular fee € 480,00
- Junior fee (under 35 years) € 380,00

**Internet access**
There is unlimited wireless LAN access at Congress Innsbruck, kindly sponsored by sanofi-aventis.

**Certificate of attendance**
All registered delegates receive a certificate of attendance.

**CME Accreditation**

Europe
The organisers have applied for accreditation of the colloquium with the subcommittee for Continuing Education of the European Union of Medical Specialists (UEMS) to grant CME credits.

Austria
Participation in the Colloquium will be honoured with 18 DFP-credits (6 per day) for Neurology resp. 3 DFP-credits for Paediatrics towards the diploma for further education of the Austrian Medical Association (Fortbildungsdiplom der ÖAK).
Switzerland
The Committee for Further Education of the Swiss Association for Neurology (Fortbildungskommissi
don der Schweizerischen Neurologischen Gesellschaft) grants 22.5 credits for Neurology (7.5 per day) for participation in the Colloquium.

Germany
German participants have to apply for accreditation with their respective medical association (Ärztekammer).

Trade exhibition
Within the scope of the Innsbruck Colloquium on Status Epilepticus, a trade exhibition of pharmaceut
cal companies, manufacturers of medical equipment and publishers is held next to the plenary room.

Coffee breaks and refreshments
Coffee and tea will be served during the official coffee breaks. Outside these official coffee breaks, refreshments are available from cash bars in the Congress Innsbruck.

City transportation
There is a good public transport system in Innsbruck and its surroundings. Most buses operate until midnight. Detailed information on bus schedules is available at your hotel or at the conference centre. Tickets can be pre-purchased from tobacconists or directly in the buses.

Parking
There is an underground car park at the Congress Centre. Participants obtain tickets at reduced rates from the doorman's booth. Please note that these reduced fares only apply to the Congress Garage and not to the adjacent CityGarage parking facilities.
Street parking in the city is available but limited to 90 minutes (indicated by a blue line). Tickets have to be purchased from a blue parking meter, where the appropriate fees are indicated.

Currency
The official currency is the EURO (€). Major credit cards are accepted in many hotels, shops and restaurants. Automatic teller machines (ATMs) are also available throughout the city.

Name badges
All registered participants receive a name badge together with their registration documents. Please make sure to wear your badge at all times while attending the meeting, exhibition and social events.

Liability and insurance
Neither the organisers, nor the congress secretariat or other suppliers accept liability for any injury, loss or damage, arising from accidents or other situations during, or as a consequence of the congress. Kindly check your personal insurance.
**Scientific Committee**

**Chair**
Eugen TRINKA, Innsbruck, Austria
Simon SHORVON, London, United Kingdom

**Committee**
Frederick ANDERMANN, Montreal, Canada
Alexis ARZIMANOGLOU, Paris, France
Michel Baulac, Paris, France
Christoph BAUMGARTNER, Vienna, Austria
Meir BIALER, Jerusalem, Israel
Hannah COCK, London, United Kingdom
Athanassios COVANIS, Athens, Greece
Helen CROSS, London, United Kingdom
Wolfgang LÖSCHER, Hannover, Germany
Dan LOWENSTEIN, San Francisco, USA
Solomon MOSHE, New York, USA
Cigdem ÖZKARA, Istanbul, Turkey
Emilio PERUCCA, Pavia, Italy
Felix ROSENOW, Marburg, Germany
Elyse SCHAUWECKER, Los Angeles, USA
Erich SCHMUTZHARD, Innsbruck, Austria
Roger SIMON, Portland, USA
Günther SPERK, Innsbruck, Austria
Matthew WALKER, London, United Kingdom
Claude WASTERLAIN, Los Angeles, USA

**Local Organising Committee**

**Chair:**
Iris UNTERBERGER, Medical University Innsbruck, Austria

**Committee:**
Gregor BRÖSSNER, Medical University Innsbruck, Austria
Judith DOBESBERGER, Medical University Innsbruck, Austria
Michael SPIEGEL, Medical University Innsbruck, Austria
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Rennweg 3, A-6020 Innsbruck, Austria
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Congress organisation
pco tyrol congress
Rennweg 3, A-6020 Innsbruck, Austria
T: +43-512-575600
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E: se2009@come-innsbruck.at
I: www.pco-tyrolcongress.at

Industrial exhibition/sponsoring
med.ex GmbH
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www.innsbruck-se2009.eu
Thursday, 2 April, 2009

09:00-09:30 Opening
Werner Poewe, Director
Department Neurology and Neurosurgery (Innsbruck, Austria)

09:30-12:15 Basic and clinical neurophysiology I
Chair: Jerome Engel (Los Angeles, USA)
Daniel Lowenstein (San Francisco, USA)

09:30-10:15 Endogenous neuroprotective mechanisms in the human brain
Roger Simon (Portland, USA)

10:15-10:45 Basic physiology of limbic SE
Matthew Walker (London, United Kingdom)

10:45-11:15 Physiology of EPC and subcortical mechanisms of SE
Renzo Guerrini (Florence, Italy)

11:15-11:45 Coffee break

11:45-12:15 Hypothermia, hyperthermia and other systemic factors in SE
Thomas Bleck (Chicago, USA)

12:15-14:00 Lunch and poster session 1

P01
Changes in cerebral P-glycoprotein function following status epilepticus in rats quantified by an improved method to measure brain uptake of(R)-[11C]-verapamil
Jens P. Bankstahl, Claudia Kuntner, Marion Bankstahl, Thomas Wanek, Johann Stanek, Markus Müller, Oliver Langer, Wolfgang Löscher (Hannover, Germany)

P02
Epidemiological characteristics and predictors of outcome in pediatric status epilepticus
Verónica Cantarín-Extremera, Juan-José García-Peñas, Juan Casado-Flores, Mari-Luz Ruiz-Falcó, Luis Gutiérrez-Solana, Anna Duat-Rodríguez, Laura López-Marín, Julián Lara-Herguedas (Madrid, Spain)

P03
4-methyloctanoic acid is an effective compound in the treatment of an animal model of status epilepticus
Pishan Chang, Matthew Walker (London, UK)

P04
Upregulation of P-glycoprotein (ABCB1) function in Peripheral Blood Mononuclear Cells with Epilepsy Patients
Kon Chu, Jae-Sung Lim, Keun-Hwa Jung, Dae-Jong Jeon, Kyung-Il Park, Sang Kun Lee (Seoul, South Korea)

P05
Permissive Role of Cortical Dysplasia on the Epileptogenesis following Prolonged Febrile Seizure
Kon Chu, Kyung-Il Park, Keun-Hwa Jung, Dae-Jong Jeon, Sang Kun Lee (Seoul, South Korea)

P06
Ketamine Combined with Atropine for the Delayed Medical Treatment of Soman-Induced Status Epilepticus
Frederic Dorandeu, Pierre Carpentier, Franck Dhote, Valerie Baille, Guy Testylier, Claire Beaup, Annie Foquin, Guy Lallement (La Tronche Cedex, France)
Plastic changes in parahippocampal regions of the rat after kainic acid-induced epilepsy
Meinrad Drexel, Günther Sperk (Innsbruck, Austria)

Neonatal status epilepticus resulting in unilateral hippocampal sclerosis and temporal lobe epilepsy
Mark Dunleavy, Sachiko Shinoda, Clara Schindler, Claire Ewart, Ross Dolan, David Henshall (Dublin, Ireland)

Pilocarpine-induced status epilepticus triggers angiogenesis in adult rat hippocampus
Xavier Ekolle Ndode Ekane, Jari Nissinen, Asla Pitkäinen (Kuopio, Finland)

Reduced hippocampal injury and epileptogenesis after status epilepticus in mice lacking the pro-apoptotic BH3-only protein Puma
Tobias Engel, Brona Murphy, Genshin Mouri, Seiji Hatazaki, Eva Jimenez, Ina Woods, Jochen Prehn, David Henshall (Dublin, Ireland)

Alterations in Blood-Brain Barrier Integrity in Pentilenetetrazole-Kindled Rats with Cortical Dysplasia
Candan Gurses, Mehmet Kaya, Rivaze Kalayci, Nadir Arican, Bulent Ahishali, Oguzhan Ekizoglu, Imdat Elmas, Mutlu Kucuk, Duran Ustek, Bilge Bilgic, Gonul Kemikler (Istanbul, Turkey)

Aggressive behaviors in the lithium-pilocarpine rat models of temporal lobe epilepsy: Resident-Intruder Test
Dae-Jong Jeon, Eun-Gee Bae, Keun-Hwa Jung, Kon Chu, Sang Kun Lee (Seoul, South Korea)

Status epilepticus at infancy and early childhood
Alexey Kholin (Moscow, Russia)

Febrile infection responsive encephalopathy of school-age (FIRES) with unexpected favorable evolution
Christian Korff, Joël Fluss, Nathalie Valenza, Sophie Déglise, Anne-Chantal Héritier-Barras, Fabienne Picard, Solène Ferrey, Jacqueline Delavelle, Peter Rimensberger, Eliane Roulet Perez, Marc Tardieu, Olivier Dulac, Caroline Menache (Geneva, Switzerland)

Effects of 2-chloroadenosine on lithium-pilocarpine status epilepticus elicited in immature rats
Hana Kubová, Markéta Skutová, PavelMareš (Prague, Czech Republic)

The influence of CDP-choline on bicuculline-evoked seizure susceptibility in hyper- and normoglycemic mice exposed to Levin’s model of oligemia/hypoxia
Konrad Rejdak, Pawel Grieb, Zbigniew Stelmasiak (Lublin, Poland)

Subtle Signs of Different Manifestations of Non-convulsive Status Epilepticus: Diagnostic and Prognostic Challenges
Radmila Sujic, M. Miladinovic, J. Lkonomovski, D. Vranjes, B. Cvetkovic, V. Nikolic, J. Malovic, S. Kostic, A. Stanic (Belgrade, Serbia)

Intravenous Levetiracetam in the Treatment of Status Epilepticus
Rute Teotónio, Conceição Bento, Francisco Sales (Coimbra, Portugal)
P19
Febrile infection responsive epileptic (FIRE) encephalopathy in children: Anon-encephalitic cause of status epilepticus
Andreas van Baalen, Rainer Boor, Martin Häusler, Ulrich Stephani, Gerhard Kluger (Kiel, Germany)

P20
Experimental study on the protein expression of NMDAR2B and ERK1/2 in hippocampus of epilepsy rats induced by kainic acid
Zan W, JUN Fu, Shuisheng Wu, Wei Hong Lin (Chang Chun, P.R.China)

P21
Experimental study on the protein expression of Erk1/2 in hippocampus and myocardium of epilepsy rats induced by kainic acid
Zan Wang, Shuisheng Wu (Chang Chun, P.R.China)

P22
Acute and long-term effects of lacosamide in an animal model of status epilepticus
Claude G. Wasterlain, Thomas Stoehr (West Los Angeles, USA)

P23
The Ketogenic Diet (K.D.)
Adel Mahmoud (Riyadh, Saudi-Arabia)

P24
Prospective Study of Seizure Occurrence and Utility of EEG Monitoring in Critically Ill Children: An Interim Analysis
Nicholas Abend, Alexis Topjian, Maureen Donnelly, Vinay Nadkarni, Dennis Dlugos (Philadelphia, USA)

P25
Stroke as a cause of Status Epilepticus in a hospital based database
Nazire Afsar, Kadriye Agan, Ipek Midi, Gulin Sunter, Sevinc Aktan, Canan Aykut-Bingol (Istanbul, Turkey)

P26
Use of intravenous levetiracetam in the treatment of status epilepticus
Maria Aiguabella, Vicente Villanueva, Pilar de la Peña, Albert Molins, Merce Falip, Irene Garcia Morales, Rosa Ana Saiz, Julio Pardo, Diego Tortosa, Gemma Sansa, Misericordia Veciana (Barcelona, Spain)

P27
Visual Aura
Tiberius-Razvan Alecu (Ploiesti, Romania)

P28
Use of the Internet to facilitate drug trials in Status Epilepticus
Peter Bergin, Tony Ip, Robert Sheehan (Auckland, New Zealand)

P29
Etiology, treatment and predictors of outcome in status epilepticus (SE) in an Austrian central hospital
Georg Caravias, Franz Gruber, Hannelore Trägner, Milan Vosko, Gerhard Ransmayr (Linz, Austria)

P30
Frontal Lobe Epilepsy May Present as Myoclonic Seizure
Yong Won Cho, Sang Doe Yi, Won Chul Shin, Ji Young Jung, Gholam K. Motamedi (Daegu, Korea (South))

P31
Clinical case of unprovoked status epilepticus after long term compensation
Andriy Dubenko (Kharkiv, Ukraine)

P32
Factors determining the outcome of status epilepticus
Berend Feddersen, Marion Einhellig, Jan Rémi, Soheyl Noachtar (Munich, Germany)
P33
Ambulatory and comatose forms of non-convulsive status epilepticus in adults: Clinical, EEG and neuroimaging features and treatment of 50 consecutive patients
José L. Fernández-Torre, Mariano Rebollo, Agustín Gutiérrez, Marián Martínez-Martínez, Francisco Casariego-Pola (Santander, Spain)

P34
A multicenter, open-label trial to assess the safety and tolerability of a single intravenous loading dose of lacosamide followed by oral maintenance as adjunctive therapy in subjects with partial-onset seizures: an interim report
Nathan B. Fountain, Gregory Krauss, Jouko Isojarvi, Deanne Dilley, Pamela Doty (Charlottesville, USA)

P35
Evaluation of Seizure Freedom and 75% Responder Rates with Lacosamide in Subjects with Partial-Onset Seizures in Phase II/III Clinical Trials
Jacqueline French, Martin Brodie, David Hebert, Jouko Isojarvi, Pamela Doty (Philadelphia, USA)

14:00-17:00 Basic and clinical neurophysiology II
Chair: Gerhard Bauer (Innsbruck, Austria)
Asla Pitkänen (Kuopio, Finland)

14:00-14:30 Experimental SE in animals; what are we modeling?
Robert Sloviter (Tucson, USA)

14:30-15:00 Canine SE: proof of principle studies
Ilo Leppik (Minneapolis, USA)

15:00-15:30 Molecular basis of self-sustaining seizures and pharmacoresistance during SE: the receptor trafficking hypothesis revisited
Claude G. Wasterlain (Los Angeles, USA)

15:30-16:00 Coffee break

16:00-16:30 Molecular mechanisms of drug resistance in SE
Wolfgang Löscher (Hannover, Germany)

16:30-17:00 The genetics of SE
Elyse Schauwecker (Los Angeles, USA)

17:00-18:00 Panel discussion
Gerhard Bauer (Innsbruck, Austria)
Jerome Engel (Los Angeles, USA)
Daniel Lowenstein (San Francisco, USA)
Asla Pitkänen (Kuopio, Finland)
**Friday, 3 April, 2009**

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<th>Time</th>
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<td>08:30-10:45</td>
<td><strong>SE in the developing brain</strong></td>
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<td>Chair: Martha Feucht (Vienna, Austria)</td>
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<td>Athanasios Covanis (Athens, Greece)</td>
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<td>08:30-09:00</td>
<td>Why is the developing brain more susceptible to SE?</td>
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<td>Solomon Moshé (New York, USA)</td>
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<td>09:00-09:30</td>
<td>Long-term effects of febrile SE: what animal models can tell us</td>
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<td>Antoine Depaulis (Grenoble, France)</td>
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<td>09:30-10:15</td>
<td>Neuronal plasticity in animal models and the epileptic human hippocampus</td>
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<td>Günther Sperk (Innsbruck, Austria)</td>
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<td>10:15-10:45</td>
<td>SE in the developing brain: long term effects seen in humans</td>
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<td>Rod Scott (London, United Kingdom)</td>
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<td>10:45-11:15</td>
<td>Coffee break</td>
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<td>11:15-12:15</td>
<td><strong>EEG in the emergency treatment of SE</strong></td>
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<td>Chair: Christoph Baumgartner (Vienna, Austria)</td>
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<td>Peter Kaplan (Baltimore, USA)</td>
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<td>11:15-11:45</td>
<td>How useful is EEG and EEG monitoring in the acutely ill and how to interpret it?</td>
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<td>Richard P. Brenner (Pittsburgh, USA)</td>
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<td>11:45-12:15</td>
<td>Basic physiology of burst suppression</td>
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<td>Florin Amzica (Montreal, Canada)</td>
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  Juan-José García-Peñas, Verónica Cantarín-Extremera, Julián Lara-Herguedas, Laura López-Marín, Anna Duat-Rodríguez, Luis G Gutiérrez-Solana, Mari-Luz Ruiz-Falcó, María Rodrigo, Manuel Leite-Cruzeiro, Nuria Gutiérrez (Madrid, Spain)

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- **P39**
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- **P40**
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Absence Status Epilepticus caused by Cannabinoids?
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Non-Rasmussen, non-vascular epilepsia partialis continua
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14:00-15:00  Emergency treatment of SE I
Chair:  Felix Rosenow (Marburg, Germany)
David Treiman (Phoenix, USA)

14:00-14:30  What is the relative value of the standard anticonvulsants: phenytoin and fosphenytoin, valproate, phenobarbital, levetiracetam?
Eugen Trinka (Innsbruck, Austria)

14:30-15:00  Pharmacodynamic and pharmacokinetic characteristics of intravenous drugs in status epilepticus
Meir Bialer (Jerusalem, Israel)

15:00-15:30  Coffee break

15:30-16:30  Emergency treatment of SE II
Chair:  Martin Holtkamp (Berlin, Germany)
Elinor Ben-Menachem (Gothenburg, Sweden)

15:30-16:00  What is the promise of new antiepileptic drugs? Focus on brivaracetam, carisbamate, lacosamide, NS-1209, topiramate
Emilio Perucca (Pavia, Italy)

16:00-16:30  Novel anaesthetics and other treatment strategies for refractory SE
Andrea Rossetti (Lausanne, Switzerland)

16:30-17:30  Panel discussion
Elinor Ben-Menachem (Gothenburg, Sweden)
Athanasios Covanis (Athens, Greece)
Christoph Baumgartner (Vienna, Austria)
Martha Feucht (Vienna, Austria)
Martin Holtkamp (Berlin, Germany)
Peter Kaplan (Baltimore, USA)
Felix Rosenow (Marburg, Germany)
David Treiman (Phoenix, USA)
SUNDAY, 4 APRIL, 2009

09:15-11:15 Infection and immunology of SE I
Chair: Frederick Andermann (Montreal, Canada)
Dimitri Kullmann (London, United Kingdom)

09:15-09:45 SE in the resource poor countries
Charles Newton (Kilifi, Kenya)

09:45-10:15 Basic mechanisms of SE due to infection and inflammation
Annamaria Vezzani (Milan, Italy)

10:15-10:45 SE due to paraneoplastic and non-paraneoplastic encephalitides
Josep Dalmau (Philadelphia, USA)

10:45-11:15 Rarer Causes of SE
Simon Shorvon (London, United Kingdom)

11:15-11:45 Coffee break

11:45-12:45 Infection and immunology of SE II
Chair: Cigdem Özkara (Istanbul, Turkey)
Erich Schmutzhard (Innsbruck, Austria)

11:45-12:15 Review of SE in HIV and tuberculosis with preliminary view of Bombay hospital experience
Nadir Bharucha (Mumbai, India)

12:15-12:45 Other central nervous system infections and SE
Gagandeep Singh (Lhuclana, India)

12:45-14:00 Lunch

12:45-13:30 Mini satellite symposium by Special Products Ltd.
Chair: Eugen Trinka (Innsbruck, Austria)
Rod Scott (London, United Kingdom)

Can buccal midazolam replace rectal diazepam to treat prolonged seizures?
Graham March (Weybridge, United Kingdom)

14:00-16:30 Medicolegal and ethical aspects of the treatment of SE
Chair: Christian Elger (Bonn, Germany)
Holger Baumgartner (Innsbruck, Austria)

14:00-14:30 Psychosis and SE: borderland or hidden cause?
Brent Elliott (London, UK)

14:30-15:00 SE as it presents to the courts
Hannah Cock (London, UK)

15:00-15:30 Coffee break
15:30-18:00 Clinical trials in SE
Chairs: Michel Baulac (Paris, France) Matthew Walker (London, United Kingdom)

15:30-16:00 Clinical trials in SE - the clinical perspective
Reetta Kälviäinen (Kuopio, Finland)

16:00-16:30 Minimum requirements for approval of a drug in SE
Michel Baulac (Paris, France)

16:30-17:00 Informed consent in off-label use and incapacitated persons
Christian Elger (Bonn, Germany)

17:00-18:00 Panel discussion
Frederick Andermann (Montreal, Canada)
Michel Baulac (Paris, France)
Holger Baumgartner (Innsbruck, Austria)
Christian Elger (Bonn, Germany)
Dimitri Kullmann (London, United Kingdom)
Cigdem Özkara (Istanbul, Turkey)
Erich Schmutzhard (Innsbruck, Austria)
Matthew Walker (London, United Kingdom)

18:00-18:15 Closing remarks

SUNDAY, 5 APRIL, 2009

09:00-13:00 Workshops

09:00-09:15 Opening and Introduction of the Workshops, Hall Grenoble
Eugen Trinka (Innsbruck, Austria)

09:15-10:30 Workshops

10:30-11:00 Coffee break

11:00-12:00 Workshops

12:00-13:00 Summary, Hall Grenoble

Workshop 1: SE in the developing brain, Hall New Orleans
Chairs: Helen Cross (London, United Kingdom) Martha Feucht (Vienna, Austria)

Workshop 2: When to change and when to stop treatment, Hall Grenoble
Chairs: Thomas Bleck (Chicago, USA) Martin Holtkamp (Berlin, Germany)

Workshop 3: Trial design in SE, Hall Aalborg
Chairs: Eugen Trinka (Innsbruck, Austria) Simon Shorvon (London, United Kingdom) Hannah Cock (London, United Kingdom)

Workshop 4: The use of EEG in diagnosis and treatment of SE, Hall Freiburg
Chairs: Peter Kaplan (Baltimore, USA) Gerhard Bauer (Innsbruck, Austria)
Interactions, dosage recommendations and further warnings:

Inspect diluted solutions before use. Use only clear and particle-free solutions. Do not add other drugs to solution for injection. Reaction capacity can be impaired.

Other warnings:

(2) Particular attention must be paid to signs of liver damage: loss of seizure control characterised by renewed occurrence or increase in seizures, physical weakness, loss of appetite, nausea or repeated vomiting, unclear epigastric symptoms, generalised or local oedema, hearing loss, disturbances of consciousness with confusion, restlessness and movement disorders. Very rarely damage to pancreas with similar clinical features also observed. Monitor infants and young children carefully. If above symptoms persistent or severe, in addition to thorough clinical examination, laboratory investigations required.

Other warnings: Inspect diluted solutions before use. Use only clear and particle-free solutions. Do not add other drugs to solution for injection. Reaction capacity can be impaired.

Interactions, dosage recommendations and further warnings: See Information for Healthcare Professionals and Package Leaflet.

(1) Rarely shortly after use of valproic acid-containing drugs: encephalopathy (pathogenesis unclear, reversible after discontinuation); in some cases with hyperammonemia, as well as increased phenobarbital levels on combination with phenobarbital. In isolated cases - especially with higher doses or in combined therapy with other antiepileptics, chronic encephalopathy with neurological symptoms and disorders of higher cortical functions, aetiology unclear.

(2) For detailed indication see local SmPC.

Warnings and Precautions: Use with special care in: young children and children with multiple disabilities and severe epilepsy, blood clotting disorders or thrombocytopenia, congenital enzyme deficiency diseases, renal failure and hypoproteinaemia, lupus erythematosus. Use in young children only in exceptional cases (special caution, strict benefit-risk assessment, if possible as monotherapy).

Pregnancy/lactation: increased risk of malformations (including neural tube defects), particularly on exposure in 1st trimester and start of 2nd and on combined therapy. Potentially increased risk of developmental delay. Administer in the lowest seizure-controlling dose and, wherever possible, as monotherapy. Advise women of child-bearing age of need to plan and monitor pregnancy before beginning treatment. Breast-feeding possible.

Side effects: Side effects attributable to use of Orfiri® 100 mg/ml solution for injection include all those associated with oral forms of valproate. On parenteral use, burning at injection site and dizziness can occur. Commonest side effects are gastrointestinal disorders (in about 20% of patients). Severe (even fatal) liver damage, especially in children given high doses or on multiple anticonvulsant therapy, has been observed. Blood and lymphatic system: common: thrombocytopenia, leucopenia; uncommon: haemorrhage, very rare: bone marrow suppression, reduction in fibrinogen and/or clotting factor VIII, impaired platelet aggregation, increased bleeding time, lympho-, neutro-, pancytopenia, anaemia. Immune system: rare: lupus erythematoses, vasculitis; unknown frequency: allergic reactions. Endocrine system: rare: hyperandrogenism. Metabolism and nutrition: common: hyperammonenaemia, weight gain or loss, appetite increased or decreased; rare: hyperinsulinaemia, reduced levels of insulin-like growth factor-binding protein 1, oedema, hypothyroidism; very rare: altered thyroid function tests. Psychiatric: rare: irritability, hallucinations, confusion, depression; very rare: hyperactivity, spasticity, ataxia, stupor, hypersalivation; very rare: encephalopathy(1), dementia associated with cerebral atrophy, parkinsonian syndrome (reversible). Gastrointestinal tract: very common: stomach pains, nausea, vomiting; rare: diarrhoea, pancreatitis. Liver and biliary tract: common: changes in liver enzymes; rare: severe liver damage(2). Skin and subcutaneous tissue: common: transient hair loss, hair thinning, curly hair if regrowth; rare: rash, erythema multiforme; very rare: Stevens-Johnson syndrome, Lyell syndrome. Kidneys and urinary tract: very rare: Fanconi syndrome, anuria in children. Reproductive system and breasts: common: amenorrhoea; rare: polycyst. ovaries. General disorders and administration site conditions: rare: inflammation at injection site; unknown frequency: tissue disorders after erroneous intra-arterial or perivenous injection, dizziness.

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Endogenous neuroprotective mechanisms in the human brain

Roger P. Simon and Martha B. Johnson, Robert Stone Dow Neurobiology Labs, Portland, Oregon, USA

Endogenous neuroprotection harnesses evolutionarily conserved mechanisms to defend the brain from a variety of insults, including ischemia, seizure, and infection. Endogenous neuroprotection can be invoked by a mild insult experienced hours to days before a severe insult. Such preconditioning prior to a challenge attenuates subsequent brain injury. The mechanisms that underlie endogenous neuroprotection therefore have therapeutic potential. To study these mechanisms we have used microarray analysis to generate the genomic profile of brain preconditioned against ischemic injury and the genomic profile of brain preconditioned against seizure induced injury. From these profiles emerge patterns whose intersection and divergence delineate principle features of endogenous neuroprotective mechanisms.

Introduction
Using a mild insult to induce endogenous neuroprotective mechanisms is known as preconditioning. When followed by a severe insult, or challenge, preconditioning results in a state of tolerance in which the injury inflicted by the challenge is mitigated. Tolerance is observed in ischemia, seizure, and infection and can be induced when the severe insult is preceded by a mild insult of the same or different type. Classical preconditioning requires new protein synthesis and confers delayed and temporary neuroprotection, taking hours to develop, peaking over the course of one to three days, and then abating (Barone et al., 1998).

Ischemia preconditioning
In rodents and humans, transient ischemic attacks (TIAs) attenuate the injury sustained from an ensuing stroke (Chen et al., 1996; Weih et al., 1999). We used microarray analysis to profile the transcriptional changes that occur in the mouse cortex after ischemic preconditioning (15 min middle cerebral artery occlusion [MCAO]), ischemic challenge (60 min MCAO), and ischemic tolerance (15 min MCAO followed 72 hr later by 60 min MCAO). The analysis showed that the genes regulated by preconditioning and the genes regulated by challenge were different. Moreover, genes regulated in tolerance were distinct from those regulated by either preconditioning or challenge. Accordingly, we propose that preconditioning reprograms the brain's response to challenge, altering the transcriptional response, and thereby producing a neuroprotected phenotype (Stenzel-Poore et al., 2003).

The reprogrammed response to ischemic challenge induced by ischemic preconditioning begins to elucidate putative mechanisms of endogenous neuroprotection. In ischemic tolerance gene expression is predominantly suppressed. Ion channels, transporters, and metabolic pathways are particularly impacted. This is reminiscent of the the endogenous neuroprotective mechanisms that allow hibernating animals to survive periods of prolonged oxygen and glucose deprivation (Storey and Storey, 1990; Hochachka et al., 1996).

Endotoxin preconditioning
The endotoxin lipopolysaccharide (LPS) is a surface component of bacteria that triggers an inflammatory response through its interaction with toll-like receptor 4 (TLR4). Exposure to a low dose of LPS precondition the brain and can produce ischemic tolerance (Tasaki et al., 1997). We used microarray analysis to profile the mouse cortex after endotoxin preconditioning (5 µg LPS), ischemic challenge (60 min MCAO) and LPS-ischemic cross-tolerance (5 µg LPS followed 72 hrs later by 60 min MCAO). The results support our conclusion that preconditioning achieves neuroprotection by reprogramming the transcriptional response to a severe insult. A majority of genes regulated in LPS-induced ischemic tolerance were not regulated in ischemic challenge (Stenzel-Poore et al., 2007).

The nature of the reprogrammed response to ischemic challenge induced by LPS preconditioning offers further insight into endogenous neuroprotection. Whereas ischemic preconditioning suppresses expression of genes influencing metabolism and transport, LPS preconditioning modulates inflammatory mediators, inducing neuroprotective cytokines and repressing pro-inflammatory molecules. This suggests that the preconditioning stimulus provides neuroprotection by reprogramming particular aspects of the response to challenge, specifically those intrinsic to the preconditioning stimulus (Davis and Patel, 2003; Stenzel-Poore et al., 2007).

Seizure preconditioning
Cell damage and death caused by a prolonged seizure diminishes when preceded by a brief, mild seizure. Various stimuli, including kindling, bicuculline, kainic acid, and electroshock effectively precondition the brain against status epilepticus (Kelly and McIntyre, 1994; Sasahira et al., 1995; Najm et al., 1998; Plamondon et al., 1999; Andre et al., 2000; Kondratyev et al., 2001; Borges et al., 2007; Hatazaki et al., 2007). We have used microarray analysis to profile the transcriptional changes that occur in the CA3 subfield of the mouse hippocampus after epileptic challenge (intra-amygdala administration of kainic acid) and after epileptic tolerance (systemic administration of kainic acid followed 24 hr later by intra-amygdala administration of kainic acid). In contrast to ischemia, many of the same genes were regulated by both epileptic challenge and epileptic tolerance. However, a substantial subset of genes were regulated only by epileptic tolerance, and, notably, these differentially regulated genes were predominantly suppressed (Jimenez-Mateos et al., 2008). Prominent among the suppressed genes were those whose products participate in calcium signaling, synaptic function, long-term potentiation, and excitatory neurotransmission. We conclude that reprogramming, albeit to a less pronounced degree, underlies the neuroprotection provided by seizure preconditioning. Moreover, seizure preconditioning specifically promotes an anti-excitotoxic phenotype particularly opposite to the inducing stimulus, as an anti-inflammatory phenotype is to LPS and hypo-metabolic phenotype is to ischemia. We note that these phenotypes are appropriate to the nature of the preconditioning stimulus and not to the nature of the challenging stimulus. As an endogenous neuroprotective mechanism this can be understood as a first insult priming the brain to respond advantageously in the likelihood of a second insult of the same kind. Yet the brain appears also to respond advantageously to a second insult of a
different kind. The basis for this is not yet clear. Our microarray studies make apparent that the response to any brain challenge is complex, engaging numerous and diverse pathways. Thus modulating metabolism, inflammation, or excitotoxicity could provide a measure of protection against diverse insults that disrupt these functions to greater and lesser degrees. Our studies show that seizure preconditioning alters the expression of inflammatory mediators after epileptic challenge in a manner similar to LPS preconditioning (Johnson and Simon, unpublished results). Thus, different preconditioning stimuli may activate common neuroprotective pathways. There may also be shared neuroprotective mechanisms not detectable at the transcriptional level. The ongoing task is to apply our understanding of endogenous neuroprotection to therapy while continuing to elucidate mechanism.

References


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The mechanisms by which seizures can progress to status epilepticus are unclear. In animal and humans, seizures are usually self-limiting lasting just a matter of seconds or minutes, implying that there are powerful mechanisms to terminate seizure activity. An important observation in both human and animal studies is an EEG progression towards status epilepticus. Initially, there are repeated seizures which merge into continuous seizure activity and eventually periodic epileptiform discharges (Treiman 1995). Moreover, studies in which electrical stimulation is used to induce status epilepticus demonstrate that the longer the stimulation occurs, the more likely self-sustaining status epilepticus is likely to occur (Mazarati et al. 1998a). Together these observations indicate a paradigm in which repeated seizures lead to a failure of the mechanisms that normally terminate seizures. The initiation and maintenance of status epilepticus, may however be mediated by different mechanisms. Further the mechanisms that maintain status epilepticus are different from those that result in neuronal death and also from those that result in the development of epilepsy (Walker 2007). It is therefore, for example, possible to prevent neuronal death without necessarily stopping the status epilepticus (Fisher et al. 2004). Experimental models of limbic status epilepticus have given us an insight into the possible mechanisms by which status epilepticus occurs. The advantages and disadvantages of such models are discussed elsewhere in this colloquium and so I will not discuss these further. There is increasing evidence that during the development of status epilepticus there are changes in both inhibitory and excitatory mechanisms that can lead to the emergence of continuous seizure activity. The models probably induce status epilepticus by generating powerful and continuous excitation which results in inhibitory dysfunction/exhaustion and a potentiation of excitation so that when the electrical stimulation stops or the convulsant has been cleared the seizure activity continues as self-sustaining status epilepticus. Most work has been aimed at revealing dysfunction of the GABAergic system. Seizures have been shown to change GABA(A) receptor trafficking, phosphorylation and expression (Naylor et al. 2005; Brooks-Kayal et al. 1998; Goodkin et al. 2005, 2008; Terunuma et al., 2008). There may also be acute changes in the chloride gradient due to seizure-induced changes in the potassium-chloride transporter, KCC2, giving rise to less hyperpolarizing or even depolarizing GABA(A) receptor mediated potentials (Rivera et al. 2004). In addition, seizures decrease modulation of excitatory transmission by presynaptic GABA(B) receptors (Chandler et al., 2003). There is also dysfunction and acute loss of interneurons and less effective recruitment of interneurons (Doherty & Dingleline 2001; Slowiter et al. 2003). Whether these changes are sufficient to induce self-sustaining status epilepticus is unclear but doubtful, because many of these changes persist even after the status epilepticus has stopped. It is therefore likely that dysfunction of other systems play an important role, and there may be dysfunction of adenosinergic, cannabinoid and peptidergic inhibitory mechanisms (Wasterlain et al. 2002; Handforth & Treiman 1994; Falenski et al. 2007). Peptides have a powerful influence on hippocampal excitability and there is increasing evidence of a shift during status epilepticus in expression from inhibitory (e.g. galanin) to excitatory peptides (e.g. substance P) in part mediated by a change in the expression of Repressor Element-1 Silencing Transcription (REST) and its truncated form, REST4 (Mazarati et al. 1998b; Liu et al 1999; Spencer et al. 2006). REST and REST4 may also play a part in other changes that occur during and shortly after status epilepticus. There is also evidence that there are changes in AMPA receptor subunit expression and release probability at excitatory synapses during or shortly after status epilepticus (Scimemi et al. 2006; Friedman et al. 1994). In addition, seizures can result in acute changes in neuronal excitability mediated by altered expression and/or function of ion channels such as HCN1 that can result in increased dendritic excitability and greater excitatory post-synaptic potential summation (Shah et al. 2004). The extent to which any or all of these changes contribute to the occurrence of status epilepticus unfortunately remains unclear and there may even be roles for regulation of network activity by other mechanisms such as metabolic effects (Huchzermeyer et al. 2008), changes in calcium homeostasis (Raza et al. 2004), acute inflammation and disruption of the blood brain barrier (Marchi et al. 2007, 2008). It is likely that there is no single mechanism at play but an accumulation of seizure-induced modifications of network and neuronal excitability.

References


IL3

Physiology of EPC and subcortical mechanisms of SE

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not submitted
Introduction: Systemic factors are often implicated in the genesis of status epilepticus (SE). In addition, there may be opportunities to use non-pharmacologic manipulation of some of these factors to treat SE or to mitigate its consequences.

Methods: Literature review

Results: The clearest associations between SE and contributing metabolic factors are with hyponatremia, hypoglycemia, nonketotic hyperglycemia, and fever. Hypoglycemia and nonketotic hyperglycemia are notable for the production of either partial or generalized SE. The association between SE and hyponatremia appears to depend primarily on the rate of decline of the serum sodium (i.e., fall in tonicity) rather than the depth of the decline. Fever can trigger SE in infants and children who are predisposed to epilepsy, but the connection is less clear in other children or in adults until they reach exceptionally high core temperatures. Although SE due to hypocalcemia seems well established in infants, the relationship in older patients is less certain because they almost always have comorbidities that may also promote seizures. Hypercalcemia is rarely associated with SE, and again comorbidities may play an important role. Hypomagnesemia is a theoretically attractive cause of SE, but again the influence of the underlying cause of the electrolyte disturbance clouds the matter. Hypophosphatemia has rarely been implicated in nonconvulsive SE. Thyroid disturbances themselves have been linked to SE, more commonly hyperthyroidism than hypothyroidism, but are more commonly associated in the setting of Hashimoto’s encephalopathy. Other autoimmune disorders may have predilections for particular brain regions, often the limbic system, with complex partial SE as the result. The relationship of other endocrine disorders to SE is usually mediated via electrolyte disturbances, such as the hyponatremia seen in the syndrome of inappropriate antidiuretic hormone. Hypothermia has recently been the subject of anecdotal reports as a treatment for refractory SE. In addition, treatment of post-cardiac arrest comatose patients with hypothermia appears to be changing the expected poor prognosis of patients who develop SE after return of spontaneous circulation.

Discussion: Although systemic factors are commonly deranged in patients with SE, the available literature is confounded by the inability to dissociate many electrolyte and metabolic disturbances from their underlying causes. However, this has minimal therapeutic implications, as treatment of the cause is often the more effective way to correct the abnormality.

Key words: status epilepticus, hyponatremia, hypoglycemia, hyperglycemia, hypocalcemia, hypomagnesemia, hyperthermia, fever
se gradually changed the early view that seizures do not cause any brain injury, to the intermediate view that excessive seizure activity damages the mature, but not the immature brain, and finally to the view that prolonged seizures can cause brain injury at both early and later stages of development (VanLandingham et al., 1998; Provenzale et al., 2008).

**Experimental status epilepticus produces a permanent epileptic state**

In addition to clarifying the relationship between seizures and brain damage, experimental status epilepticus has been widely used to produce brain injury and a chronic epileptic state in rodents (Pisa et al., 1980). Although the first detailed description of the pathologies caused by kainic acid clearly showed that systemically administered kainate only minimally involved the hippocampus (Schwob et al., 1980), kainate-treated rats were soon presented as models of hippocampal-onset temporal lobe epilepsy (Nadler, 1981; Tremblay and Ben-Ari, 1984), despite there being no reason to believe that the relatively minimally affected hippocampus was the source of the seizures that defined these animals as epileptic. Rodents treated with pilocarpine have been similarly represented as animal models of hippocampal-onset temporal lobe epilepsy (Cavalheiro et al., 1991) despite the fact that these animals also exhibit widespread extrahippocampal brain damage, high lethality, and, like kainate-treat rats, a mixture of excitotoxic and ischemic injury (Sloviter, 2005). Pilocarpine more reproducibly involves the hippocampus than kainate, reliably resulting in dentate hilar neuron loss, but the spontaneous seizures that develop in pilocarpine-treated animals do not appear to arise from, or even frequently recruit, the hippocampus (Harvey and Sloviter, 2005). Nearly 30 years after kainate’s first use as a systemic method for inducing convulsive status epilepticus and chronic epilepsy, we are left, in my view, with a variety of incompletely characterized animal models that involve so much lethality, brain damage, and minimal latency before spontaneous seizures of unknown origin develop, that it is difficult to determine which of the many effects produced in these animals may be causally epileptogenic, and which effects are confounding epiphenomena. Perhaps most remarkably, delayed secondary mechanisms have been assumed to play epileptogenic roles because a latent period lasting for several weeks had been assumed to follow the initial injury. The belief in the latent period clearly implied that neuron loss is primarily a trigger of a delayed epileptogenic process, rather than being a primary cause of epileptogenesis, because epilepsy was assumed to develop some time after the initial injury. The recent observations, following continuous monitoring, that epilepsy develops immediately after initial brain injury in pilocarpine- or perforant pathway stimulated rats (Raol et al., 2006; Goffin et al., 2007; Jung et al., 2007; Bumanglag and Sloviter, 2008), before any delayed secondary processes have time to develop, would seem to be an issue worthy of reconsideration. The primary appeal of the systemic chemoconvulsant-based status epilepticus models is clearly the ease with which they are produced. However, does that justify their continued use when so few questions can be answered definitively because of the high mortality; variability among surviving animals, and the fact that the limited hippocampal involvement makes studies of hippocampal epileptogenesis so problematic? Following the burst of activity that was so fruitful in clarifying the role of glutamate in the development of seizure-induced brain damage, it might be prudent to evaluate the appropriateness of the systemic chemoconvulsant-based animal models for the much more reductionist and mechanistic questions now being asked, and given the need to develop and assess neuroprotective and anti-epileptogenic treatments, which require minimal inter-animal variability.

**References**


Canine Status Epilepticus: Proof of Principle Studies

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Canine status epilepticus (SE) is a naturally occurring condition, not a model, and may provide a setting in which proof of principle studies of new therapies for both humans and canines can be evaluated. Current treatment of human status epilepticus (SE) is based on clinical studies performed decades ago using drugs developed before the 1970s (Cranford et al, 1978). Successful treatment rates in a comprehensive clinical study were only 67% with lorazepam and 51% with phenytoin (Trieman et al 1998). These drugs now form the basis of international treatment guidelines (Kalvainen, 2007). In a recent international workshop, it was stated *regulations in their current form for undertaking studies in the emergency situations in patients unable to give consent pose serious obstacles for future research* (Shorvon et al, 2008). There is an urgent need for developing treatments for SE using newer agents. Two new intravenous (IV) antiepileptic drugs (levetiracetam and lacosamide) are now available and two are being developed (carbamazepine and topiramate). These may have significant advantages over current therapy but evidence is required before they can be incorporated into guidelines. A major obstacle for performing studies with drugs for SE is that although it is possible to obtain "continuing consent" in emergency treatment situations, the Institutional Review Boards (IRBs) allow this only if there is some evidence to indicate that the test drug has potential for being superior to accepted therapy. This is a high bar for new drugs if the only evidence for efficacy and safety is based on SE studies performed in small animals with experimental SE. These experimental SE have two shortcomings which make it difficult to apply results to treating SE in humans: 1) none of the models have counterparts in the human condition; 2) they are usually induced by various chemicals or use of electrical kindling (Sloviter et al, 2007). These laboratory models are inadequate to support applications for human studies presented to the FDA for an IND or obtain support from local IRBs. There are many similarities between human and canine epilepsy (Berendt et al, 2004). Canine SE is commonly encountered in veterinary practice, and the causes are similar to those seen in humans (Platt and Haag, 2002; Bateman and Parent, 1999). This naturally occurring SE is comparable to the human condition in terms of underlying pathophysiology, clinical course and response to conventional treatment.
therapy. Evaluating drugs for SE in dogs has three advantages: 1) studies could provide proof of principle evidence for efficacy and safety; 2) the doses and plasma drug concentrations needed to control canine SE provide much more relevant information about the design of effective dosing regimens in humans; and 3) being able to perform a placebo-controlled study in dogs significantly increases the power of the study. We were able to obtain approval for a double-blind placebo controlled study of levetiracetam (LEV) in canine SE because there is no widely accepted treatment or successful treatment for this condition. Approximately 4 to 6 dogs per month present at the U of MN Veterinary Hospital, but because of the cost of the ICU stay, most owners have chosen not to participate, electing to have their dogs euthanized. Informed consent is obtained from the owner. If seizures continue after Phenobarbital or diazepam, the subject is randomized to a loading dose of LEV or saline and admitted to the Intensive Care Unit. The primary endpoints are: number of hours from admission until 24 hours without an observed seizure, number of seizures until 24 hours seizure free, number of episodes of status epilepticus (5 or more minutes of seizure activity), and % all cause mortality while hospitalized. After administration of the study agent, further therapy may be used for refractory SE. Secondary endpoints are: hours of hospitalization, number of bolus injections of diazepam given, % of dogs receiving a constant rate infusion of diazepam (CRI), hours of CRI of diazepam, % of dogs receiving either propofol or pentobarbital treatment, hours of propofol or pentobarbital treatment. Power analysis calculations indicated that 10 dogs in the active and 10 in the placebo group would detect a 40% difference in the number seizure free at the end of a 24 hour observation period with an alpha of 0.05 and beta of 0.20. In the LEV study dogs were randomized in blocks of 10, 5 LEV and 5 placebo receiving 30 mg/kg LEV or saline. Interim analysis without unblinding found a group difference: in one group, 3 of 5 (60%) had no more seizures for 24 hours and in the other group 1 had no more seizures (20%). The second group of 60 mg/kg is now underway. Another development in the US that will facilitate studies of SE is the existence of the Neurological Emergencies Treatment Trial (NETT) Network. Severe neurological illnesses or injuries such as SE require immediate intervention to preserve life or reduce mortality. The, NETT has been funded by the National Institute of Neurological Disorders and Stroke. The NETT conducts multi-centered clinical trials of potential new therapies for a wide range of neurological problems. The NETT includes not only academic centers, but also community and rural sites, in order to enroll patients who are cared for in diverse settings. The NETT consists of a Clinical Coordinating Center, located at the University of Michigan and a Statistical and Data Management Center at the Medical University of South Carolina. Patient enrollment into clinical trials occurs at 11 “hubs” which, in turn coordinate the activity of between 3-10 “spokes”. The hub provides local resources, support and administration of the activities of the NETT, and to ensures proper patient enrollment and adherence to protocols and regulatory requirements. Each spoke is a hospital whose emergency department is involved with the acute care of patients with neurological emergencies. By performing proof of concept studies in canine SE and then utilizing the NETT for human studies, it may be possible to advance the treatment of SE in humans.

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Molecular Basis of Self-sustaining Seizures and Pharmacoresistance during SE: The Receptor Trafficking Hypothesis Revisited

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During status epilepticus (SE), seizures become self-sustaining (Wasterlain, 1974), and pharmacoresistance to benzodiazepines develops progressively, and can result in a 20-fold reduction of response to diazepam after 30 min. of experimental seizures (Kapur & MacDonald 1997, Mazarati et al 1998, 1999). This time-dependent pharmacoresistance is not mediated by classical transporter mechanisms (Brandt et al 2008), but may reflect seizure-induced internalization of synaptic GABA_A receptors (GABA_A R) containing the β3 and/or γ2 subunits (Naylor et al 2005, Goodkin et al 2005), while tonic currents, generated by extrasynaptic receptors, actually increase (Naylor et al 2005, Goodkin et al 2008). This presents therapeutic challenges, since GABA_A R internalization occurs quickly (Naylor & Wasterlain,
reducing the therapeutic target for benzodiazepines and other GABAergic drugs. As a result, the therapeutic response to the drugs of choice against SE declines, and this makes it difficult to control seizures, since very early treatment of SE is rarely possible.

However, changes in glutamate receptors and in other transmitter systems also play a role in hippocampal hyperexcitability during SE. We will present evidence that hippocampal slices prepared from rats after 60 min of lithium/pilocarpine SE display an increase in the amplitude of NMDA-mediated miniature excitatory postsynaptic currents on granule cell somas, suggesting an increase in number of functional NMDA receptors (NMDAR) per synapse. After an hour of SE in vivo, we observed a movement of NMDAR (visualized by immunocytochemistry of the NR1 subunit and confocal microscopy) from the cytoplasm to the vicinity of synapses in granule cells, and in CA1 and CA3 pyramids, suggesting activity-dependent trafficking of NMDAR to synapses. Since both the loss of synaptic GABA<sub>R</sub> and the increase in synaptic NMDAR are proconvulsant, this suggests that the traditional treatment of SE by enhancing GABA inhibition leaves glutamatergic excitation unchecked, and that polytherapy is needed to simultaneously stimulate the remaining GABA<sub>R</sub> and reduce the activity of NMDAR. Our data show that in a very severe model of SE (5 mEq/kg lithium, 320 mg/kg picrotoxin), which is refractory to anesthetic doses of diazepam (20 mg/kg), seizures can be stopped without depressing consciousness, using a low dose of diazepam (1 mg/kg, devoid of any measurable effect on SE when given alone) combined with an NMDA antagonist (dizocilpine, in a dose which had no measurable anticonvulsant effect when given alone at that same time point, or ketamine). This strongly suggests that initial treatment with a combination of a GABA<sub>R</sub> agonist and an NMDAR antagonist is more effective and less toxic than monotherapy, and that pharmacoresistance during SE can in part be overcome by reversing the physiological changes resulting from receptor trafficking. Further increases in treatment potency could be achieved by adding, to the GABA<sub>R</sub> agonist/NMDA antagonist combination, a third drug which enhances inhibition by non-GABA, non-glutamatergic mechanisms (e.g. valproate, brivaracetam). Receptor trafficking-targeted polytherapy also reduced the long-term sequelae of SE.

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Figure 1. In hippocampal slices prepared from rats in lithium/pilocarpine-induced SE for 1 hour, GABA<sub>A</sub> miniature inhibitory post-synaptic currents (IPSCs) recorded from granule cells were reduced compared to controls (A, upper left graph). This indicates a reduction of the number of GABA<sub>A</sub> receptors from 38 ± 15 to 20 ±6 per granule cell synapse. Exposure of hippocampal slices to GABA produces similar changes (B, graph on upper middle). Tonic currents generated by extrasynaptic GABA<sub>A</sub> receptors are increased in slices from rats in SE, reflecting (at least in part) increased extracellular GABA concentration during SE. In control granule cells (D, bottom left) the β2-3 subunits of GABA<sub>A</sub> receptors (red) localize to the vicinity of the presynaptic marker synaptophysin (green), while after an hour of SE induced by lithium and pilocarpine (D, bottom right), many have moved to the cell interior.
Molecular mechanisms of drug resistance in status epilepticus

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Status epilepticus (SE) is a neurological emergency, characterized by continuous or intermittent seizures without full recovery of consciousness between seizures, which can result in death or neurological sequelae. In about one third of patients, SE is unresponsive to sequential treatment with first- and second-line antiepileptic drugs (AEDs). The two most important variables which influence the response of SE to AEDs are the underlying etiology and the duration of SE. With respect to etiology, acute structural brain disorders (e.g., encephalitis, stroke, trauma) resulting in SE in previously non-epileptic patients are particularly likely to be refractory (Neligan and Shorvon, 2008). Conversely, in cases of acute SE in previously non-epileptic patients, where no etiology is found, the outcome is usually much better. With respect to duration of SE, the longer the seizure persists (typically >1 hour), the more likely is the seizure to be unresponsive to AED therapy, the higher is the mortality and the worse is the prognosis in survivors. Similar observations have been reported in rat models of SE. In rats, SE can be induced with chemical agents or by electrical stimulation. Chemical models of SE include systemic administration of the convulsants kainic acid or pilocarpine, while electrical models include hippocampal or amygdala stimulation via depth electrodes. In such models, seizures rapidly become self-sustaining and continue long after the withdrawal of the convulsive stimulus. Various molecular and functional changes are thought to play a role in the transition from single seizures to self-sustained SE and in the development of time-dependent pharmacoresistance in rat SE models (Chen and Wasterlain, 2006). These changes include alterations in the functional properties of hippocampal GABA<sub>A</sub> receptors and trafficking of GABA<sub>A</sub> receptors (or receptor subunits) from the synaptic membrane to the cytosol, resulting in a loss of GABA-mediated inhibition. At the same time, glutamate receptor subunits, including AMPA and NMDA receptor subtypes, move to the synaptic membrane where they form additional excitatory receptors. These changes are likely to explain progressive resistance to AEDs acting on GABA<sub>A</sub> receptors, whereas anticonvulsant NMDA or AMPA antagonists remain highly effective in terminating SE. These findings, however, do not easily explain resistance to AEDs such as phenytoin that do not primarily act via GABA receptors. It is conceivable that AED targets other than GABA or glutamate receptors are also affected by sustained seizure activity. For instance, molecular and functional changes in voltage-dependent sodium channels, which are targets of phenytoin and various other major AEDs, have been found after a pilocarpine-induced SE in rats (Ellerkmann et al., 2003). Another explanation for the progressive loss of AED efficacy with ongoing SE activity would be increased expression of drug efflux transporters such as P-glycoprotein at the blood-brain barrier, thus leading to reduced concentrations of AEDs at their brain targets (Löscher, 2007). However, recent experiments in two rat models of SE did not result in any evidence supporting this possibility (Bankstahl and Löscher, 2008). Furthermore, apart from target or transporter alterations, the severity of SE may play a role for response to AED treatment. We recently demonstrated in rats that SE induced by pilocarpine was more resistant to AEDs than an electrically induced SE, and also induced more severe brain damage than determined in the electrical model (Bankstahl and Löscher, 2008). So one may speculate that drug resistance, at least in part, is a mere expression of higher SE severity (and/or the severity of the underlying condition), rather than of molecular or functional alterations developing as a result of sustained seizure activity.

References


The Genetics of Status Epilepticus

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Introduction

Many common diseases and disorders, such as hypertension, diabetes, arthritis, and epilepsy, have a genetic component with a complex genetic architecture. Evidence for a genetic influence on epilepsy emerged in twin studies that reported concordance rates consistently higher in monozygotic than in dizygotic twins (Lennox, 1951; Sillanpää et al., 1991; Berkovic et al., 1998). The causation of epilepsy is multifactorial (a combination of environmental and genetic risk factors) and the genetic part is very complex (polygenic). For example, mutations in different genes can cause the same syndromes in different families (Cossette et al., 2002; Suzuki et al., 2004). Equally concerning is the second complication of variable expressivity, in which mutations in a single gene can produce different epilepsy phenotypes in different individuals as a result of modifying genetic or environmental fac-
tors (Kanai et al., 2004; Mulley et al., 2005). Thus, similar to many other complex diseases, it has been suggested that epilepsy is a polygenic syndrome, influenced by the effect of variation at several or multiple genes (reviewed in Ottman et al., 1996; Anderson et al., 2002).

Identification of the genetic causes of status epilepticus

Numerous studies have mapped and identified relevant genes that influence resistance and susceptibility to epilepsy using a variety of both family-based and population-based approaches and mapping genes using mouse models. However, the replication of findings and the localization of these genetic loci continue to be a challenge for complex traits, such as epilepsy. As susceptibility to status has a multifactorial etiology, no single strategy is likely to identify all of the potential genes involved in susceptibility to epilepsy as all study designs have limitations. Thus, it is important to supplement human experimental approaches with the investigation of animal models, as animal models offer several advantages for the study of multi-factorial human diseases. While there are no known inbred strains that spontaneously develop status, researchers have used induced models of status in experimental animals such as mice. Genome-wide scan can be performed readily in experimental animals such as mice. Even in advantage of identifying specific gene, such studies can identify the chromosomal locations of quantitative trait loci; information that can be used to prioritize genes for candidate analysis in humans. Similarly, because of the lack of a clear understanding of the pathogenesis of epilepsy and the biological pathways that may be disturbed in this disorder, using animal models may be critical for paving the way for identifying genes that increase the susceptibility to epilepsy.

Genome-wide linkage studies of seizure susceptibility in mice

Since the early 1990’s, the traditional linkage methods of human genetics have been applied in rodents to map quantitative trait loci (QTL) for seizure susceptibility. A number of studies have demonstrated the genetic influence on seizure susceptibility and sensitivity in animal models (Weinshenker et al., 2001; Vezzani et al., 2002; Akbar et al., 2003; Mazarati et al., 2004; Fedele et al., 2006). Conducting whole genome linkage analysis derived from seizure-susceptible and relatively seizure-resistant inbred strains constitutes the primary step toward identification of seizure susceptibility quantitative trait loci (QTLs). With the use of this approach, information on chromosomal location, the magnitude of the effect, and the mode of inheritance of each causative locus can be obtained. So far, 11 QTLs for seizure susceptibility have been mapped in crosses between various mouse lines. The identified QTLs map to chromosomes 1, 2, 4, 5, 7, 10, 11, 12, 15 and 18, with the highest density on chromosomes 1, 5, 7, and 10, where QTLs from several different crosses coincide. Some of the QTLs identified by genetic linkage analysis have been corroborated by substitution mapping studies using congenic mouse strains (Ferraro et al., 2004; 2007). However, at present, further studies involving substitution mapping either are in progress or are needed to resolve each of these QTLs and identify the underlying genetic causes for susceptibility to experimental epilepsy.

Genome-wide linkage studies of status susceptibility in mice

The application of this approach to studies of status susceptibility, particularly status-induced neuronal damage, have been fewer, likely due to the inherent complexity of separating those loci responsible for differences in seizure susceptibility versus those responsible for susceptibility to seizure-induced cell death. Nevertheless, based on initial studies demonstrating that mouse strains show remarkable genetic differences in susceptibility to the neuropathological consequences of the kainate model of status epilepticus (Schauewecker and Steward, 1997), the identification of genes responsible for these strain-dependent differences can be assessed using QTL analysis, as well. By using information on the chromosomal polymorphisms evident between these two strains, three chromosomal regions were identified that contain genetic loci responsible for strain differences in kainate-induced excitotoxic cell death (Schauewecker et al., 2004). The most significant linkage, on distal chromosome 18, termed Sced1 (seizure-induced cell death 1), is associated with increased susceptibility to kainate-induced excitotoxic cell damage in the hippocampus. In subsequent studies, the existence of the QTL on chromosome 18 was confirmed through the creation of congenic mouse strains. Through creation of overlapping congenic recombinant strains in which the Sced1 QTL interval was dissected into smaller chromosomal fragments, we found a nearly 89% reduction in the extent of seizure-induced excitotoxic cell death in an interval-specific congenic line, which carries a reduced ‘resistant’ strain-derived region of chromosome 18 on an ‘susceptible’ strain-derived background. Utilizing this particular strain, we have initiated candidate gene studies to identify those genes responsible for conferring this effect. At present, we have found that basal hippocampal expression of galanin receptor 1 (GalR1) is differentially expressed among strains susceptible versus resistant to seizure-induced cell death (Kong et al., 2008). Future studies will need to confirm the candidacy of this gene through functional complementation studies.

Conclusion

Unraveling the genetic factors that play a role in status epilepticus is very difficult, as the causation of status is multifactorial and the genetic part is very complex. Unfortunately, many of the epilepsy susceptibility genes identified in mice have not been investigated in human epilepsy and vice-versa. As our current understanding of gene function is too limited to let us predict a priori which genes are involved with a particular trait, a combined approach of mouse genetics and transcriptomics, together with studies involving human patients with diverse epilepsy phenotypes, will yield the fastest progress. It is hoped that future studies will take advantage of discoveries of candidate genes in mouse models which can yield significant insights into the complexity of defining epilepsy genetics and provide a complementary approach to determine the significance of suspected candidate genes in the human population as well.

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**IL10**

**Why Is The Developing Brain More Susceptible To Se?**

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Epidemiological studies suggest that early in life, the brain is unusually susceptible to seizures and especially SE, particularly in the neonatal period. This may be related to a failure of intrinsic antiepileptic mechanisms in the brain that lead to seizure termination with maturation. Experimental studies suggest that basal ganglia networks that involve the substantia nigra pars reticulata (SNR) are critically involved in the control of seizures. In our ongoing studies, we have provided evidence that the ability of the SNR to control the expression of seizures in rats is age- and sex-dependent.
The SNR is a major component of the basal ganglia. With projections both intrinsic and extrinsic to the basal ganglia system, it is involved in cognition, the coordination of motor functions as well as in the control of seizures. The SNR contains high amounts of GABA, GABA-sensitive neurons in the SNR regulate susceptibility to clonic seizures in rats. In the adult SNR, there are two distinct regions, SNR anterior and SNR posterior that have different roles in seizure propagation and control. Metabolic data show that there is a sequence of events that takes place in the SNR as seizure emerges: prior to the seizure onset, there is increased uptake in SNR posterior, which could act as a “gateway” for seizure propagation. After clonic seizures occur, there is increased DG uptake in SNR anterior. This may reflect an attempt of the SNR to curtail the seizure; during a clonic seizure there is increased GABA release from the striatonigral terminals, silencing SNR neurons leading to disinhibition of SNR output systems and the arrest of the ongoing seizure. This is consistent with anticonvulsant effects of bilateral, strictly local injections of GABA_A receptor agonists in the SNR anterior and nigral lesions. Thus, a key feature of the mature phenotype is the presence of a GABA_A-sensitive region located in the SNR anterior that can attenuate seizures (the ‘anticonvulsant’ region). This region is present in both males and females and its appearance may be crucial for the control of generalized clonic seizures in mature animals.

In the immature brain, the SNR does not show any increases in DG uptake during seizures. Furthermore, infusions of GABA_A agonists in PN15 male rats have proconvulsant effects and are ineffective in PN15 female rats. The seizure controlling effects of SNR anterior on clonic seizures are observed in both male and female rats at least from PN25 (female) and PN30 (male). These data suggest that the maturation of the GABA_A-sensitive SNR anterior is crucial for the control of generalized clonic seizures and the lower propensity for the development of SE observed in male and female rats from PN30 on.

The maturation of the GABA_A-sensitive SNR may depend on GABA_A receptor signaling. During development, the direction of GABA_A receptor signaling is influenced by the maturational changes in chloride homeostasis. Early in life, the relative abundance of the sodium potassium chloride cotransporter NKCC1 favors the intracellular accumulation of chloride. As a result, GABA_A receptor activation depolarizes neurons, activates voltage sensitive calcium channels, increases intracellular calcium, and activates calcium-sensitive signaling processes that are important for neuronal differentiation, function, and survival. Later on, the developmental increase in potassium chloride cotransporters that extrude Cl- to the extracellular space (such as the neuronal specific isoform KCC2) eventually dominate; GABA_A receptors assume their classical hyperpolarizing mode of action observed in mature neurons and cannot activate calcium signaling. The timing of GABA_A receptor switch differs among regions, and at least in the SNR, also between sexes. The delayed developmental rise in KCC2 and GABA_A receptor switch observed in male SNR neurons, prolongs the developmental window period during which GABA_A receptors can activate calcium signaling, amplifying the differences in SNR function between sexes.

The mechanisms available to terminate seizures in otherwise normal healthy brain may not be available to terminate seizures in a brain that has already experienced seizures. SE in developing rats does not produce neuronal injury in the SNR. Nevertheless, ongoing studies indicate that the development of the SNR anterior is distorted if infant rats experience 3 episodes of SE (3SE) prior to PN6 irrespective of gender by preventing the emergence of the SNR anterior GABA-sensitive anticonvulsant region at PN30. However, in the SNR, 3SE accelerate the developmental increase of KCC2 mRNA; accelerate the E_GABA switch with sex-specific features, occurring earlier in females than in males; induce changes in GABA_A receptor subunit expression and alter the responsiveness of SNR anterior neurons to GABA_A agents. If 3SE are induced in PN14-16 male rats (a period during which the E_GABA switch naturally occurs), the SNR anterior GABA_A-sensitive anticonvulsant region develops normally. The data then suggest that, during a specific developmental window, the 3SE may shorten the period during which the normal GABA_A-mediated differentiation of the SNR occurs. The detrimental effects of 3SE occur within days after SE. This may provide a possible means for intervention based on short-duration treatments that may prevent or revert the 3SE-induced increases in KCC2 expression.

Understanding the spectra of SE induced changes on the networks involved in the control of seizures as a function of age and sex may lead to the identification of neuroprotective/disease modifying treatments specific for the developing CNS to ameliorate the outcome after SE is terminated.

Supported by grants NS 20253, NS 45911 and NS 48856 from NINDS and the Heffer Family Foundation.

**LONG-TERM EFFECTS OF FEBRILE STATUS EPILEPTICUS: WHAT ANIMAL MODELS CAN TELL US**

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**Febrile seizures and mesial temporal lobe epilepsy**

Febrile seizures (FS) are the most common type of seizure in childhood, occurring in 2−5% of children between 6 months and 5 years of age. FS are short-lasting in about 75% of children and are called “simple FS”. However, FS may have a prolonged duration (>15 min), a focal onset and/or unilateral post-ictal deficit, and/or recurrence within 24 h. These seizures are termed “complex FS”. In addition, complex FS can potentially result in long-term effects such as mesial temporal lobe epilepsy (MTLE) or hippocampal dysfunction. Observations by Falconner et al. (1964) based on 100 patients who had undergone surgery for intractable MTLE suggested that the presence of hippocampal sclerosis was associated with a history of prolonged FS in 30% of patients. Several recent studies have supported this association and have suggested that complex FS are an initial trauma triggering MTLE. Neuroimaging studies dealing with the consequences of complex FS or febrile status epilepticus generally show hippocampal swelling during the acute stage. Magnetic resonance imaging (MRI) studies performed in children with complex FS (48 h and 4−8 months post-seizure) have revealed an increase in hippocampal volume and prolongation of T2 relaxation time. This suggests that complex FS can result in acute hippocampal edema which resolves within several months (Scott et al., 2002; Scott et al., 2003). Although many neuroimaging studies report acute hip-
pocampal damage and subsequent atrophy after complex FS, it is not known whether these patients go on to develop MTLE. A combination of neuroimaging and long-term follow-up studies is required to clarify this issue although this will be difficult as confirmed complex FS are not common in children. From clinical studies it is difficult to determine whether early complex FS damage the hippocampus and cause hippocampal sclerosis. In addition, the hypothesis that children have complex FS because their hippocampus was previously damaged as a result of prenatal or perinatal insult and/or by genetic predisposition (Cendes et al., 1995) is an important alternative.

Animal models of complex febrile seizures

In order to better understand the impact of complex FS on the developing brain and the consequences of previous hippocampal damages on FS, animals models have recently been developed in which hyperthermic seizures (HS) are induced (Baram & Shinnar, 2002). Experimental HS can be evoked in rat or mouse pups around P10–11, which corresponds to the stage of hippocampal development in children at the age of FS occurrence. A regulated stream of heated air (42±2°C) induces hyperthermia and seizures are rapidly observed which are characterized by both behavioral and electroencephalographic criteria. Recording of epileptic discharges requires the placement of depth electrodes within the amygdala and hippocampus (Baram et al., 1997), but these are often associated with behavioral arrest. When such recurrent seizures are induced for 30 min, approximately 95% of animals survive and the long-term consequences can be evaluated. HS in young animals result predominantly in an alteration of neurons in the hippocampus and amygdala of adult animals. These changes are observed only when prolonged seizures are observed during hyperthermia; when HS are prevented by benzodiazepines, few histological changes are observed. Few neurons show apoptotic changes such as DNA fragmentation following HS and these changes appear to be transient (Toth et al., 1998). Further analyses have shown that neuronal loss, neurogenesis and mossy fiber sprouting are limited whereas enhanced sensitivity of the hippocampus is observed (Bender et al., 2003). In 30% of rats exposed to prolonged and repeated HS, clear enhancement of hippocampal excitability was observed electrophysiologically and pharmacologically (Dube et al., 2006). However, these changes were only observed after brief but frequent experimental HS whereas a single experimental seizure has few consequences (Chang et al., 2003).

Febrile seizures and dual pathology

The observation of humans with a history of typical MTLE syndrome, associated with cortical dysplasia or other lesions in the same hemisphere, has led authors to propose the concept of dual pathology. According to this concept, FS probably lead to hippocampal sclerosis, especially in the presence of a preexisting lesion. In animal models, the presence of a localized microgyrus induced in neonatal rats by a cryolesion at P0 resulted in prolonged HS (Scantlebury et al., 2004; Scantlebury et al., 2005). Furthermore, cortical focal lesions predisposed rat pups exposed to HS to chronic limbic seizures together with deficits of learning and memory without histological evidence of cell loss (Scantlebury et al., 2005), and resulted in reductions in whole brain and ipsilateral hemispheric, cortical and hippocampal volumes, which persisted at P22.

Conclusion

Clinical and experimental studies on FS suggest that febrile status epilepticus is not associated with massive cell death in the limbic regions and may not be solely responsible for hippocampal sclerosis, as observed in MTLE. However, the interaction of these prolonged seizures with existing dysplasia or lesions appears to increase the risk of developing MTLE after complex FS. Animal studies exploring the interactions between changes in brain development and HS may increase our understanding of the role of febrile status epilepticus in the initiation of MTLE.

References


Neuronal plasticity in animal models and the epileptic human hippocampus

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Prolonged status epilepticus in humans as in experimental animals can initiate the development of temporal lobe epilepsy (TLE) (Kapur, 1999). Thus, application of potent convulsant substances like kainic acid model or pilocarpine in rats induce acute status epilepticus that, after a silent period of one to two weeks, is followed by spontaneous convulsions. The status epilepticus is characterized by severe limbic seizures and a sequela of neuropathological signs including opening of the of the blood brain barrier, local brain edema, bleeding into the brain, activation of microglia and astrocytes followed by neurodegeneration in the hippocampus, amygdala, entorhinal cortex and other brain areas (Sperk et al., 1983; Du et al., 1993; Rizzi et al., 2003). Induced by the seizure activity, neurotransmitters like GABA, glutamate or amine transmitters released from their stores and mechanisms of their re-synthesis are strongly activated (Sperk et al., 1983). Besides this, pronounced changes in the expression of multiple functionally important proteins have been found brains of experimental animals and humans (Herdegen et al., 1993; Sperk, 1994; McNamara, 1999; Morimoto et al., 2004).

Some of these dynamic neurochemical changes persist also in the chronically epileptic state or may be altered or substituted by other changes. They are accompanied by progressing rearrangement of neuronal circuitries, characterized by continuing neurodegeneration and by axonal outgrowth. The best-characterized example of such plastic changes is the sprouting of mossy fibers to the inner molecular layer of the dentate gyrus terminal area where they seem to substitute the loss of associational/commissural fibers arising from dentate mossy cells (Houser et al., 1990).

We are here reviewing some of our and others’ findings on neurochemical and morphological changes in related to GABAergic and peptidergic neurotransmission (Table 1).

There are clear indications for a loss of excitatory as well as of inhibitory GABA-ergic neurons early after induction of the status epilepticus. At the same time, expression of immediate early genes and of many proteins becomes severely altered, mostly activated presumably leading to an altered functioning of neuronal circuitries (Herdegen et al., 1993; Sperk, 1994; Morimoto et al., 2004). Expression of the GABA synthesizing enzymes glutamate decarboxylases GAD65 and GAD67 and of an embryonic form of GAD67 becomes enhanced (Sperk et al., 1983; Esclapez and Houser, 1999; Szabo et al., 2000; Sperk et al., 2003) indicating enhanced GABA synthesis in the surviving neurons. Also at the receptor level GABAergic transmission appears to be markedly altered. In human TLE, as in animal models, GABA_\alpha\_2 and GABA_\alpha\_3 receptors undergo dynamic changes in their expression. Whereas expression of GABA_\alpha\_1 receptors is decreased initially after status epilepticus (perhaps resulting in enhanced release of glutamate), it is increased in chronic TLE patients (Furtinger et al., 2003; Furtinger et al., 2003). Changes in the expression of GABA_\alpha\_2 receptor subunits are complex. In animal models, typically expression of the \beta-1 subunits (\beta-1, \beta-2 and \beta-3 containing the binding site for GABA, and of \alpha-2 and \gamma-2, contributing to the binding of the anticonvulsant benzodiazepines is increased. On the other hand, levels of subunits presumably comprising extrasynaptic receptors involved in tonic GABA mediated inhibition, such as \delta and \gamma-6 (in mice) become decreased in the dentate gyrus after the status epilepticus. Interestingly in human TLE most subunits expressed in the hippocampus seem to be up-regulated (notably subunits \alpha-2, \alpha-5, \beta-1-3, \gamma-2 and \delta) indicating little functional changes but consistent up-regulation of the receptors presumably leading to generally enhanced GABAergic transmission.

Neuropeptides are co-transmitters of classical neurotransmitters. They are rapidly released during status epilepticus but are considerably slower re-synthesized than classical neurotransmitters (Vezzani et al., 1996). It has been well documented that synthesis of neuropeptides is dynamically regulated in by seizures and that neuropeptides may potently influence later epileptic events in different ways. Thus the peptides thyrotropin releasing hormone (TRH) and neuropekin B exert pro-convulsive and neuropeptide Y (NPY), galanin and dynorphin potent anticonvulsive actions (Vezzani et al., 1999; Mazarati and Wasterlain, 2002). Expression of all of these peptides is altered by the status epilepticus. NPY exerts its anticonvulsive effects through presynaptic Y2 receptors located presynaptically on glutamate neurons and mediating inhibition of the release of the excitatory transmitter (Vezzani et al., 1999; Furtinger et al., 2001). Seizures not only cause marked up-regulation of NPY but also of Y2 receptors in mossy fibers of rats and TLE patients (Furtinger et al., 2001). Interestingly, whereas NPY is ectopically expressed in principal neurons of epileptic rats and may act there on presynaptic receptors, it becomes over-expressed in GABA/NPY neurons that prominently sprout in human TLE. In contrast to the rat, the peptide may there be released from interneurons upon nerve endings of excitatory neurons and may result in impaired glutamate release (Furtinger et al., 2001).

Other than for NPY, expression of dynorphin becomes decreased in the hippocampus epileptic rats (Douglas et al., 1991). Thus its endogenous action may be limited in epileptic rats. In contrast, in patients with TLE expression dynorphin is markedly up-regulated in mossy fibers. mRNA levels are especially high in patients that experienced seizures within a 24 hours period prior to epilepsy surgery indicating a confounding effect of seizures on dynorphin expression (Pirker et al., submitted for publication). Since dynorphin exerts anticonvulsive actions (mediated by \kappa-opioid receptors) in experimental animals, it may act as an endogenous anticonvulsant peptide in human TLE up-regulated by a previous seizure episode. The anticonvulsant potency of various neuropeptides, notably of NPY and galanin has recently lead to the concept of using viral vectors over-expressing the neuropeptides, that then may be selectively released during epileptic seizures and may exert an anticonvulsive action. Acknowledgement: The work was supported by the Austrian Science Foundation (P 19.464 and SFB 35-12) and European Union Grant FP6 EPI-CURE (LSH-CT-2006-037315).
References


**Fachkurzinformation zu Inserat ZONEGRAN Seite 4**

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**Table 1.** Parameters of GABA-ergic and peptidergic neurotransmission altered after kainic acid induced status epilepticus and in temporal lobe epilepsy

↑ increased; ↓ decreased; -, not altered; +, induced.

STATUS EPILEPTICUS IN THE DEVELOPING BRAIN; LONG TERM EFFECTS SEEN IN HUMANS

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Convulsive status epilepticus (CSE) is the most common neurological emergency in childhood with an incidence of 18-20/100,000/year in children <16 years of age. CSE is associated with adverse outcomes including increased mortality as well as increased rates of subsequent epilepsy, cognitive impairments and behavioural disorders. The relationships between aetiology of CSE, the impact of CSE itself and these long term outcomes will be discussed.

There is enormous variability in the estimates of frequencies for outcomes following CSE in children; estimates for mortality range from 0-43%, for subsequent epilepsy from 3.5 to 100% and for cognitive/behavioural disorders from 0-83%. It is unlikely that this extreme variability is entirely due to biological effects. A systematic review of the literature relating to outcomes from childhood CSE revealed that the estimates of all adverse outcomes are lower in higher quality studies supporting the view that CSE may not be as harmful as previously suggested. However, even the lower estimates are likely to be important and deserve investigation.

**Mortality**

In the studies of highest quality, the short term mortality is between 2.7% and 5.2%. The most important factor associated with mortality is aetiology and the evidence for increased case fatality in children with longer seizures is weak and usually confounded by aetiology. Children with symptomatic CSE are most likely to die and those with prolonged febrile seizures or idiopathic CSE are very unlikely to die within 30 days of the acute event. Long term case fatality (up to 10 years after the event) is approximately 3% in children who survived for at least 30 days after the CSE. Children that had their CSE when they were under the age of 1 year had a long term mortality of about 16%. Again, it was the children with symptomatic CSE that were most likely to die. No standardised mortality ratios have been reported for children who have had CSE; a statistic that will help in the understanding of whether CSE has long term implications for mortality. Therefore, although there is a mortality associated with CSE it is primarily determined by aetiology and not by seizure length.

**Subsequent Epilepsy**

Focal epilepsies are the most common epilepsies identified in children who have had an episode of CSE, although generalised epilepsies, infantile spasms and Lennox-Gastaut Syndrome have all been reported. The overall rate of epilepsy following a first seizure that lasts at least 30 minutes is 25-40% which is similar to the 37% risk of subsequent epilepsy reported following a first short seizure. Again, the risk is highest in the subgroup with acute symptomatic CSE. Thus, the overall risk of epilepsy is not dependent on the length of the initial seizure and is more likely to be related to the cause.

The risk of epilepsy following prolonged febrile seizures (the most common type of CSE in children) is estimated to be between 4 and 21% (3,6). The relationship between prolonged febrile seizures and later temporal lobe epilepsy associated with mesial temporal sclerosis (MTS) is important as if this relationship were causative then the incidence of epilepsy following a prolonged febrile seizure could potentially be reduced by intervening with neuroprotective and/or antiepileptogenesis strategies. There is wealth of evidence from animal models supporting the view that CSE can cause hippocampal injury that matures into a disorder resembling human MTS. In humans there is evidence for acute hippocampal injury following prolonged febrile seizure and some data suggesting that early magnetic resonance imaging findings may provide a biomarker for permanent hippocampal injury. Although the retrospective data from epilepsy surgery programmes provide evidence for a relationship between prolonged febrile seizure and MTS, prospective evidence is still poor although there are ongoing studies which could provide the required definitive evidence.

**Cognitive / Behavioural Problems**

This is an area that has so far been under-researched and only 2 reported studies have used standardised neuropsychological testing in a systematic way. Cause, again, emerges as the main determinant of these morbidities. Although adverse outcomes have also been associated with longer seizure durations and with younger age at the time of CSE, it is uncertain whether these effects are independent of aetiology. There are long term adverse social and educational outcomes in children with epilepsy. In one study, which was prospective, there was no additional impact of CSE whilst in another study which was retrospective and hospital based, the major determinant of IQ in children with "generalised idiopathic epilepsy" was a history of CSE.

Therefore, further work that defines the relationships between long term outcomes, aetiology and CSE is required before strategies that minimise the adverse outcomes following CSE can be devised. This is likely to be most rigorously carried out by systematic long term prospective follow-up of population based cohorts of children who have had an episode of CSE.

**References**


Emergency EEGs are most often requested in patients with acute alterations in mental status. The EEG may indicate that a diffuse CNS disorder, a focal process, or ongoing seizure activity, often without motor manifestations, such as nonconvulsive status epilepticus (NCSE), is responsible for the clinical presentation.

EEG findings in encephalopathies include diffuse slowing of background rhythms (the most common finding), frontal intermittent rhythmic delta activity (FIRDA) and triphasic waves (TWs), a pattern present in a variety of metabolic encephalopathies, most commonly hepatic failure. Other patterns include an alpha-theta coma pattern, a spindle coma pattern, periodic patterns, such as periodic epileptiform discharges (PEDs) that can be lateralized or generalized, and a burst-suppression pattern. Findings, such as focal polymorphic delta activity or localized attenuation of faster frequencies, suggest a focal lesion. The EEG can be helpful in making a diagnosis, contribute to an established diagnosis, as well as ruling out a diagnosis. It can aid in prognostication, particularly if the etiology is known, and in the treatment of epileptic disorders (Varelas et al., 2003; Firosh Khan et al., 2005; Praline et al., 2007).

The possibility of status epilepticus (SE), particularly NCSE, is the primary indication for an emergent or stat EEG (Quigg et al., 2001; Benbadis, 2008). These patients are often obtunded or comatose, and frequently there is no clear etiology of coma or the mental status changes. Because of the spectrum of EEG ictal patterns and the diversity of clinical presentations, "is it nonconvulsive status epilepticus (NCSE)?" is often a difficult question for an electroencephalographer to answer, particularly in an ICU setting (Brenner, 2002). Although an EEG is required for diagnosis, criteria for NCSE are controversial in obtunded/comatose patients. In addition, the diagnosis is often delayed due to the absence of motor findings, or if findings are present, they often consist of subtle facial, limb or nystagmoid movements and diagnosis is often delayed (Drislane et al., 2008). The situation is clearer in ambulatory, confused patients with NCSE ("walking wounded"), as in absence status epilepticus or complex partial status, than it is in the "ictally comatose" (Walker, et al, 2005).

In critically ill patients with marked mental status changes, and frequent nonconvulsive seizures (NCS), defined as electrographic discharges lasting greater than 10 seconds and evolving with changes in frequency, amplitude and distribution, the diagnoses of NCSE is relatively straightforward. In contrast to EEG discharges that show a clear evolution, there are a number of periodic EEG patterns, such as periodic lateralized epileptiform discharges (PLEDs), bilateral independent PLEDs (BIPLEDs), generalized periodic epileptiform discharges (GPEDs), as well as triphasic waves (TWs), and stimulus-induced rhythmic periodic or ictal discharges (SIRPIs) reported as being associated with NCSE (Kaplan, 1999; Brenner, 2004; Hirsch et al., 2004; Kaplan, 2007), that are controversial, particularly as to whether or not they are ictal. Although often interictal, at times they can represent an ictal pattern. Furthermore, these periodic discharges are not specific and like NCSE can occur in toxic-metabolic encephalopathies, degenerative disorders, CNS infections, following anoxia or after convulsive seizures (Treiman et al., 1990; Brenner, 2005). Where these periodic patterns fit in an ictal-interictal continuum, and which patterns warrant aggressive treatment, is uncertain (Chong and Hirsch, 2005). This has lead to a concerted effort by a number of North American neurophysiology centers to help standardize nomenclature, create a central database and perform multicenter studies to help answer these questions (Hirsch et al., 2005; Gerber et al., 2008)).

Faster frequency generalized discharges (greater than 2.5–3 Hz) are more consistent with an ictal pattern than are slower ones (Young et al., 1996; Chong and Hirsch, 2005; Kaplan, 2007). However, the EEG alone often cannot answer whether or not the patient is in status, and needs to be interpreted in the clinical context (Korabathina and Benbadis, 2007). A test dose of a benzodiazepine can sometimes be useful to indicate if the patient is in NCSE, particularly if there is a good clinical response or marked improvement of the EEG. Unfortunately, some EEG patterns, including TWs due to hepatic or renal encephalopathy, may improve as well (Fountain and Waldman, 2001). Furthermore, although treatment may improve the EEG, with resolution of the epileptiform activity, the patient often does not improve clinically, perhaps because of the underlying brain disorder or the sedative effects of the drug. Failure to improve following treatment does not mean that the patient is not in SE; rather, no conclusion can be reached regarding the presence or absence of NCSE (Jirsch and Hirsch, 2007).

With advances in computer technology, storage capacity, networking and telecommunications, the use of EEG in evaluating acutely ill patients in the ICU has increased considerably. The goal of continuous EEG (CEEG) monitoring, which consists of prolonged EEG monitoring, often in conjunction with digital video recording, is to help detect and protect patients with an acute brain injury from secondary injuries, such as seizures or cerebral ischemia. Indications include: identification of NCS, the most common type of seizure in the ICU or NCSE, characterization of clinical spells, detection of ischemia, management of a burst-suppression pattern, monitoring treatment and prognosis (Claassen et al., 2004). The most frequent use of CEEG involves monitoring seizures, as well as status epilepticus. Monitoring for 24 hours is probably adequate to detect seizures in noncomatose patients without PEDs; longer periods (48 hours) may be required for comatose patients (Claassen et al., 2004). Following successful treatment of SE, monitoring should be continued for 24 hours, as some patients will have seizures, or go back into status (DeLorenzo, et al., 1998).

Since monitoring for several days generates gigabytes of data, quantitative EEG tools are helpful in reducing the raw EEG data to review. There are a number of programs utilizing quantitative EEG (QEEG), to help identify seizures and trends (Scheuer and Wilson, 2004). Fig. 1 is a 1 hour QEEG displaying 5 seizures in a 71 year-old man, while Fig. 2 A, B, and C show the raw EEG data during the 4th seizure.

**How useful is EEG and EEG monitoring in the acutely ill and how to interpret it?**

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What does the future hold for CEEG? Real time monitoring will improve, as will remote monitoring via cell phones and technology yet to be realized. There will be increased automation, including detection and notification alerts. However, at present CEEG is technically difficult, time-consuming and expensive (Fountain, 2007). Identifying those conditions in which CEEG is most cost-effective and results in better outcomes needs to be determined.

References

Figure 1. A one hour QEEG display in a 71-year-old man having seizures.

The top two panels (left hemisphere and right hemisphere electrodes respectively) are rhythmic run detectors that display rhythmicity from 1-24 Hz that becomes darker when there is rhythmic or periodic activity, and will show a dark band at the frequency of the rhythmic pattern. This allows detection of evolution at times as well (via a diagonal line as the dominant rhythmic frequency gradually changes). Five right-sided seizures are shown (arrows).

The third and fourth panels also represent the left and right hemispheres. Time is shown along the x axis, frequency on the y-axis (0-20 Hz), and power in the z axis, with power shown on a color scale where the highest power is white, followed by pink and red (see color scales in the upper right of each panel). There are bursts of power on the right during the seizures (4th panel).

The 5th panel measures symmetry. The asymmetry index shows total absolute asymmetry in yellow. This measure goes up with asymmetry in any frequency or direction. The green relative asymmetry tracing shows laterality: downgoing indicates more power on the left, and upgoing on the right. Note in this case the green tracing is upgoing during the seizures, indicating more power on the right.

The 6th panel in red and blue is an asymmetry spectrogram. It shows asymmetry at each frequency from 1-18 Hz averaged over the entire hemisphere. Red means more power on the right in that frequency, while blue indicates more power on the left. During the seizures, the right hemisphere becomes dominant.

The seventh and eighth panels represent the amplitude-integrated EEG (aEEG), for a single left (F3-C3) and right channel (F4-C4). There is an increase in amplitude on the right during the seizures.

The bottom panel does not show anything in this case. It is often helpful in those cases in which suppression is occurring.

Figure 2 A, B, C. The EEG of the 4th seizure (cursor line -Figure 1A) begins with right-sided beta activity (A), slows to the alpha frequency (B) and ends with delta activity (C).

**FIGURE LEGENDS**

**Figure 1.** A one hour QEEG display in a 71-year-old man having seizures.

The top two panels (left hemisphere and right hemisphere electrodes respectively) are rhythmic run detectors that display rhythmicity from 1-24 Hz that becomes darker when there is rhythmic or periodic activity, and will show a dark band at the frequency of the rhythmic pattern. This allows detection of evolution at times as well (via a diagonal line as the dominant rhythmic frequency gradually changes). Five right-sided seizures are shown (arrows). The most striking finding in this graphical display of EEG activity is that there marked periodic changes evident across multiple panels simultaneously.

The third and fourth panels also represent the left and right hemispheres. Time is shown along the x axis, frequency on the y-axis (0-20 Hz), and power in the z axis, with power shown on a color scale where the highest power is white, followed by pink and red (see color scales in the upper right of each panel). There are bursts of power on the right during the seizures (4th panel).

The 5th panel measures symmetry. The asymmetry index shows total absolute asymmetry in yellow. This measure goes up with asymmetry in any frequency or direction. The green relative asymmetry tracing shows laterality: downgoing indicates more power on the left, and upgoing on the right. Note in this case the green tracing is upgoing during the seizures, indicating more power on the right.

The 6th panel in red and blue is an asymmetry spectrogram. It shows asymmetry at each frequency from 1-18 Hz averaged over the entire hemisphere. Red means more power on the right in that frequency, while blue indicates more power on the left. During the seizures, the right hemisphere becomes dominant.

The seventh and eighth panels represent the amplitude-integrated EEG (aEEG), for a single left (F3-C3) and right channel (F4-C4). There is an increase in amplitude on the right during the seizures.

The bottom panel does not show anything in this case. It is often helpful in those cases in which suppression is occurring.

**BASIC PHYSIOLOGY OF BURST-SUPPRESSION**

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Burst-suppression (BS) is an electroencephalographic (EEG) pattern consisting of alternative periods of slow waves of high amplitude (the burst) and periods of so-called flat EEG (the suppression) (Swank and Watson, 1949). It is generally associated with comatose states of various etiologies (hypoxia, drug-related intoxication, hypothermia, childhood encephalopathies, but also anesthesia). It has been extensively studied at the EEG level (see review by Brenner, 1985, also this issue), but only sparse information is available with respect to the cellular and ionic mechanisms underlying its patterns. Some of the most fascinating questions pertain to the genesis of bursts: are they truly spontaneous, who trigger them, what mechanism dictates their quasi-periodicity? Moreover, in clinical practice bursting activities during BS are often associated with jerks resembling those present during epileptic fits. Is there any common link to known seizure mechanisms?

At the cortical level, EEG bursts are always associated with phasic synaptic depolarizing intracellular potentials, occasionally crowned by action potentials, in virtually all recorded neurons (Steriade et al., 1994). The same study has shown that suppression episodes are due to absence of synaptic activity among cortical neurons. However, it was also shown that some thalamocortical neurons display a rhythmic activity in the frequency range of delta oscillations (1-4 Hz) during suppressed periods. Recently we have further shown that BS represents a distinct behavioral frame during which the cortical network is in a hyperexcitable...
state and that bursting activity may be triggered by subliminal stimuli (Kroeger and Amzica, 2007). The cortical hyperexcitability was demonstrated under various anesthetics ranging from those enhancing Cl− inhibition (propofol, barbiturates) to those boosting glutamate uptake (isoflurane). In the latter case, hyperexcitability resulted from the reduction of cortical inhibition (Ferron et al., 2009) which was corroborated with an outburst of extracellular Cl−, probably reflecting the lesser activity of GABA, inhibitory synapses. It results that the excitatory-inhibitory balance leans toward the excitation. The bursting process is limited in time because bursting activity is accompanied by a depletion of extracellular cortical Ca2+ at levels that are incompatible with synaptic transmission. This generates an overall disfacilitation in cortical networks (Kroeger and Amzica, 2007), which ultimately is responsible for the arrest of neocortical neuronal activities and the ensuing flat EEG. During suppression, the synaptic silence allows neuronal pumps to restore interstitial Ca2+ levels at control levels. At this moment, any external (or intrinsic) signal is able to trigger a new burst in the hyperexcitable cortex. Thus the pseudo-rhythmicity of the burst-suppression pattern is dictated by the degree of extracellular Ca2+ depletion and the ability of neurons to restore this concentration. These phenomena are modulated by the general state of the nervous system, therefore the etiology and the seriousness of the condition. As coma deepens, bursting episodes become shorter, while the opposite happens to the suppression, leading eventually to continuous isoelectric EEG. The impaired ability of the central nervous system to keep extracellular Ca2+ ions at normal levels might be precipitated by the fact that, at least as demonstrated with isoflurane, the permeability of the blood-brain barrier is compromised during BS (Tétrault et al., 2008).

An interesting issue concerns the similarity between symptoms associated with bursts during BS and spike-wave seizures. Moreover, both occur on a background of impaired inhibition. This calls for one of the two possibilities: either BS is included in the already complex syndrome of epilepsies (with complicating issues regarding mechanisms and curative strategies), or it is regarded as distinct processes with distinct mechanisms. The latter alternative is supported by the fact that volatile anesthetics (isoflurane in particular) are used to counteract status epilepticus, further suggesting that bursts of BS do not reflect an epileptic pathology.

References


What is the relative value of the standard anticonvulsants: phenytoin and fosphenytoin, phenobarbital, valproate, and levetiracetam?

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Status epilepticus (SE) is a serious epileptic condition associated with significant morbidity and mortality that requires prompt medical management. Outcome is largely contingent on the age of the patient, the etiology and duration of the condition before treatment with antiepileptic drugs (AEDs) (Delorenzo et al., 1999;Towne et al., 1994). Treatment is evolving as new medications become available. This summary will give a brief overview on the use of phenytoin (PHE) fosphenytoin(fPHE), valproic acid (VPA), phenobarbital (PB), and levetiracetam (LEV) in generalised convulsive status epilepticus(GCSE).

Currently used first line AEDs: Benzodiazepines

First-line treatment for GCSE is intravenous (IV) administration of 4 mg of lorazepam or 10 mg of diazepam directly followed by 15-18 mg/kg of phenytoin or equivalent fosphenytoin (Meierkord et al., 2006) (Alldredge et al., 2001) (Prasad et al., 2005;Prasad et al., 2007;Treiman et al., 1998). The advantage of lorazepam over diazepam or midazolam is its long lasting clinical effect, determined by the pharmacological properties of the drug. Diazepam is more lipophilic and is subject to extensive redistribution decreasing the concentration of diazepam in the brain (Trinka, 2009). However, clonazepam has similar pharmacokinetic properties like lorazepam and is also widely used in some European countries, but comparative studies are not available. There is wide agreement that any recommendation of first line treatment in SE includes lorazepam, depending of the availability in the given country (Shorvon et al., 2008). Results from two large randomised controlled trials investigating the efficacy of treatments in first stage of SE reveal, that the most effective drug, lorazepam, was successful in 65% and 59% of the treated patients (Treiman et al., 1998) (Alldredge et al., 2001). Therefore at least one third of patients with SE will need a second stage treatment, but there are virtually no adaequate studies available comparing different treatment regimens.

Phenytoin and Fosphenytoin

The main advantage of PHE is the lack of a sedating effect. However, a number of potentially serious adverse effects may occur. Arrythmias and hypotension have been reported, particularly in patients older than 40 years (Cranford et al., 1978;Cranford
et al., 1979). In addition, local irritation, phlebitis and dizziness may accompany IV administration of PHE. Though intravenous PHE was available since 1956 (Carter, 1958), but it was not until 1968 when adequate doses were used to successfully treat SE (Wallis et al., 1968). Although experience is used as an agrument in favour for PHE, there are only six studies available as full paper including 595 patients (adults and children) (McWilliam, 1958) (Leppik et al., 1983) (Wallis et al., 1968) (Wilder et al., 1977) (von Albeert, 1983) (Treiman et al., 1998). The overall success rate ranged between from 44% in the randomised controlled study, up to 90% in the uncontrolled studies. Notably PHE was not always used after BDZ had failed. In most studies it was used in the first stage.

The water soluble produrg of PHE, fosphenytoin (fPHE), is approved for SE since 1996 (FDA). Although it partially overcomes some of the major problems of PHE (e.g. local irritation), it is highly expensive and many hospital formulary committees are unwilling to pay the difference.

**Phenobarbital**

Is one of the oldest AEDs still in clinical use, but its value in the treatment of SE is controversially discussed. Phenobarbital (PB) has fallen from favour in many countries across Europe because of anecdotal evidence of hypotension, arrhythmias and hypopnea. In fact there are only very limited studies available assessing the efficacy of PB in SE. Shaner et al (Shaner et al., 1988) compared prospectively the efficacy of 18 patients treated with PB and 18 patients treated with PHT+DZP. PB was given at a dose of 100mg/minute until 10mg/kg had been reached. Sixteen of 18 patients (89%) were rapidly controlled with PB although 2 of them received additional PHT. The mean time to control seizures with PB was 5 minutes compared to 9 minutes with PHE+DZP. Two of 18 patients (11%) with PB had Hypotension and 1/18 had arrhythmias. PB was also used as one of four treatments in the VA study (Treiman et al., 1998). In this study 15mg/kg PB at 100mg/min controlled 58% of patients with verified diagnosis and 24% of patient with subtle status. There was no difference in efficacy compared to the lorazepam group. Though adverse events with PB were frequent with 34% hypotension, 13% hyperventilation and 3% arrhythmias, there was no difference compared to the other treatment groups. In the VA study serum levels of 31.2±372µg/ml were achieved after infusion. Serum levels of 70µg/ml or above will compromise the level of consciousness in almost all patients and might therefore contribute to postictal coma. The polypropylene solvent may cause local irritation, necrosis or hemolysis and infusion syndrome after prolonged use. Its use in established status epilepticus is widely accepted (Shorvon et al., 2008).

**Valproate**

The availability of IV valproate (VPA) since the 1980s provides an interesting alternative, since PHE/IPHE cannot be used in all patients, including those with allergic reaction to PHE and some forms of progressive myoclonus epilepsy. In addition elderly patients and cardiorespiratory instable patients may be at increased risk for adverse reactions due to PHE/IPHE (Cranford et al., 1978). A number of studies on IV VPA used to control various types of SE (GCSE, partial NCSE, status myoclonicus, absence status) in a variety of patient populations, ranging from children to elderly patients with cardiovascular instability, showed a low incidence of adverse events especially no hemodynamic adverse effects (Sinha and Naritoku, 2000), even when VPA was administered at higher than recommended infusion rates (Whelless et al., 2004) (Venkataraman and Whelless, 1999) (Lindm et al., 2005; Lindm et al., 2007; Lindm and Faught, 2000). To date there are 19 prospective or retrospective series and 3 randomised open trials published including 633 adults or children (recently reviewed in (Trinka, 2007b)). These studies suggest that IV VPA is as effective as PHE/IPHE in resolving SE in patients who have previously failed conventional first-line therapies such as benzodiazepines. Success rate between 60% and 83% have been reported. In around 75% of cases, seizure control was achieved during valproate infusion or within twenty minutes. Three recent randomised comparative trials from India deserve some further comments. One study compared IV VPA with IV PHE as first line treatment (Misra et al., 2006). The results are in favour for IV VPA (66% vs. 42%), but the study suffers from low statistical power (calculated 95% CI were [50-81%] vs. [26-59%]; number needed to treat 4.3 [2.2-429.9]) and inappropriate use of one sided t-test (Rossetti, 2007). Another study investigated 40 children with refractory SE (aged 5-12 years) (Mehta et al., 2007). Initial treatment for all children was IV DZP (0.2 mg/kg) followed by IV PHE (20 mg/kg followed by an additional 5-10 mg/kg if seizures did not stop) if necessary. Non responders were randomized to IV VPA (30 mg/kg over 2-5 min, followed as needed by a 10 mg/kg bolus 10 min. later, then by infusion at 5 mg/kg/hr) or DZP infusion (at 10 µg/kg/min, increased every 5 min. if seizures continued until control or 100 µg/kg/min was reached). Treatment failures received thiopental. The reported success rates of 80% (VPA) and 85% (DZP). Ther was a significant (p<0.01) advantage of VPA regarding the central depressant effects. While none of the children in the VPA group had arterial hypotension or hypopnea leading to ventilatory support, 60% of those in the DZP group required ventilation. 50% had hypotension and 40% required vasopressors. 95% of patients treated with IV DZP were admitted to the ICU while only 55% of the VPA treated children needed intensive care. Though there was no difference in efficacy there was a clear advantage of VPA compared to DZP in safety measures. Another study compared IV VPA with IV PHE treatment after BDZ have failed (Aagarwal et al., 2007). 50 patient were randomised and according to the publication reached. The success rate was 88% with VPA and 84% with PHE. Ther was no difference in efficacy or adverse effects between the treatment groups. The most commonly reported effective doses were between 15 and 45mg/kg in bolus (6mg/Kg/min) followed by 1 mg/kg/h infusion. The incidence of adverse events (mainly hypotension, dizziness and thrombocytopenia) was low (less than 10%) and independent of infusion rate. Only few cases of acute VPA encephalopathy were reported (Embacher et al., 2006) and the pharmacovigilance data reveal no increased incidence of encephalopathy with the IV use (sanofi aventis data on file; personal communications). This issue has to be carefully addressed in future studies. Though adaequate RCTs are missing, consensus guidelines produced in Belgium (van Rijckevorsel et al., 2005), Spain (Serrano-Castro et al, 2005) and Germany (Kramer et al, 2005;Kurthen et al, 2008) recommend the use of intravenous valproate as an alternative second-line treatment to phenytoin in patients with SE who fail to respond to intravenous benzodiazepines. A recent European concensus statement listed IV VPA as an option in stage 2 of convulsive SE, when BDZ have failed (Shorvon et al., 2008).
Levetiracetam
In 2006, an intravenous (IV) formulation of LEV has been approved for the treatment of patients with epileptic seizures who are temporary unable to swallow. Moreover it allows the clinician a rapid titration in seizure emergency situations, like seizure clusters or status epilepticus (SE). IV LEV is not licensed for treatment of SE, but has been widely used since it was available and several open case series are published (Abend et al., 2008; Altenmuller et al., 2008) (Farooq et al., 2007; Goraya et al., 2008; Knake et al., 2007; Ruegg et al., 2008; Schulze-Bonhage et al., 2007) (recently reviewed in (Trinka and Dobesberger, 2009). Levetiracetam (LEV) has a wide spectrum of action and a favorable pharmacokinetic profile. The mechanism of action is unknown but seems to involve the synaptic vesicle protein 2A (SV2A). The pharmacodynamic mechanisms appear distinct from that of classic AEDs and unrelated to known mechanisms of neurotransmission (Surges et al., 2008). In addition neuroprotective effects have been described in animal models (Gibbs et al., 2006). The IV formulation is bioequivalent to the oral preparation and it is well tolerated even at higher doses and/or at faster infusion rates than proposed (Ramael et al., 2006a; Ramael et al., 2006b).

Open label experience with retrospective case series is accumulating and until now 156 patients who were treated with IV LEV for various forms of SE have been reported with an overall success rate of 65.4% (Trinka and Dobesberger, 2009). The most often used initial dose was 2000-3000 mg per day over 15 minutes. Adverse events were reported in 7.1%; and were mild and transient.

Although IV LEV is an interesting alternative for the treatment of SE due to the lack of centrally depressive effects and low potential of drug interactions, one has to be aware of the non randomised retrospective study design, the heterogenous patient population and treatment protocols, as well as the publication bias inherent in these type of studies. Only a large randomised controlled trial with an adequate comparator will reveal the efficacy and effectiveness of this promising new IV formulation. However, in a recent consensus document of the ILAE Task Force on Status Epilepticus summarising the results of the workshop held at the First London Colloquium on Status Epilepticus, IV LEV is listed as a “treatment option for the stage of established SE” (Shorvon et al., 2008).

Treatment algorithms in early and established SE
As it is evident from the few randomised controlled trials in the early stage of status epilepticus, lorazepam (LZP), is the most effective drug tested in these trials and therefore all available evidence based recommendation take this into consideration (Kurthen et al., 2008; Meierkord et al., 2006; Minicucci et al., 2006; Serrano-Castro et al., 2005; Shorvon et al., 2008; van Rijckevorsel et al., 2005). However LZP was only successful in 65% and 59% of the treated patients (Treiman et al., 1998) (Allredge et al., 2001) and other options as first line treatment, like clonazepam were not tested. After failure of LZP only a further 73% will respond to PHE. Effect size for VPA, PB or LEV after LZP failure is unknown. Evidence based recommendations for the treatment of established status after failure of LZP are not available and it has been proposed that treatment options should guide the treating physician until data from a RCT will solve the question of best treatment in this stage of SE (Kurthen et al., 2008; Shorvon et al., 2008; Trinka, 2007a).

Reference List


Ref Type: Journal (Full)


TOPAMAX
Breites Wirkspektrum – hohe Effektivität

schnell und zuverlässig\textsuperscript{1,2} gut verträglich\textsuperscript{1,3} niedrig dosierte Monotherapie

Sicherheit in der Epilepsietherapie

\textsuperscript{1} Arroyo S et al.; Randomized Dose-Controlled Study of Topiramate as First-line Therapy in Epilepsy; Acta Neurol Scand 2005; 112: 214-222,
\textsuperscript{2} Grošelj J et al.; Experience with Topiramate Monotherapy in Elderly Patients with Recent-onset Epilepsy; Acta Neurol Scand 2005; 112: 144-150,
\textsuperscript{3} Faught E et al.; Tolerability and Safety of Topiramate as First-line Monotherapy in 1000 + Epilepsy Patients; Epilepsia 2003; 44 (Suppl. 9): 100

\textsuperscript{*} Behandlung bei Epilepsien, die durch andere Antiepileptika ungenügend kontrolliert sind


Diazepam (DZP) injection contains 0.5% DZP in a mixture of 40% propylene glycol, 10% alcohol and 50% water for injection at pH 6.2-7. DZP has a complete oral bioavailability (F=100±14%), low total clearance (CL) that is mainly metabolic or hepatic (CL = 0.38±0.06 mL/min/kg), a volume of distribution (V) of 1.1±0.3 L/kg and a long half-life (t1/2) of 43±13 h (Greenblatt et al., 1980; Friedman and Greenblatt, 1992). DZP is extensively metabolized to several active metabolites including desmethyldiazepam (DMD), temazepam (3-OH-DZP) and oxazepam (3-OH-DMD) that is a DZP secondary metabolite formed from either DMD or DMD accumulation in blood to concentrations sevenfold higher than DZP (Anderson and Miller, 2002).

Lorazepam (LZP) injection contains 0.2% LZP in a mixture of 40% propylene glycol, 10% alcohol and 50% water for injection at pH 6.2-7. LZP has a complete oral bioavailability (F=100±14%), low total clearance (CL) that is mainly metabolic or hepatic (CL = 0.38±0.06 mL/min/kg), a volume of distribution (V) of 1.1±0.3 L/kg and a long half-life (t1/2) of 43±13 h (Greenblatt et al., 1980; Friedman and Greenblatt, 1992). DZP is extensively metabolized to several active metabolites including desmethyldiazepam (DMD), temazepam (3-OH-DZP) and oxazepam (3-OH-DMD) that is a DZP secondary metabolite formed from either DMD or DMD accumulation in blood to concentrations sevenfold higher than DZP (Anderson and Miller, 2002).
propylene glycol, 10% alcohol and 50% water for injection. LZR has a complete oral bioavailability (F=93±10%), low total clearance (CL) that is mainly metabolic or hepatic (CL=1.1±0.4 mL/min/kg) and a volume of distribution (V) of 1.3±0.2 L/kg. LZP has a half-life shorter than DZP (t_{1/2}=14±15h) due to its threefold higher CL (Greenblatt, 1981; Anderson and Miller, 2002). Unlike DZP whose metabolism is mediated by CYPs 2C19 and 3A4, LZP is extensively metabolized by the hepatic UDP glucurononyltransferases (UGTs) to LOR-3-O-glucuronide (inactive).

Midazolam (MDZ), a third short-acting benzodiazepine is available in a parenteral aqueous preparation and is used for SE treatment. MDZ injection contains 0.5% MDZ hydrochloride in an aqueous solution to form a benzophenone derivative. Its reverse cyclization reaction to MDZ occurred in vivo at physiologic pH (pH=7.4) and in vitro when an acidic solution was neutralized (Garzone and Kroboth, 1989; Lowenstein and Cloyd, 2007). MDZ has a partial oral bioavailability (F=44±17%), due to extensive first-pass metabolism by intestinal and hepatic CYP3A4. The bioavailability appears to be dose-dependent: 35% to 67% at 15 mg, and 12% to 47% at 2 mg oral dose, possibly due to saturable first-pass intestinal metabolism (Thummel et al., 1996). MDZ has a high total (metabolic) clearance (CL) (CL=6.6±1.8 mL/min/kg), a volume of distribution (V) of 1.1±0.6 L/kg, and short half-life (t_{1/2}=1.1±0.6h). The following characterizing preparation of commercially stable water-soluble salts; b) short t_{1/2} due to the methyl at position 1 on the imidazole ring that undergoes CYP-mediated oxidation more rapidly than the methylene group at position 4 of the classical benzodiazepine nucleus, and c) enhanced potency due to its high affinity to the benzodiazepine receptors (Garozne & Kroboth, 1989). MDZ is exclusively metabolized by CYP3A4 and therefore has been used as a probe for this CYP (Thummel et al., 1996).

The most common treatment protocols for SE specify DZP or LZP as the first drug therapy followed by PHT or fosphenytoin (FOS) as a second-line therapy, then phenobarbital (mainly) or VPA or general anesthetic (Lowenstein, 2006). The goals of pharmacological therapy of SE are to terminate seizures early and prevent recurrence. Two recent large clinical studies have shown the benefit of early administration of benzodiazepines to control SE and then FOS (Claassen et al., 2003; Holtkamp et al., 2003). Claassen et al. also conducted a meta-analysis on the advantages and disadvantages of pentobarbital, MDZ and propofol that showed that pentobarbital appears to be superior in effectively controlling refractory SE (Claassen et al., 2002). When administered intravenously all three benzodiazepines rapidly enter the CNS and the resulting onset of effect occurs within 1-5 min. However, DZP and MDZ quickly redistribute to muscle and fat tissue because their lipophilicity (assessed by the octanol/water partitioning) is 4-6 times higher than that of LZP (Lowenstein & Cloyd, 2007). However, DZP redistributes rapidly to peripheral fats and consequently its clinical effectiveness is limited to 20-30 min. Therefore, DZP treatment of SE needs to be followed with a second drug such as LZP that has a more favorable pharmacokinetic profile than DZP and a duration of action exceeding 12 hr.

Phenobarbital (PB) is a weak acid (pKa=7.3) that is sparingly soluble in water (1mg/mL). PB sodium salt (PB-Na) has better water solubility than PB per se (free acid) and consequently, has been utilized in PB parenteral preparations. Nevertheless, a PB injection is not an aqueous solution but contains 20% PB-Na in a mixture of 90% propylene glycol and 10% water at pH=10-11. PB has a complete oral bioavailability (F=100±11%), very low total clearance (CL=0.06±0.01 mL/min/kg) that is 75% (hepatic) metabolic and 25% renal, a volume of distribution less than the total body water (V=0.54±0.03 L/kg) and a long half-life (t_{1/2}=99±18h) (Browne et al., 1985; Anderson, 2002). PB is mainly metabolized to two inactive primary metabolites: p-hydroxy-PB that is excreted in the urine as free and glucuronide conjugate and an N-glucoside conjugate of PB (Anderson, 2002). Phenobarbital’s long half-life and the presence of an active metabolite DMD are drawbacks in terms of adverse effects.

The differences between aqueous and hydroalcoholic parenteral preparations of AEDs are best illustrated by the development of FOS. FOS is a disodium phosphate ester of 3-hydroxymethyl phenytoin developed as a replacement for standard injectable phenytoin sodium. The water solubility of fosphenytoin is 75,000 mg/L versus only 20 mg/L for phenytoin sodium. Consequently, fosphenytoin was designed and developed as an aqueous parenteral prodrug to phenytoin to avoid the local complications associated with parenteral phenytoin such as iv fluid incompatibilities, patient discomfort, vein irritation/tissue damage and muscle necrosis after im administration. The parenteral preparation of phenytoin sodium (50 mg/mL) is a hydroalcoholic mixture of 40% propylene glycol, 10% alcohol and 50% water with the pH adjusted to 12. Fosphenytoin is administered either by iv or im route and is rapidly and completely converted enzymatically to phenytoin (conversion t_{1/2}=3 min in dogs, 1 min in rats) (Browne & La Duc, 1995). Admixtures of fosphenytoin solutions diluted to phenytoin concentrations of 1, 8 and 20 mg/ml in 0.9% NaCl, D5W and other iv fluids were physically compatible and chemically stable. Clinical studies in adults and children indicate that im and iv of fosphenytoin were well tolerated, safe and rapidly and completely converted to phenytoin (Bialer et al., 2002). Phenytoin or its parenteral prodrug fosphenytoin are also utilized in the treatment of SE with a loading dose of 1 g or 20mg/kg administered at a maximal rate of 50 mg/min. In the absence of a clinical effect, an additional 10 mg/kg is given because many patients may require PHT plasma levels of 25-30 mg/L to achieve seizure control. The most common side effects of PHT iv dosing are cardiovascular including hypotension and QT prolongation. Phenobarbital has been shown to be effective for the treatment of SE, but it is considered a third-line drug in the algorithms designed to treat SE because of its serious adverse effect profile.

Sodium valproate injection (Depacon®) was approved in the US in 1996 for intravenous use in epileptic patients for whom oral administration of VPA is temporarily not feasible. At a median dose of 375 mg administered over 1 hr infusion, sodium valproate was safe and well tolerated in 318 patients hospitalized for seizures (Devinsky et al., 1995; Bialer et al., 2004). Naritoku and Mueed demonstrated the safety of an iv (loading) dose of sodium valproate when a rapid increase in VPA serum level was required to stop recurrent seizures. A mean dose of 19.4 mg/kg infused at 20 and 50 mg/min was well tolerated in 20 patients with epilepsy (Naritoku & Mueed, 1999). Cloyd et al. studied the pharmacokinetics of VPA in 122 epileptic patients following an iv dosing of sodium valproate (up to 15 mg/kg) given as an iv infusion at a rate of 1.5 or 3 mg/kg/min (Cloyd et al., 2003). VPA peak plas-
Carbamazepine (CBZ), a neutral water-insoluble compound, presents difficulties when formulating in a parenteral preparation. However, the water solubility of CBZ can be greatly enhanced by solubilizing it in (or forming a complex with) the cyclodextrin derivative, 2-hydroxypropyl-ß-cyclodextrin (Loscher et al., 1995). Studies in dogs indicated that iv administration of the CBZ cyclodextrin complex was well tolerated. Clinical trials with a patent-protected parenteral formulation of CBZ is ongoing to characterize the pharmacokinetics of CBZ after iv administration and to provide a consistent transition therapy for patients on oral CBZ. Such iv formulations offer valuable, short-term treatment options for patients scheduled for surgery and for patients who cannot be treated with oral CBZ due to emergency situations, loss of consciousness, or GI disturbances. Finally, such parenteral preparations could prove useful in acute, critical care situations such as status epilepticus (SE).

An iv formulation of levetiracetam (LEV) has been developed and was recently approved by FDA and EMEA after it was found to be bioequivalent to the commercially available oral formulation of levetiracetam (Ramel, 2006a). The recommended dose of 1000-3000 mg/day must be diluted in >100 mL compatible diluents (e.g. 0.9% NaCl, D5W) and administered as a 15-min infusion. This formulation has been approved in the European Union and by the FDA (Bialer, et al., 2007 & 2009). Intravenous levetiracetam appears to be well tolerated in healthy adults even at fast infusion rates (1500-2500 mg administered over 5 min) and provides a useful alternative for patients unable to take levetiracetam orally (Ramel, 2006b; Ruegg et al., 2008; Knake et al., 2008). Treatment experience with intravenous LEV of the first 50 critically ill patients showed efficacy, defined as cessation of seizure activity or prevention of its recurrence in 41 of 50 patients (82%) (Ruegg et al., 2008). The lack of drug interactions and hypnotic side effects coupled with minimal cardiac and peripheral venous effects make LEV a possible and more attractive alternative than benzodiazepines, PB or PHT (Reugg et al., 2006). The lack of drug interactions and provides a useful alternative for patients unable to take levetiracetam who temporarily become unable to take oral medications. Intravenous lacosamide is a stable aqueous solution that does not require dilution prior to administration and is intended to deliver 200 mg lacosamide over 30- or 60 min (Karuss, 2006; Biton et al., 2008). In phase I clinical trials it was well tolerated and the reported adverse events were mostly mild and similar to the ones described for oral lacosamide (Bialer et al., 2004). Bioequivalence has been demonstrated between oral and iv infusion (30 and 60 min) of lacosamide. The highest single dose was 300 mg (Kropell et al., 2004; Bialer et al., 2007). Infusion over 15 min was nearly bio-equivalent, with a slightly higher C max and equivalence for AUC (Bialer, 2009). A recent study in 60 patients randomized showed that iv lacosamide, administered as 60- or 30-min infusion twice daily (200-600 mg/day) has a similar safety and tolerability profile to oral lacosamide when used as replacement therapy (Biton et al., 2008). In August, 2008 the European Medicines Agency (EMEA) approved lacosamide (Vimpatt®) in convenient-to-administer formulations (oral tablets, iv and syrup) for the adjunctive treatment of partial-onset seizures. Subsequently, the FDA approved lacosamide in October, 2008. The availability of aqueous iv preparation of lacosamide will stimulate its use in SE.

In conclusion, parenteral formulations of AEDs are quite feasible for water soluble AEDs. In order to be administered in an aqueous injection, water-insoluble AEDs need to be formulated in a chemical drug delivery or a prodrug (e.g. fosphenytoin) or via solubilization in a pharmaceutical drug delivery system (e.g. CBZ). Parenteral preparations contribute significantly to the antiepileptic armament and are essential in the treatment of patients who cannot be given AEDs orally. The global sales of fosphenytoin (only available parenterally) in 2004 and 2005 were $63 and $70 million, respectively, compared to $326 million for oral phenytoin (IMS, 2006). Although the market for parenteral AEDs per se is small (as reflected by fosphenytoin), the fact that injectable formulations serve as an introduction for oral medication to which patients will be switched upon release from the hospital is an incentive for the pharmaceutical industry to develop parenteral formulations for additional AEDs even if they are water-insoluble compounds.

References


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**WHAT IS THE PROMISE OF NEW ANTI-EPILEPTIC DRUGS? FOCUS ON BRIVARACETAM, CARISBAMATE, LACOSAMIDE, NS-1209, AND TOPIRAMATE**

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The vast majority of potential antiepileptic drugs (AEDs) are initially evaluated for their ability to prevent recurrence of seizures, usually in patients with partial-onset seizures, and clinical studies in status epilepticus are performed only exceptionally prior to regulatory approval. However, it is increasingly common to characterize the potential activity of a candidate AED in animal models of status. Information from these studies can be useful in determining whether a specific compound bears promise for the treatment of acute seizure conditions, and in finalizing administration protocols for clinical studies. This presentation will review preclinical and, where applicable, clinical findings on the potential value of brivaracetam, carisbamate, lacosamide, NS-1209, and topiramate in the treatment of status.

Among these agents, topiramate has been in clinical use for longest. Its mechanisms of action include blockade of sodium channels, enhancement of GABAergic transmission and antagonism of AMPA/kainate receptors. Topiramate shows “neuroprotective” or “disease modifying” activity in a number of experimental models (1), including some models of epileptogenesis and brain damage secondary to status epilepticus (2,3). Case reports and small case series provide suggestive evidence that topiramate can be clinically effective in terminating drug-refractory status (4). The lack of a parenteral formulation, however, is a limitation in this context.

Lacosamide received recently approval from the European Medicines Agency as adjunctive treatment for refractory partial-onset seizures. Its mode of action includes enhancement of slow-inactivation of voltage-gated sodium channels and a functional interaction with collapsin-responder mediator protein 2 (5). Lacosamide is effective in the perforant path model of self-sustained status epilepticus in rats, where it reduces cumulative seizure duration and status-induced hippocampal damage. It also displays neuroprotective activity in ischemia models. Although no data are available on its clinical activity in status epilepticus, an intravenous formulation is commercially available for use as replacement therapy in patients temporarily unable to take oral medication.

The three remaining agents discussed in this review are in Phase II-III clinical development. Carisbamate shows broad spectrum activity in animal models of seizures and epilepsy through an as yet unidentified mechanism which, however, does not seem to replicate the modes of action of established anticonvulsants (6). In the lithium and pilocarpine models of status epilepticus in rats, carisbamate is effective in preventing the onset of status, in terminating established status, and in protecting against status-induced neuronal damage and post-status epileptogenesis. Brivaracetam is a synaptic vesicle protein 2A (SV2A) ligand, with much higher affinity than levetiracetam for this target (6). It shows broad spectrum anticonvulsant activity in preclinical models and, in particular, reduces cumulative seizure duration in the rat model of self-sustained status epilepticus induced by stimulation of the perforant path. Another compound of particular interest as a potential new treatment for acute seizure conditions is NS-1209, a water-soluble AMPA antagonist, which has been found to potentely protect against status epilepticus induced by electrical stimulation of the amygdala or by subcutaneous administration of kainic acid in rats (7). NS-1209 also displays some neuroprotective activity against status-induced hippocampal neurodegeneration. Clinical testing of NS-1209 in the treatment of refractory status epilepticus has already initiated.

In conclusion, each of the five compounds discussed above shows properties which are potentially useful in the treatment of status. Since their mechanisms of action differ fully or partly from those of benzodiazepines, phenytoin, barbiturates and valproic acid, the possibility exists that at least some of these agents will prove to be of value in the management of status refractory to currently used drugs.

**References**


**Novel anesthetics and other treatment strategies for refractory status epilepticus**

Andrea O. Rossetti 
Service de Neurologie, Lausanne, Switzerland

**Keywords**: lidocaine, isoflurane, ketamine, hypothermia, verapamil, VNS

Refractory status epilepticus (RSE) - i.e., seizures resistant to at least two antiepileptic drugs (AED) - is generally managed with barbiturates, propofol, or midazolam, despite a low level of evidence (Rossetti, 2007). When this approach fails, the need for alternative pharmacological and non pharmacological strategies emerges. These have been investigated even less systematically than the aforementioned compounds, and are often used in cases of extreme refractoriness, sometimes in succession (Robakis and Hirsch, 2006). Several possibilities are reviewed here. In view of the marked heterogeneity of reported information, etiologies, ages and co-medications, it is extremely difficult judge on a given evidence (Rossetti, 2007). When this approach fails, the need for alternative pharmacological and non pharmacological strategies emerges. These have been investigated even less systematically than the aforementioned compounds, and are often used in cases of extreme refractoriness, sometimes in succession (Robakis and Hirsch, 2006). Several possibilities are reviewed here. In view of the marked heterogeneity of reported information, etiologies, ages and co-medications, it is extremely difficult judge on a given method, not to say to compare different strategies among them.

**Pharmacological approaches**

Isonflurane and desflurane may complete the anesthetics’ armamentarium, and should be employed in a “close” environment, in order to prevent intoxication of treating personnel. GABA_α receptor potentiation represents the putative mechanism of action. In an earlier report, isoflurane was used for up to 55 hrs in 9 patients, controlling seizures in all; mortality was however 67% (Kofke et al, 1989). More recently, the use of these inhalational anesthetics was described on seven subjects with RSE, for up to 26 days, with an end-tidal concentration of 1.2% - 5%; all patients required vasopressors, and paralytic ileus occurred in three; outcome was fatal in three patients (43%) (Mirsattari et al, 2004).

Ketamine, known as an emergency anesthetic because of its favorable hemodynamic profile, is an NMDA antagonist; the interest for its use in RSE relates to animal works showing loss of GABA_α efficacy and maintained NMDA sensitivity in prolonged status epilepticus (Mazarati and Wasterlain, 1999). However, in order to avoid neurotoxicity (Ubogu et al, 2003), it appears safer to combine ketamine with GABA-ergic compounds (Jevtovic-Todorovic et al, 2001), also because of a possible synergistic effect (Martin and Kapur, 2008). There are very few reported cases in humans, describing progressive dosages up to 75 mg/kg.h for several days (Pruss and Hultkamp, 2008; Quigg et al, 2002; Sheth and Gidal, 1998), with moderate results. Paraldehyde acts through a yet unidentified mechanism, and appears to be relatively safe in terms of cardiovascular tolerability (Ramsay, 1989; Thulasimani and Ramaswamy, 2002), but due to the risk of crystal formation and its reactivity with plastic, it should be used only as fresh prepared solution in glass devices (Beyenburg et al, 2000). There are virtually no recent reports regarding its use in adults RSE, whereas use of rectal paraldehyde in children with status epilepticus resistant to benzodiazepines seems less efficacious than intravenous phenytoin (Chin et al, 2008). Etomidate is another anesthetic agent whose exact mechanism of action is also unknown, which is also relatively favorable regarding cardiovascular side-effects, and may be used for rapid sedation. Its use in RSE was reported in eight subjects (Yeoman et al, 1989). After a bolus of 0.3 mg/kg, a drip of up to 72 mg/kg.h for up to 12 days was administered, with hypotension occurring in five patients; two patients died. A reversible inhibition of cortisol synthesis represents an important concern, limiting its widespread use and implying a careful hormonal substitution during treatment (Beyenburg et al, 2000).

Several non-sedating approaches have been reported. The use of lidocaine in RSE, a class Ib antiarrhythmic agent modulating sodium channels, has been reviewed in 1997 (Walker and Slovis, 1997). Initial boluses up to 5 mg/kg and perfusions of up to 6 mg/kg.h have been mentioned; somewhat surprisingly, at times lidocaine seemed to be successful in controlling seizures in patients refractory to phenytoin. The above mentioned dosages should not be increased, in order to keep lidocaine levels under 5mg/l and thus avoid seizure induction (Hamano et al, 2006). A recent pediatric retrospective survey on 57 RSE episodes (37 patients) described a response in 36%, and no major adverse events; mortality was however 67% (Hamano et al, 2006).

Verapamil, a calcium-channel blocker, could inhibit P-glycoprotein, a multidrug transporter that may diminish AED availability in the brain (Potschka et al, 2002). Few case reports on its use in humans are available; this medication nevertheless appears relatively safe (under cardiac monitoring) up to dosages of 360mg/day (Iannetti et al, 2005). Magnesium, a first-line agent for seizures elicited by eclampsia, has also been anecdotally reported in RSE (Robakis and Hirsch, 2006). The rationale may be found in the physiological blockage of NMDA channels by magnesium ions (Hope and Blumenfeld, 2005).

Ketogenic diet has been prescribed for decades, mostly children, to control refractory seizures. Its use in RSE, as “ultima ratio” has been occasionally described in pediatric (Francois et al, 2003) and adult (Bodenfant et al, 2008) patients; it displays its effect subacutely over several days to a few weeks. Since “malignant RSE” seems at times to be the consequence of immunological processes (Hultkamp et al, 2006), a course of immunomodulatory treatment is often advocated in this setting, also in the absence of definite autoimmune etiologies (Robakis and Hirsch, 2006); steroids, ACTH, plasma exchanges, or intravenous immunoglobulines may be used alone or in sequential combination.
Non-pharmacological approaches

These strategies are described somewhat less frequently than pharmacological approaches. Acute implantation of vagal nerve stimulation has been reported in RSE (De Herdt et al., 2008; Patwardhan et al., 2005; Winston et al., 2001). Stimulation was mostly initiated in the operation room, and intensity progressively adapted over a few days up to 1.25 mA (with various regimens regarding the other parameters), allowing subacutely a seizure control, and only one transitory episode of bradycardia/asystole (De Herdt et al., 2008). Of course, pending identification of a definite seizure focus, resective surgery may also be considered in selected cases (Lhatoo and Alexopoulos, 2007). Low-frequency (0.5 Hz) transcranial magnetic stimulation (TMS) at 90% of the resting motor threshold has been described to be successful for about 2 months, with a weaning effect afterwards and the need for a repetitive use, in a patient suffering from epilepsy partialis continua (Misawa et al., 2005). More recently, TMS was applied in a combination of short “priming” high frequency (up to 100 Hz) and longer runs of low-frequency stimulations (1 Hz) at 90%-100% of the motor threshold, with mixed results (Rotenberg et al., 2008).

Paradoxically, even electroconvulsive treatment may be found in cases of extremely resistant RSE. A recent case report illustrates its use in an adult patient with convulsive status, with 3 sessions (3 convulsions each) carried out over three days, resulting in a moderate recovery; the mechanism is believed to be related to modification of synaptic release of neurotransmitters (Cline and Roos, 2007).

Finally, therapeutic hypothermia, which is increasingly used in postanoxic patients (Oddo et al., 2008), has been the object of a recent case series in RSE (Corry et al., 2008). Reduction of energy demand, excitatory neurotransmission, and neuroprotective effects may account for the putative mechanism of action. Four adult patients in RSE were cooled to 31°-34°C with an endovascular system for up to 90 hours, and then passively rewarmed over 2-50 hours. Seizures were controlled in two patients, one of whom died; also one of the other two patients in whom seizures continued subsequently deceased. Possible side effects are related to acid-base and electrolyte disturbances, coagulation dysfunction including thrombosis, infectious risks, cardiac arrhythmia, and paralytic ileus (Cereda et al., 2008; Corry et al., 2008).

Conclusion

A wide spectrum of pharmacological (sedating and non-sedating) and non-pharmacological (surgical, or involving electrical stimulation) regimens have been described in RSE. Their use should be considered only after refractoriness to AED or anesthetics displaying a higher level of evidence. While it seems unlikely that these uncommon and scarcely studied strategies will influence the RSE outcome in a decisive way, some may be interesting in particular settings. However, since the main prognostic determinant in status epilepticus appears to be related to the underlying etiology rather than to the treatment approach (Rossetti et al., 2005; Rossetti et al., 2008), the safety issue should always represent a concern for the prescribing physician.

References


Status Epilepticus in the Resource Poor Countries

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Status epilepticus is common in patients admitted to hospitals in resource poor countries (RPC). However, there appear to be differences in the epidemiology, aetiology and outcome of status epilepticus in these regions compared to the West, although there is little data about the former regions. Most studies on status epilepticus in RPC describe convulsive status epilepticus (CSE)\(^1\), since non-convulsive epilepticus is rarely detected in these regions. In one study non-convulsive status epilepticus was detected in 11% of adults with altered mental status\(^2\). The incidence of convulsive status epilepticus appears to be higher in RPC than the West, although there has been only one epidemiological study conducted. In this study the incidence of CSE in Kenyan children admitted to a District general hospital was 35/100,000/year, although 268/100,000/year in children aged 1-11 months old. These figures are likely to be an underestimate, since many children with CSE are not admitted hospital. This rate is 2-5 times that of London, United Kingdom\(^3\). CSE appears to be more common in children than adults, usually as acute symptomatic seizures or seizures associated with febrile status. A significant proportion of people with epilepsy have an episode of CSE, usually in childhood and often as the first reported seizure. Most CSE is symptomatic, with the increased incidence attributed to the increased incidence of infections\(^4\), 5. In malaria endemic areas, malaria is an important cause of CSE in children\(^6\), whilst bacterial meningitis and viral encephalitis are important causes in other areas\(^6\). Patients appear to be in status for longer periods, although there is little reliable data on the duration of CSE in patients presenting to hospital. The increase duration may be due to the lack of treat-
Experimental evidence has shown that the induction of SE in rodents using either electrical stimulation of limbic brain regions or systemic, as well as intracerebral, administration of convulsant drugs, elicits pronounced brain inflammation involving glia, endothelial cells and neurons (for review see Vezzani and Granata, 2005; Vezzani and Baram, 2007; Oby and Janigro, 2006). In adult rat or mouse, the induction of brain of interleukin-1 beta, a prototypical inflammatory cytokine, occurs within the first 60 min of SE and is observed in the areas of seizure origin and generalization. Up-regulation of this cytokine in glia precedes seizure-associated neuronal cell loss and it may contribute to it (Ravizza et al, 2008; Bernardino et al, 2006). Brain inflammation induced by SE can become chronic and be detectable at significant levels also during the epileptogenesis phase preceding the onset of spontaneous seizures, as well as in chronic epileptic tissue (De Simoni et al, 2000; Gorter et al, 2006; Ravizza et al, 2008). The induction of inflammatory processes by SE is age-dependent occurring in rodent from postnatal day 15 onwards (Rizzi et al, 2003) with the notable exception of hyperthermia-induced prolonged seizures (Vezzani and Baram, 2007). In this febrile seizures model, brain inflammation is indeed detectable in 9-day old rats and persists for at least 24 h after the end of SE. No irreversible neuronal cell loss occurs in this model, indicating that inflammation is not a mere consequence of cell death. However, studies in adult rodent brain suggest that the presence of degenerating neurons may contribute to perpetuate brain inflammation (Vezzani et al, 1999; Ravizza et al, 2008).

Pharmacological, biochemical and electrophysiological studies showed that brain inflammation contributes to promote neuronal network excitability acting at several steps, namely by altering glutamate receptor subunit composition and membrane receptor levels, NMDA-dependent calcium fluxes into neurons, extracellular glutamate levels, BBB permeability function (Vezzani and Granata, 2005; Oby and Janigro, 2006). In particular, pharmacological studies in in vivo models of seizures show that inhibition of specific pro-inflammatory pathways such as blockade of the production of IL-1beta or of PGE2 dramatically reduces seizures and retards epileptogenesis (Vezzani and Granata, 2005; Jung et al, 2006). Mimicking systemic infection by administration of lipopolysaccharide (LPS) in adult and immature rats reduces the threshold for seizure induction; in immature rodents LPS administration transiently increases brain cytokines and primes immature rats to develop more damage during SE (Auvin et al, 2007). In addition, seizure threshold is reduced and seizure-induced damage is enhanced after SE elicited in adult rats pre-exposed to LPS at post-natal day 7 or 14 (Galic et al, 2008). Thus, a transient inflammatory event occurring post-natally induces a chronic hyperexcitable neuronal network in the hippocampus. Finally, evidence of the presence of brain inflammation has been reported also in human epileptic tissue and increased cytokine levels have been measured in blood following different kinds of seizures in humans (Vezzani and Granata, 2005).

These findings highlight that brain inflammation plays a role in the mechanisms of hyperexcitability occurring during repetitive or prolonged seizures; the establishment of chronic inflammation after SE or the occurrence of infection-mimicking events can prime persistent excitability changes and may contribute to epileptogenesis.

References


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Andrea: diagnosed with epilepsy in 1990

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Josep Dalmau  
University of Pennsylvania, Department of Neurology, Philadelphia, USA

There is increasing recognition of immune-mediated encephalitides resulting in seizures and status epilepticus. These disorders can be divided into limbic and cortical extralimbic encephalitides and may have a paraneoplastic or non-paraneoplastic etiology.\(^1\)\(^2\) Table 1 shows the most frequent antibodies identified in autoimmune encephalitides that may result in seizures and status epilepticus. In addition, there are other encephalitides that are likely immune mediated but at the present time the associated syndrome or antibody specificity is unclear. These disorders are often defined with descriptive terms (e.g., steroid-responsive limbic encephalitis).

Table 1: Antibodies Associated with Encephalitides and Seizures

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Syndrome</th>
<th>Clinical significance</th>
<th>Location of epitopes</th>
<th>Response to immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu</td>
<td>Limbic, cortical encephalitis</td>
<td>High</td>
<td>Intracellular</td>
<td>Infrequent</td>
</tr>
<tr>
<td>CV2/CRMP5</td>
<td>Limbic encephalitis</td>
<td>High</td>
<td>Intracellular</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Ma2</td>
<td>Limbic, diencephalon, upper brainstem encephalitis</td>
<td>High</td>
<td>Intracellular</td>
<td>Moderate</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Limbic encephalitis, Stiff person-syndrome</td>
<td>High</td>
<td>Intracellular</td>
<td>Poor</td>
</tr>
<tr>
<td>GAD</td>
<td>Limbic encephalitis, refractory epilepsy, Stiff-person syndrome</td>
<td>High</td>
<td>Intracellular</td>
<td>Moderate</td>
</tr>
<tr>
<td>VGKC (Kv1.2, Kv1.2)</td>
<td>Limbic encephalitis, Morvan’s syndrome</td>
<td>High</td>
<td>Extracellular</td>
<td>Frequent</td>
</tr>
<tr>
<td>NMDAR (NR1)</td>
<td>Psychosis, dyskinesias, autonomic instability, hypoventilation</td>
<td>High</td>
<td>Extracellular</td>
<td>Frequent</td>
</tr>
<tr>
<td>NMDAR (NR2B or GluIR2)</td>
<td>Multiple types of encephalitides</td>
<td>Unclear*</td>
<td>Extra and intracellular</td>
<td>N/A</td>
</tr>
<tr>
<td>NMDAR (NR2A/2B)</td>
<td>Neuropsychiatric lupus</td>
<td>Low</td>
<td>Extracellular (DWEYS)**</td>
<td>N/A</td>
</tr>
<tr>
<td>AMPAR (GluR1/2)</td>
<td>Limbic encephalitis (frequent relapses)</td>
<td>N/A***</td>
<td>Extracellular</td>
<td>Frequent</td>
</tr>
<tr>
<td>AMPAR (GluR3)</td>
<td>Rasmussen’s encephalitis</td>
<td>Low</td>
<td>Extracellular?</td>
<td>Infrequent/moderate</td>
</tr>
<tr>
<td>Thyroid peroxidase, thyroglobulin</td>
<td>Hashimoto’s encephalitis</td>
<td>Low</td>
<td>Intracellular</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

\*Described in multiple unrelated disorders, including among others: limbic encephalitis, non-specific encephalitis, viral encephalitis, degenerative disorders

\**DWEYS pentapeptide consensus sequence present in NR2A and NR2B

\***N/A: not available, too early to assess significance.

*italics* indicate syndromes that are almost always paraneoplastic.

CRMP5: Collapsin response mediator protein-5; GAD: glutamic acid decarboxylase; VGKC: voltage-gated potassium channels; NMDAR: N-methyl-D-Aspartate receptor; AMPAR: alpha-amin-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.
Paraneoplastic syndromes

Any paraneoplastic encephalitis involving the limbic system or cerebral cortex may result in seizures and status epilepticus. The associated antibodies include, Hu, Ma2, CV2/CRMP5, and amphiphysin. While there is strong evidence that the first three immune responses are mediated by cytotoxic T-cells responses, there are studies indicating that amphiphysin antibodies may be directly pathogenic. Of these 4 immune responses, the anti-Hu antibodies are those most frequently described with seizures, epilepsy partialis continua, and status epilepticus. The underlying tumors are small-cell lung cancer (all antibodies), germ-cell tumors of the testis (Ma2), and thymoma (CRMP5). With the exception of encephalitides associated with Ma2 antibodies, in which approximately 30% of patients respond to tumor removal and immunotherapy, the other disorders are rarely treatment-responsive.

Autoimmune encephalitides

These include all the immune responses of Table 1 that are not in italics. A frequent feature of these immune responses (except for GAD and thyroid antibodies) is that the autoantigens are extracellular and therefore accessible by circulating antibodies. While the presence of antibodies to GAD, VGKC, or the NR1 subunit of the NMDAR associates with a limited set of syndromes and therefore provides useful diagnostic tests, the clinical significance of the other antibodies is unclear. For example, some antibodies of patients with lupus (e.g. directed to DWEYS consensus sequence of NR2B and NR2B) provide interesting animal models of brain autoimmunity, but their relevance in the human disease is unclear.

GAD antibodies usually associate with non-paraneoplastic stiff-person syndrome and cerebellar dysfunction, but there are increasing number of reports showing that these antibodies also associate with subtypes of limbic encephalitis and refractory epilepsy.

VGKC antibodies associate with limbic encephalitis, Morvan’s syndrome, and neuromyotonia. Seizures and status epilepticus may occur in the first two disorders. The frequent development of hyponatremia may also favor seizures. About 20 of patients with VGKC antibodies have thymoma, SCLC, or less frequently other tumors. The disorder usually responds to corticosteroids, intravenous immunoglobulin or plasma exchange.

Antibodies to the NR1 subunit (or NR1/NR2 heteromers) of the NMDAR associate with a characteristic syndrome that presents with behavioral change or psychosis and usually progresses to a decline of the level of consciousness, catatonia, dyskinesias, autonomic instability, and frequent hypoventilation. Partial or generalized seizures occur frequently at early stages of the disease and in some patients may persist along the entire clinical course. The combination of true epileptic seizures and complex, elaborate orofacial and limbic movements (without EEG correlates) complicates the clinical recognition of the seizures. The EEG shows focal or diffuse slow activity with a poorly organized background, with or without epileptic activity. The disorder usually affects young women, 60% with ovarian teratoma, but it is being increasingly recognized in men and children. Less than 45% of girls have an underlying teratoma. Despite the severity and duration of the disorder, patients often respond to immunotherapy and, when appropriate tumor removal; some patients improve spontaneously. The recovery is slow and may take many months. After recovery, most patients remain free of seizures.

Other autoimmune disorders resulting in seizures

A recent study on limbic encephalitis showed that 64% of patients had antibodies to neuronal cell surface antigens, including VGKC and NMDAR, but in 24% the identity of the antigens was unknown. The fact that these types of antigens are localized in specific brain regions, such as hippocampus, and the epitopes are extracellular, suggest that the associated symptoms, including seizures, are potentially responsive to immunotherapy. An example is the recent characterization of one of these antigens as the GluR1/2 subunits of the AMPA receptor. Patients with these antibodies develop a classic picture of limbic encephalopathy with frequent seizures that are responsive to immunotherapy, but have a tendency to relapse. In 7 of 10 patients the disorder was a paraneoplastic manifestation of tumors of the thymus, lung, or breast. In summary, recent studies in the field of paraneoplastic syndromes and autoimmune encephalitides provide several clues that suggest the autoimmune etiology of some seizure disorders that may result in status epilepticus, including the acute presentation of symptoms, the frequent detection of CSF pleocytosis and oligoclonal bands in the context of negative viral studies, and the detection of CSF antibodies reacting with the neurolip of hippocampus and the cell surface of neurons.

References

Rarer causes of status epilepticus

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Two statements are often made – first, that any disorder of the grey matter can result in status epilepticus (SE), and second that any cause of epilepsy can also result in status epilepticus. However, epidemiologically-based surveys of aetiology actually show that the range of causes of SE is both rather restricted and also is rather different from the range of causes of epilepsy (table 1). It has been known for many years that SE differs from epilepsy in being far more of the result of; (a) an acute brain injury rather than a chronic injury; (b) symptomatic rather than idiopathic epilepsy (table 1); and also (c) SE is more common in pathology in the frontal region than other cortical regions (for review, see Shorvon 1994).

<table>
<thead>
<tr>
<th></th>
<th>Rochester, Minn, USA</th>
<th>French speaking Switzerland</th>
<th>Bologna, Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population (denominator)</td>
<td>1,090,055</td>
<td>1,735,420</td>
<td>336,876</td>
</tr>
<tr>
<td>Number of cases</td>
<td>199</td>
<td>172</td>
<td>44</td>
</tr>
<tr>
<td>Incidence of SE (per 100,000 per year)</td>
<td>18.3 (adjusted)</td>
<td>9.9 (raw)</td>
<td>10.3 (adjusted)</td>
</tr>
<tr>
<td>Female:male ratio of cases</td>
<td>1:1.9²</td>
<td>1:1.7²</td>
<td>1:0.74²</td>
</tr>
<tr>
<td>History of prior epilepsy</td>
<td>44%</td>
<td>32.8%</td>
<td>39%</td>
</tr>
<tr>
<td>Epilepsy type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute symptomatic</td>
<td>50.3%</td>
<td>62.7%</td>
<td>34%</td>
</tr>
<tr>
<td>Remote symptomatic</td>
<td>19.6%</td>
<td>28.4%</td>
<td>34%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>13.6%</td>
<td></td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>16.6%</td>
<td></td>
<td>25%³</td>
</tr>
<tr>
<td>Unknown</td>
<td>8.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Causation of status in five population-based studies

The common causes of SE are; acute anoxia, acute stroke, acute trauma, acute cerebral infection, intoxication or metabolic disturbance and fever (in infants). The literature on the rarer causes of SE is though restricted to case reports and small open case series. At an anecdotal level too, there are a number of pathologies which are far more frequently encountered in clinical practice as a cause of SE than of epilepsy, and are sometimes the presenting feature of the condition. In this presentations, some of these rarer causes will be highlighted.

Autoimmune and Inflammatory disorders - A number of rare autoimmune disorders seem commonly to result in SE. These include the autoimmune limbic encephalitides (including those due to voltage-gated potassium channel and Hashimoto’s encephalopathy), NMDA channel antibodies, and SLE. Rasmussen encephalitis is another inflammatory disorder commonly causing focal motor status. Hennoch schoenlein purpura can present with SE. Mitochondrial disease - Alpers disease is now known to be due to a mutation in nuclear DNA causing a mitochondrial defect, and typically presents with SE. Other mitochondrial diseases are also common causes of SE, including focal motor SE.

Infections - Viral infection can cause both epilepsy and SE, and neocortical viral infection often results in SE. Many virus’ can be implicated including rare virus’ some of which have a curious disposition to cause SE and HIV. Bacteria also can result in status including Bartonella henselae and Bartonella claridgeiae which cause cat scratch fever, Cosiella Burnetti causing Q fever and tuberculosis. Parasitic disease can also cause SE, especially cerebral malaria and occasionally neurocysticercosis (although seizures not SE seems a more common presentation, perhaps because of the usual subcortical position of the cysts).

Drugs, metabolic disorders and toxins – These can cause isolated seizures, epilepsy and SE. The drugs most commonly implicated in SE are antibiotics (especially the penicillin antibiotics), psychotropic drugs and isoniazid. Carbon monoxide poisoning can present with SE, as can aluminium poisoning. Other poisons presenting with SE include tetramine, a rodenticide, neem oil, endosulphan a pesticide, and soman. Poisoning with domoic acid, an NMDA agonist found in tainted mussels, causes severe SE. Chromosomal abnormalities and inborn errors of metabolism – Many such conditions can result in epilepsy or SE. Nonconvulsive SE is characteristic of ring chromosome 20, and also other chromosomal disorders (ring chromosome 14, monosomy 1p36, inverse duplication of chromosome 15), and also commonly epilepsy. In most inborn errors of metabolism, isolated seizures are more common than SE.

The features of conditions which typically cause SE rather than isolated seizures will be discussed in the presentation and require to be further investigated.

References


**Review of Status Epilepticus (SE) in HIV and Tuberculosis with Preliminary View of Bombay Hospital Experience**

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From the 1Department of Neurology and 2Department of Neuroepidemiology, Medical Research Centre, Bombay Hospital Institute of Medical Sciences, Mumbai, India

**Abstract**

The roles of HIV and tuberculosis in SE must be addressed in the context of SE as an entity, since multiple factors are responsible for the production and outcome of SE. It would be reasonable to assume that at least 70% of the burden of epilepsy, HIV and tuberculosis are to be found in the developing world where there is a substantial treatment, knowledge and research gap for all three conditions. Timely management of SE is even more difficult, with resulting poor outcome.

There are no population-based studies of SE in developing countries. Any data from these countries is hospital-based and subject to bias and lack of adequate follow-up. Data on non convulsive status epilepticus are largely unavailable from developing countries. It is estimated to comprise 20-25% of all SE (Shneker and Fountain, 2003). In a study in India (Narayanan and Murthy, 2007) it was found in 10% of ICU patients with altered consciousness.

In the review by Chin et al, 2004, of seven population-based studies of SE, all from developed countries there was no mention of HIV or tuberculosis. In the north-London study, CNS infection accounted for 19% of febrile childhood SE, acute bacterial meningitis being the commonest cause (Neville and Chin, 2007).

In a Kenyan, rural, hospital-based study of children with SE, the aetiology was infection in 71%; but malaria was the primary diagnosis in 53% of SE (Sadarangani et al, 2008).

In a review of 147 patients with CNS infection from a hospital in South Korea (2000-2005), acute symptomatic seizures occurred in 34 and SE in 10 of the 34 (Kim et al, 2008). Of 147 patients, 44 had encephalitis, 63 had tuberculous meningitis (TBM), 36 bacterial meningitis and 4 fungal meningitis. No neurocysticercosis was found. Encephalitis, rather than meningitis, was 14 times more likely to cause acute symptomatic seizures.

Although acute symptomatic seizures occur in tuberculous meningitis with varying frequency (Garcia-Monco JC, 1999; Misra et al, 2000; Sutlas et al 2003) and can be a presenting feature in 10% (Kennedy and Fallon, 1979), parenchymal involvement occurs to a lesser degree in tuberculous meningitis than in encephalitis. In encephalitis there is brain inflammation, with release of pro-inflammatory cytokines that decrease the seizure threshold (Vezzani and Granata, 2005). If there are tuberculomas involving the parenchyma, seizures can occur in up to 60% (Tiel and Roseneblum, 1996). Tuberculomas in India before CT scanning, were commonly identified by the pathologist (Dastur et al, 1968). In the CT scan era, single enhancing lesions were frequently identified in patients with acute symptomatic seizures and SE in India. Most of these are now believed to have been neurocysticercosis. Tuberculomas reflect cell mediated immunity and sometimes paradoxically enlarge or even appear for the first time during the course of otherwise successful treatment. Breakthrough seizures and SE can occur. An important clinical distinction is from drug resistant tuberculosis because steroids are indicated in paradoxically enlarged lesions but they would worsen drug resistant tuberculosis. In neurotuberculosis, hyponatraemia and isoniazid can also precipitate status epilepticus (Vasu and Saluja, 2005).

In Murthy et al’s study (2007) of SE from Hyderabad, India, CNS infections accounted for 24 of 85 patients (28%) from 1994-1996. There were 6 patients with tuberculous meningitis, but no HIV in this study. Neurocysticercosis was commoner than TB.

In a study of 93 adults with SE from Lucknow, India by Misra et al (2008), 37 had CNS infection (39.8%). Tuberculosis (meningitis and granulomas) accounted for 9 of 93 patients (9.7%). Viral encephalitis was the commonest cause of status. There was no HIV.

A review of 166 registry entries for CNS tuberculosis in the Bombay Hospital from 2007-2008 revealed no patients coded for SE, but individual chart review of 100 of these showed 5 SE. For the same period we identified 23 patients coded for SE and looked at individual records (22/23). No patients had confirmed neurotuberculosis, but two patients had HIV. Further chart review and analyses are necessary and being undertaken.

A retrospective Ethiopian study of hospital records of 119 patients with SE found 43 patients (36.1%) with CNS infection (Amare et al, 2008). Toxoplasmosis was the commonest (18 cases). Eight patients had tuberculoma and 2 presumed tuberculous meningitis. HIV/AIDS was present in 24 (20.2%) and was associated with significant mortality (OR=6.7). The frequency of occurrence of seizures in HIV infected patients is 2-20% (Holtzman et al, 1989; Wong et al, 1990; Van Paeschen et al, 1995; Sinha et al 2005; Satischandra and Sinha 2008). New onset seizures occurred in 3% to 20% of HIV infected people (Pascual-Sedano et al 1999; Wong et al 1990; Chadha et al 2000; Levy and Bredesen 1988). Status Epilepticus occurs in 8-18% of patients with HIV and seizures (Holtzman et al 1989, Wong et al 1990, Van Paeschen et al 1995, Sinha et al 2005).

The total number of admissions to Bombay Hospital coded for HIV from 1.1.2003 to 31.12.2008 was 1204. Seven (0.58%) were coded for SE. The rate of SE could have been low as HIV in several patients was picked up only on routine pre-operative evaluation and could have been asymptomatic. Also there probably were deficiencies in coding SE. We reviewed the first 100 consecutive charts for patients with HIV and found 25 pre-surgical pick-ups, 9 with seizures but no patients with status.

The cause of seizures in those with HIV in the 2 large Indian studies was opportunistic infection, 93.9% (Sinha et al 2005) and 65.4% (Chadha et al 2000). HIV encephalopathy is a more common cause of seizures in studies from developed countries (Kellinghaus 2008; Holtzman 1989; Pesola 1998). The greater burden of infection and non-availability of HAART in developing countries could account for this.

Specific risk factors for SE in HIV are IV drug abuse, hypoglycaemia, renal failure (Van Paeschen et al, 1995) and the drug efavirenz which is a component of HAART (Nijhawan et al 2008). Another important complication of HAART is the immune reconstitution inflammatory syndrome (IRIS). CNS inflammatory lesions including tuberculomas and tuberculous meningitis can manifest or worsen. Therefore HAART should start and steroids be considered after initial, adequate tuberculosis treatment.

Pharmaco-kinetic drug interactions pose a major problem in managing epilepsy in those infected with HIV and/or tuberculosis,
particularly with those drugs affecting CYP450 in the liver. Most relevant is use of phenobarbital which reduces the level of nevirapine by 50%, resulting in failure of HAART (Lancet Neurology, 2007). This has disastrous consequences in developing countries where newer AEDs are unaffordable.

References


Other Central Nervous System Infections and Status Epilepticus (SE).

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Although credibly, the occurrence of status epilepticus (SE) is a serious and portentous event during the course of a neurological infectious disorder, it is surprising how sketchy are descriptions of the association between CNS infections and SE. This review focuses on CNS infections other than HIV infection and tuberculosis. A list of infections that have been reported in the literature to cause SE is given in Table 1. Several questions arise in the reappraisal of CNS Infections and status SE: (1) What proportion of cases of SE are caused by CNS infections? (2) How commonly does SE occur in various CNS infections? (3) How does the occurrence of SE influence the outcome and mortality of CNS infection? (4) What is the prognosis and mortality in SE that is caused by CNS infections? (5) How commonly does refractory SE occur in CNS infections? (6) How commonly does non-convulsive status epilepticus (NCSE) occur in CNS infections? (7) Are there any special considerations in the treatment of SE in CNS infections? (8) What are the rates of epilepsy / unprovoked seizures following an episode of SE complicating a CNS infection.

CNS Infections as a cause of status epilepticus

In population-based studies from western countries, CNS infections have accounted for a small proportion of cases (0.6-3%) of SE (DeLorenzo et al., 1995; Wu et al., 2002). In contrast, although population-based data is not available from the less developed countries, the proportion of CNS infections is considerably higher and varies between 9 and 72% in various published case series (Mbodj et al., 2000; Misra et al., 2008; Murthy et al., 2007). The proportion of CNS infections as a cause for SE appears to be very much higher in children (Sadaranagani et al., 2008). There are virtually no community-based data on the incidence and frequency of CNS infections as a cause for SE in the less developed countries. Hospital-based data may grossly underestimate the incidence of SE due to CNS infections as an unknown proportion of cases do not reach hospital due to poor access to the hospital facility or socio-economic reasons.

Frequency of occurrence of SE in CNS infections

Most CNS infection episodes that manifest with seizures do so with few seizures that are easily controlled with medications. The frequency of occurrence of SE depends mainly on the aetiology of the infective episode. Viral encephalitis (most commonly due to Herpes simplex virus) is most commonly cited as a cause of SE. Among various infectious disorders, de novo SE occurs more frequently in acute infections (e.g., acute bacterial meningitis) in comparison to chronic infections (e.g., chronic meningitis due to fungal agents). Likewise, although, seizures are a very common occurrence in neurocysticercosis, the occurrence of SE is an uncommon happening (Carpio and Hauser, 2002).

Mortality and prognosis in CNS infection-associated SE

The risk of death due to SE associated with a CNS infection episode is far higher in comparison to several other causes of SE, for instance alcohol-related SE, metabolic disorders and SE complicating pre-existing epilepsy (Amare et al., 2008; Li et al., 2009; Misra et al., 2008). This is because, the CNS infection episode is in itself is associated with a high mortality risk.

It has been shown that the stay in intensive care unit is prolonged and resource requirements increased when SE is associated with a prior or subsequent infection. The increased resource requirements are presumably the need for infection control protocols that are required for nursing of infected patients. The risk of developing an unprovoked seizure following an episode of SE associated with a neurological infection may be elevated 7-fold (Hesdorffer et al., 1998).

Refractory SE and NCSE in CNS infections

Although both refractory SE and NCSE have been described in various acute CNS infections, their exact frequencies have not been systematically studied.

Treatment considerations in CNS infection-associated SE

Although the treatment protocol for SE remains essentially the same in CNS infections, additional emergent considerations are the establishment of aetiology of the CNS infection and institution of treatment of the infectious disorder. When seizures are accompanied by fever in older children, a lumbar puncture for obtaining cerebrospinal fluid for cytological and microbiological studies may not be undertaken if consciousness is restored soon after the seizure. However, in the case of fever accompanying SE, wherein the patient does not regain consciousness, a lumbar puncture is indicated in all ages. An important aspect of the management of SE due to CNS infection is the prompt institution of appropriate antimicrobial as well as adjunctive (e.g., corticosteroids in acute bacterial meningitis) treatments. It is not clear if prompt antimicrobial treatment improves the prognosis of control of SE, although its effect on overall prognosis is indisputable. There are very few pharmacokinetic studies of the administration of antiepileptic drugs in status epilepticus due to CNS infection (Ogutu et al., 2003).

References

Infections.

Aetiologies of status epilepticus associated with CNS infections:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Aetiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Viral encephalitis including Herpes simplex encephalitis, varicella zoster encephalitis, West Nile virus encephalitis, rabies, Eastern Equine encephalitis, Western equine encephalitis, influenza, rubella encephalitis</td>
</tr>
<tr>
<td>2</td>
<td>Bacterial meningitis, including tubercular</td>
</tr>
<tr>
<td>3</td>
<td>Cerebral malaria</td>
</tr>
<tr>
<td>4</td>
<td>Parasitic disorders: neurocysticercosis, toxoplasmosis</td>
</tr>
<tr>
<td>5</td>
<td>Rare infectious disorders: paracoccidiomycosis, cryptococcal meningitis, Q fever, cat scratch disease</td>
</tr>
<tr>
<td>6</td>
<td>Antibiotic-induced</td>
</tr>
<tr>
<td>7</td>
<td>Electrolyte imbalance</td>
</tr>
</tbody>
</table>

Table 1: Aetiologies of status epilepticus associated with CNS infections.

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**Psychosis and Status Epilepticus: Borderland or Hidden Cause?**

Brent Elliott
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**ABSTRACT**

Psychiatry, over the past century, has tended to echo the view of Hughlings-Jackson, that 'compound mental states cannot be owing to an epileptic discharge' (Taylor, 1958). The approach to investigating psychosis in patients with epilepsy has been to concentrate on the empirical use of descriptive psychopathology in order to delineate the various psychiatric syndromes and determine to what extent the various abnormalities of affect, thought (delusions) and perception (hallucinations) are similar to or differ from those seen in the 'functional' psychoses in patients without epilepsy.

An almost entirely separate 'positivist' tradition has evolved within neurology. The central theorem of this school is that hallucinations occur as a consequence of the activation of a localised group of neurones which can be investigated by cerebral recording and cerebral stimulation. The 'Gold Standard' investigation has been intracranial stereoelectroencephalography (SEEG).

Key differences between these two approaches lie in the definition of an hallucination and in the concept of a 'compound mental state'. David defines 'hallucination' from the psychiatric perspective as 'a sensory experience which occurs in the absence of corresponding external stimulation of the relevant sensory organ, has sufficient sense of reality to resemble a veridical perception, over which the subject does not feel s/he has direct and voluntary control, and which occurs in the awake state' (David, 2004), usually these may be auditory, but tactile and olfactory hallucinations are also seen in functional psychoses such as schizophrenia. The neurological definition of an hallucination is undoubtedly broader, according to Denis Williams 'an hallucination, which is a percept without a stimulus may be organic or psychotic...Local disturbance of the brain has evoked a perceptual response...[yet] there can be no fundamental difference between sensations felt in a limb or through the eye as a result of a local epileptic discharge....[crucially] the feelings called fear, depression or pleasure arising during the attack [also] have no local reference and for physiological purposes can be considered to be organic hallucinations' (Williams, 1959).

In psychiatry the presence of hallucinations is usually taken to signify psychosis (i.e., complex mental states), yet whilst most psychiatrists would consider a patient experiencing complex auditory hallucinations or persecutory delusions to be 'psychotic' probably none would extend this term to include those experiencing ictal affects such as fear, rage or depression. At the phenomenological level the reduction of all these symptoms into the single category 'hallucination' is both confusing and unhelpful. At the electrophysiological level however, distinction between many of these diverse psychopathological categories is often not possible. It can
be demonstrated that repeated seizures of a single area within the same patient can produce different psychic responses whilst stimulation of widely distinct areas within the same individual can produce remarkable similar phenomena (Fish, 1993).

Penfield noted that auras could be reproduced by electrical stimulation of the temporal lobe (Penfield, 1938). He was interested in the evocation of memory and distinguished between what he called experiential (mental events from the patients personal past) and interpretive phenomena (to do with the present circumstances of the patient). A key element of his later thinking was that experiential responses occur virtually only in seizures arising from the lateral temporal isocortex, where the stimulus was strong enough to provoke an after discharge (Penfield & Perot, 1963).

The anatomical basis was revised further by Gloor who imputed a key role for limbic structures rather than temporal neocortex (Gloor et al, 1982). He considered that the experiential phenomena were not the result of a loss of inhibitory control, as Hughlings-Jackson believed, but were the result of positive activation of limbic structures. In his matrix theory, he proposed that ‘an epileptic discharge within the temporal lobe at the onset of a seizure, when it has not yet become too diffuse or too intense, may be able to recreate a specific matrix that may be similar or identical to that normally encoding a natural experience. Repeated discharge through mechanisms of synaptic plasticity... may have strengthened the interconnectivity of the neurons constituting such a matrix’ (Gloor, 1990).

It is clear that ‘experiential’ phenomena differ markedly from the complex psychotic symptoms seen in the functional psychoses or in the psychoses of epilepsy. However, the development of intracranial stereoelectroencephalography (SEEG) has allowed a variety of psychological symptoms (both affective and hallucinatory) to be recorded in patients undergoing surgical assessment (using arrays of recording electrodes typically placed in the hippocampus, parahippocampal gyrus, amygdale and cingulate gyrus) during periods of ongoing seizure activity, particularly if this activity was prolonged, therefore amounting to limbic status epilepticus (Gloor et al, 1982). These symptoms occupy a separate category between experiential and interpretive phenomena and the ‘complex mental states’ of psychosis and some such states have been recorded on SEEG (e.g., Weser, 1983).

The question remains however, can complex psychotic states occur as a consequence of an epileptic discharge? The best evidence to support this hypothesis can be found in SEEG recordings during episodes of complex partial status epilepticus and during certain cases of apparent ‘post-ictal’ psychosis. Any review of this literature relies on a limited number of individual case reports:

Trimble for example, provides a case of non-convulsive status producing a state resembling schizophrenia in a 22 year old man with complex partial and generalised tonic-clonic seizures since the age of 3 1/2. He complained of the sudden onset feeling that rays were being passed through his body to sterilise him as well as voices in the second and third persons criticising him. He was admitted to a psychiatric hospital and diagnosed with schizophrenia. An EEG, which included sphenoidal electrodes was carried out. The main features included frequent sharp waves on the right side with phase reversals in the right sphenoidal leads which occurred during a period of florid paranoid psychosis. The mental state and EEG both demonstrated a quick response to intravenous diazepam (Trimble, 1991). Takeda et al (2001) provide a further example of SEEG data recorded in a 25 year old woman with intractable temporal lobe epilepsy who developed a postictal psychotic episode two days after a cluster of eighteen seizures. Her intracranial EEG during the psychotic episode demonstrated frequent discharges of the left amygdala which were absent prior to the episode. Kanemoto (1997) reports the case of a 24 year old woman with complex partial seizures since the age of four who developed a pericentral Capgras syndrome (the delusion that a person close to the patient has been replaced by one or more impostors). During her presurgical assessment one episode of postictal Capgras syndrome occurred in association with 15 isolated ictal fears and two complex partial seizures, all 17 of these seizures showed clear cut epileptiform discharge in the left amygdalo-hippocampal region. There have however been other reports which demonstrate no convincing link between psychotic states and EEG abnormalities as recorded by intracranial electrodes (So et al, 1990, Mathern et al, 1995). Oshima et al, (2006) suggest that postictal psychosis should therefore be subdivided into two types; first, a nuclear type representing the established clinical picture as described by Kanner and Barry (2001; Table 1) and occurring as an indirect effect of seizure activity, and second an atypical pericentral type, occurring as a direct manifestation of limbic epileptic discharge. It is however the psychopathology of interictal psychosis that is closest in nature to the complex psychotic states seen in the functional psychoses. Kristensen and Sindrup (1978) reviewed sphenoidal electrode recordings in 96 patients with partial seizures who developed a paranoid/hallucinatory psychosis after a median of 18 years, and compared these with an epileptic control group. They found that the psychotic patients had a significantly larger number of temporal medio-basal independent spike foci than controls. Patients with psychosis also had significantly more frequent bilateral rather than unilateral medio-basal spike foci than controls. Interestingly, Hughes (1985) found that the incidence of bilateral as opposed to unilateral foci in temporal lobe epilepsy increased with age at a rate of almost 1% per year. The possibility that at least some of these ‘complex’ psychotic states may, at least in part, be ‘driven’ by ongoing discharges in limbic structures is an interesting one. Unfortunately, the absence of less invasive means for identifying limbic ictal activity in psychotic patients with epilepsy impedes our understanding in this area. However, as Weser (1983) notes ‘paralleled by clear-cut time related epileptic discharges in hidden brain areas the phasic psychical disturbance of some patients would not have been accepted as an epileptic dysfunction without depth recordings. Such observations are perhaps first steps in building a long desired bridge to psychiatry.’

References


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**Table 1. Common findings among different case series of the features of postictal psychosis.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay between the onset of psychiatric symptoms and the time of last seizure</td>
<td>RELATIVELY SHORT DURATION OF PSYCHOSIS; AFFECT-LADEN SYMPTOMATOLOGY; THE CLUSTERING OF SYMPTOMS INTO DELUSIONAL AND AFFECTIVE-LIKE PSYCHOSES; AN INCREASE IN THE FREQUENCY OF SECONDARY GENERALISED TONIC-CLONIC SEIZURES PRECEDING THE ONSET OF POSTICTAL PSYCHOSIS; THE ONSET OF POSTICTAL PSYCHOSIS AFTER A LONG DURATION OF EPILEPSY (FOR A MEAN PERIOD OF MORE THAN 10 YEARS); A PROMPT RESPONSE TO LOW DOSE ANTIPOWERCHIOTICS OR BENZODIAZEPINES.</td>
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**Status as it presents to the courts**

Hannah Cock  
St George’s University of London & Atkinson Morley Regional Neuroscience Centre, Epilepsy Group, London, United Kingdom

INTRODUCTION: Little is published in the medical literature on this topic, which wasn’t one I chose myself.

METHODS: A search of all case reports available internationally, via the World Legal Information Institutes and member sites (www.worldlii.org), covering appeal court, international, and case-law/law reform cases from around 1995 onwards, using the terms “status epileptus” and/or “epilepsy” was undertaken.

RESULTS: 28 Case reports featuring SE were reviewed from Canada (10), UK (9), Australia (5) and USA (3), together with a single case from the Philippines. No cases were identified from Asia, Hong Kong, Kenya, New Zealand, Pacific Islands or South Africa. Other countries (and 3/10 Canadian reports), were not in English and thus not reviewed. Of 25 remaining, SE was mentioned but I considered not material to the principle issues in 17 cases. This included 3 of 78 cases reported separately as part of the Australian Royal Commission into aboriginal deaths in custody, though it is notable in itself that almost 4% of the deaths occurred in individuals with a history of epilepsy/status epilepticus. A further UK case (Toth v Jarman, UK Civil Appeal Court, 2006), is also worth comment as one which has lead to a standard disclosure statement now recommended for experts with respect to potential conflicts of interest.

Those where I did consider SE was a primary issue are as follows:

2. Latin V Hospital for Sick Children, Toronto 2007. Unsuccessful claim for negligence relating to 14m girl who suffered severe brain damage following prolonged & recurrent seizures in context febrile illness
3. HC v Loos, Canada, 2003. Unsuccessful appeal against liability and partially successful appeal against damages in relation to severe brain injury, and episode of SE 3y later following a traffic accident, complicated by drug and alcohol abuse.
4. Queen v Parker, Canada 1999. A man with severe refractory epilepsy, including several prior episodes of SE, successfully defended himself against charges of cannabis possession on the grounds that he needed it for medical use, and his life would otherwise be threatened (SE). Two attempts by the state to appeal this decision failed.
5. Miranda v Munoz & Munoz, 1985, USA Appeal Court. Relatives of a 19y man who died after developing SE in prison, following lack of access to his usual phenobarbitalone, had already been awarded damages against the prison doctor, warden & assistant warden, but charges against 4 additional supervisory officials had been dismissed. On appeal, the original damages were upheld, and the 4 additional officials directed for a re-trial.
6. UK Family High Court, Ms D vs NHS, 2005. The court agreed with the NHS, against the wishes of her family, that it was not in the interests of Ms D, who was in a vegetative state as a result of progressive mitochondrial disease, to receive further invasive treatment. Movements, present since an episode of SE, that the family considered indicators of awareness were judged to be myoclonic jerks by experts.
7. MG vs Health Authority, UK Civil Appeal Court, 2001. MG had surgery for a benign brain tumour causing epilepsy. After a brief initial recovery, seizures and other complications developed, and severe brain damage ensued. Experts disagreed on the relative contribution of hypoxia vs. SE. Whilst acknowledging shortcomings in documentation, the negligence claim was again dismissed.
8. St George v Home Office, UK court of Appeal, 2008. A 29y known drug/alcohol user with known previous withdrawal seizures was allocated a top bunk in prison, had a seizure, fell from the bunk and developed SE 4 days later, leaving him with permanent severe disabilities. The HO was found liable at trial and on appeal (in allocating him a top bunk) for his injuries, as it was accepted that the head injury from the fall probably triggered the SE, rather than the SE being purely from drug/alcohol withdrawal.

CONCLUSIONS: Publicly available legal documents, much like the published medical literature, are readily accessible via the internet. However, in common with medicine, sorting “the wood from the trees”, and understanding the jargon is sometimes difficult. Although subject to methodological biases, it appears SE is a primary issue for the courts infrequently, but can be the basis for complex legal and medical debates. The review has reinforced my views that expert witness work should not be undertaken lightly and must be kept within boundaries of expertise, that courts sometimes struggle to fit medical uncertainties into rigid legal statutes, and that Judges and experts are generally exceptionally clever people – but not always right. Consent issues in relation to SE and treatment have not been highlighted in the courts, but are a major issue for future research.
Good outcome after SE usually means cessation of seizures within a certain time period after the drug administration and absence of seizure recurrence within next 24 hours and return to baseline neurological function. The control of seizures can mean only clinical control or both clinical and electrographical control of SE. Secondary outcome measures include: Clinical outcome with a functional scale, incidence of focal neurological deficits, incidence of epilepsy, incidence of cognitive decline, response by initial EEG finding, 30-day mortality, need for intensive care unit (ICU) treatment, time of ventilator treatment in patients treated at ICU, incidence of thromboembolism, incidence of infectious complications requiring specific treatment, incidence of hypotension requiring specific treatment, incidence of propofol infusion syndrome or other specific complications/adverse effects. It is also extremely important to follow carefully the vital signs and ECG as well as laboratory values when testing a new molecule.

There are several areas requiring attention in future research in SE. A universally acceptable definition of premonitory, early, established and refractory status needs to be agreed upon and used consistently by investigators. Agreement on the definition of outcomes and method of data presentation is also desirable to facilitate meta-analysis.

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Informed consent in off-label use and incapacitated persons

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(The assumptions made here are based only on German law. Laws from other countries cannot be taken into consideration as they are unknown, and their legal ramifications cannot be determined by medical doctors.)

The German Grundgesetz guarantees the freedom of research (Art. 5, Abs. 3 GG), but according to the ethical principle of autonomy (Art. 1 and 2 GG), no one can be enrolled in a study against his will.

The informed consent procedure requires that the person understands the purpose of the study and can evaluate the possible risks and benefits. Furthermore, the person must be able to withdraw consent whenever he wishes to. Those 14 years or older can give informed consent. Legal capacity is a necessary condition for consenting. Time is needed for comprehensive information and a two-day interval between information and consent is recommended.

In Germany, informed consent is required for those studies testing medication based on a defined study plan (Arzneimittelgesetz, AMG) or for studies testing medical products (Medizinproduktegesetz, MPG). However, it is not required for individual treatment trials without study plan (Heilversuch / “off-label use”) or clinical observation trials (Anwendungsbeobachtung) with therapeutic treatments strictly following individual medical decisions (no study plan, retrospective study design). In Germany, using drugs “off label” is possible in the context of a Heilversuch, even when a person is unable to provide informed consent. The focus here is for clinical trials (according to the AMG) in emergency patients (e.g. status epilepticus). Because standard treatment may never be withheld, these studies will usually focus on adjunctive treatments (add-on).

Undoubtedly, scientific medical research with valid (i.e. randomized controlled) study designs is necessary in order to improve the treatment of those conditions severely affecting the life and autonomy of a person. However, in most emergency situations, it will be impossible to obtain informed consent for study participation (time pressure, cognitive disturbances, loss of consciousness). This results in an ethical dilemma. Medical research aims at saving or re-instituting the autonomy of patients. However, this research would appear to be impossible as the consequences of this very autonomy prevent subjects from being enrolled in research studies without their agreement.

According to German legal regulations, scientific studies that do not benefit the patient or patient group are generally not permitted and no one can be enrolled in a study against his will. But the law assumes that some patients want to contribute to research and actually would have given informed consent if it were possible. This provides the ethical rationale which allows us to examine procedures that might replace the usual informed consent process without violating patient autonomy.

Anticipating informed consent: Informed consent can only be given for a specific study, not as a general allowance. Therefore, providing informed consent for a study in a future emergency case within a predefined timeframe (i.e. anticipating informed consent) appears feasible for the population of epilepsy patients with more frequent status epileptici, if they are usually treated in the same intensive care unit. However, it may be difficult or undesirable to restrict a medication study to epilepsy patients suffering from recurrent status epileptici.

Waiving consent: In this procedure, medical researchers can include a patient in a study under the assumption that this is according to the person’s will. Informed consent must be formally obtained after recovery. Therefore, “waiving consent” only applies for those persons able to provide informed consent upon recovery. This procedure does not require the consent of relatives, legal guardians or guardianship courts and, thus, appears highly appropriate for studies involving emergency situations. Actually, the AMG and the MPG permit “waiving consent” for adults, but only under the following restrictions: informed consent is inaccessible but can be obtained upon recovery; an emergency prevents postponing the study until recovery; the study promises important medical insights; the study can not be done in subjects who are able to provide informed consent; and, most importantly, the study proceeds that might replace the usual informed consent process without violating patient autonomy.
promises individual benefit. Patient group benefit is insufficient reason for waiving consent. Such studies are more or less equivalent to individual treatment trials (Heilversuch).
Anticipating and waiving consent leaves the decision making to the subject. However, this may not be feasible for some studies. In emergency situations, the AMG allows studies in persons who are generally unable to give informed consent (including children below the age of 14 years). However, the study must be a low risk and low burden study. Furthermore, the study must promise individual benefit for those adult patients. For children, the AMG allows studies also for patient group benefit. Hence, "patient group" is defined by the condition for which the patient needs treatment. These studies may even be placebo controlled studies, because patient group benefit is not referred to each single study arm, but rather to the entire study sample.
It is highly remarkable (and questionable) that the AMG permits children, but not adults, to be enrolled in medication studies which promise a benefit only at the patient group level. Even more surprising, the AMG does not state whether consent by parents, legal guardians or the guardianship court is needed in emergency situations before enrollment. The AMG does not even mention waiving consent.

The Declaration of Helsinki (2004) is not enforceable in Germany. It recommends, but does not require, that studies waive consent if the patients are unable to provide informed consent. It even permits scientific studies which do not benefit the individual patient or patient group. It neither mentions the assumed patient's will nor does it restrict the waiving consent procedure to low risk and low burden studies.

The 'Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research' of the Council of Europe (2005) is not enforceable in Germany because it has not been signed or ratified. This protocol allows any treatment or intervention that promises a health benefit for the individual patient in emergency cases. Beyond this, it allows low risk and low burden studies with a possible patient group benefit in patients unable to provide informed consent irrespective of age. However, requiring persons to contribute to medical research appears questionable from a juridical and ethical perspective.

Reference
Inserat GE
Can Buccal Midazolam Replace Rectal Diazepam to Treat Prolonged Seizures?
Graham March (Special Products, Weybridge, United Kingdom)

This lecture discusses the reasons for selecting midazolam as an alternative benzodiazepine to diazepam, together with the merits of the buccal administration route. Three research papers are then discussed. The first one describes the pharmacokinetics of midazolam absorption from the buccal cavity, showing that brain activity was affected after 5-10 minutes without respiratory depression. Having shown that buccal midazolam is potentially an effective therapy, the second paper describes a small clinical trial in children with prolonged seizures. It showed that buccal midazolam is at least as safe and effective as rectal diazepam when administered shortly after the commencement of a prolonged seizure. The third paper addresses the question of the efficacy of buccal midazolam treatment after a delay caused by transporting the patient to the Emergency Room in four paediatric hospitals. This much larger study showed that buccal midazolam stopped prolonged seizures faster than rectal diazepam and also tended to prevent the reoccurrence of another seizure for a longer time.
Changes in cerebral P-glycoprotein function following status epilepticus in rats quantified by an improved method to measure brain uptake of (R)-(11C)-verapamil.

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Introduction: Multidrug efflux transporters like P-glycoprotein (Pgp) at the blood-brain barrier (BBB) are believed to play an important role in resistance to antiepileptic drug treatment. Positron emission tomography (PET) can be used to measure Pgp function, but low brain uptake of (R)-(11C)verapamil hampers the mapping of Pgp function in different brain regions. We investigated if Pgp modulation prior to PET imaging is suitable to quantify differences in Pgp expression after status epilepticus (SE) in rats.

Methods: To study regional differences of cerebral Pgp activity, paired (R)-(11C)verapamil PET scans, before and 2 h after administration of the third generation Pgp inhibitor tariquidar (3 or 15 mg/kg), were performed both in naive female Sprague-Dawley rats and in rats 48 h after pilocarpine-induced SE. Results: The 15 mg/kg tariquidar dose uniformly increased radioactivity distribution across different brain regions, both in naive and SE rats. In SE but not in naive rats, the 3 mg/kg tariquidar dose resulted in obvious regional differentiation of brain radioactivity distribution, with lowest uptake observed in cerebellum. Immunohistochemical staining demonstrated an almost 2-fold increased Pgp content in the cerebellum of SE rats as compared to control rats.

Conclusion: Our data suggest that (R)-(11C)verapamil PET in combination with administration of moderate doses of Pgp inhibitors can be used for the mapping of regional Pgp function in the brain. The current data will help to study changes in Pgp-function at the BBB in further models of SE as well as in pharmacoresistant epilepsy patients. (Supported by the EU [EURIPIDES]).

4-methyloctanoic acid is an effective compound in the treatment of an animal model of status epilepticus.

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Purpose: The antiepileptic drug valproic acid (VPA) is a branch chain fatty acid that has been used in status epilepticus (SE). In animal models of SE, VPA has neuroprotective effects and partly prevents behavioral alterations following status epilepticus. Here, we asked whether another branch chain fatty acid, 4-methyloc tanoic acid (MA) is effective in SE. Methods: We tested the efficacy of VPA and MA (1 mM) in in vitro models of SE induced in hippocampal-entorhinal -cortex slices using pentetetrazol (2 mM) or low magnesium. We then tested these compounds (400mg/kg) in an in vivo model of self-sustaining SE (SSSE) using electrical stimulation of the perforant path. Result: The in vitro experiments indicated that MA is more potent than VPA in decreasing spike frequency. In the in vivo experiments, VPA initially decreased spike amplitude, which then increased to a mean amplitude of 121±20% of amplitude prior to treatment; the frequency remained unchanged (102±14%). In contrast, MA significantly suppressed the spike amplitude and frequency (mean amplitude: 23%±13% of amplitude prior to treatment; frequency: 11±6%, P<0.01 compared to VPA-treated group). VPA treated rats had stage 2 behavioral seizures, whilst the behavioral seizures were abolished in the MA treated group. Conclusion: 4- methyloctanoic acid exerts a powerful antiepileptic effect in both in vitro and in vivo models of status epilepticus, and it is more potent than VPA.
Upregulation of P-glycoprotein (ABCB1) function in Peripheral Blood Mononuclear Cells with Epilepsy Patients

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The P-glycoprotein (Pgp) is reported as the major multidrug resistance (MDR) protein which mediates the resistances in the various tissues including astrocytes, endothelial cells of blood-brain barrier. The functional status of Pgp on PBMNCs in the epilepsy patients are not reported yet. The patients who have recurrent seizures despite of adequate treatment were included through outpatient department. The basic demographic and clinical data were inquired. We conducted the MDR shift and efflux assay with PBMNCs, and analyzed these results with the various clinical parameters. Total 38 epilepsy patients and 30 normal control subjects were included. In the epilepsy groups, the mean age was 379 years old and the mean duration of epilepsy was 18.9 years. The 3.8 anti-epileptic drugs (AED) were prescribed in average and the mean frequencies of seizure were 0.48 per months. The efflux assay of monocytes showed increased function in the epilepsy patients compared with those of the normal control group. When the patients were categorized into the subgroups as low, intermediate, high functional according to the efflux assay results of monocytes, the seizure frequencies were significantly higher in the high efflux group. Although the shift assays of monocytes were significantly increased in the epilepsy group, there were no meaningful correlations with the various clinical findings. In conclusion, the Pgp efflux function of the monocytes might be correlated with the current burden of epilepsy that is represented with seizure frequencies. These findings could help physicians to decide the treatment strategies for the refractory epilepsy patients.

Permissive Role of Cortical Dysplasia on the Epileptogenesis following Prolonged Febrile Seizure

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While atypical febrile convulsion (FC) is well known to be a risk factor of temporal lobe epilepsy (TLE), there is a lack of evidence as to whether FC provokes HS and subsequent TLE. Since the cortical dysplasia (CD) is prevalent in the surgical specimen of TLE patients, CD may link FC and TLE. In this study, we investigated that inborn CD would increase the risk of later epilepsy formation by prolonged FC in the rat model. The experimental CD model was made by in utero injection of methylazoxymethanol (MAM). Rat pups from MAM-treated or control rats were subjected to prolonged FC. We examined morphological changes in the hippocampi of the epileptic rat brain, and evaluated spontaneous recurrent seizures (SRS) by longterm video-EEG monitoring. The MAM+FC group showed a significantly decreased hippocampal cell density in the CA1 area (50%-52% vs. FC-only, MAM-only, and normal control) and dentate hilus (80-81% vs. FC-only, MAM-only and normal control). A robust increase in mossy fiber synaptogenesis was also detected in the MAM+FC groups. Furthermore, later SRS occurred in all rats in the MAM+FC group, while did in 50% and 25% of the rats in the FC-only and MAM-only group, respectively. The frequency and total duration of SRS is higher in the MAM+FC group. Our study provides a model for deeper insight regarding epileptogenesis in dual pathology. Pre-existing CD in the immature brain is likely to play a permissive role in epileptogenesis induced by prolonged FC.

Ketamine Combined with Atropine for the Delayed Medical Treatment of Soman-Induced Status Epilepticus

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INTRODUCTION: Organophosphorus nerve agents (NA), such as soman, are known to induce severe seizures and status epilepticus (SE), seizure-related brain damage (SRBD) and lethality. An effective and quick management of the initial seizures is critical. However, field conditions may delay this treatment. A survey of the NA literature shows that, with the exception of NMDA receptor antagonists, no drug that can be used out of the hospital proves protective when seizures are left unabated for one hour or more. METHODS: Using different models of soman-induced SE, we evaluated 1) in guinea-pigs, the efficacy of combinations of atropine sulfate and either ketamine (AS/KET) or S(+)-ketamine on neuropathology and lethality and 2) in mice, the effects of comparable combinations on central neuroinflammation 48 h post intoxication. RESULTS: In the guinea-pig model, repeated injections of racemic KET combined with AS could fully protect the animals from death and provided a good neuroprotection although recurrent short seizures could still be observed at day one. The S(+) KET exerted similar properties but at lower doses. In mice, the AS/KET combination was able to limit cellular brain damage, glial activation, as well as the increase in mRNA and related pro-inflammatory markers (selected cytokines and adhesion proteins) provoked by the poisoning. CONCLUSIONS: Ketamine, a NMDA antagonist in clinical use, combined with atropine, could constitute an effective treatment of severe NA-induced life-threatening SE. However, further studies should be conducted to identify possible deleterious interactions with poisoning and SE and better define the mechanisms of the therapeutic actions.
Plastic changes in parahippocampal regions of the rat after kainic acid-induced epilepsy
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The subiculum is the main output region of the hippocampus receiving input from the CA1 region and projecting to the entorhinal cortex (EC), septum, mamillary nuclei, and the amygdala. It remains largely preserved in temporal lobe epilepsy (TLE) and therefore is importantly involved in the generation of epileptic activity arising from the hippocampus. Using histochemical methods we investigated changes in the subicular-EC complex and its projections in the kainic acid (KA) model of TLE. We observed severe losses of neurons in the EC and in the subiculum accompanied by signs of reactive gliosis. The number of GAD67-ir interneurons was reduced in the subiculum and EC at late intervals after KA-injection, but labeling for GAD67 and the vesicular GABA transporter was enhanced in the superficial layers of the subiculum and the EC. In these layers, also somatostatin-ir was elevated. The number of parvalbumin-ir interneurons was reduced in the subiculum and the deep EC. We observed increased (or de novo) expression of NPY mRNA in pyramidal neurons throughout all parahippocampal areas and increased NPY-ir in the respective projections. Our data indicate activation of pro-epileptogenic and antiepileptic mechanisms. Loss of parvalbumin-ir GABAergic basket- and axo-axonic cells may result in decreased inhibition of pyramidal neurons. On the other hand, increased expression of NPY and of other neuropeptides in axon terminals of pyramidal neurons and interneurons indicates neurochemical and morphological plasticity resulting in activation of endogenous anticonvulsive mechanisms. Supported by the Austrian Research Funds (P 19464) and the European Union Grant FP6 EPICURE (LSH-CT-2006-037315).

Neonatal status epilepticus resulting in unilateral hippocampal sclerosis and temporal lobe epilepsy
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Hippocampal sclerosis is the most common pathology associated with temporal lobe epilepsy. Early life status epilepticus (SE) has been implicated as a potential causal factor. Despite the development of spontaneous seizures in a sub-population of animals following neonatal seizures, the immature brain remains largely resistant to the development of hippocampal sclerosis. In the current study we examined the electrophysiological and pathophysiological consequences of focally-evoked status epilepticus in post-natal (P10) rat pups triggered by intra-amygdala microinjection of kainic acid. Neonatal SE resulted in extensive death of neurons in the ipsilateral hippocampal CA1 and CA3 subfields, as assessed by double-stranded DNA fragmentation and Fluoro-

Pilocarpine-induced status epilepticus triggers angiogenesis in adult rat hippocampus
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Angiogenesis is one of the processes triggered by status epilepticus (SE). However, the spatiotemporal evolution angiogenesis and its association with other reorganization processes in the hippocampus are not yet understood. To address the association of angiogenesis, neurogenesis, and neurodegeneration we used pilocarpine-induced SE model of temporal lobe epilepsy. Using immunohistochemistry together with unbiased stereology, we assessed vascular morphometry, number of proliferating endothelial cells and neurodegeneration in the subfields of the hippocampus and dentate gyrus at 2 d, 4 d, and 14 d post-SE. There was a decrease in total vessel length in the hippocampus at 2 d post-SE (P<0.05) as compared to controls. The total vessel length increased back to control level in 2 weeks. Subfield analysis indicated decrease in vessel length in the CA1 (P<0.01 as compared to controls) at 2 d post-SE. At 14 d post-SE, vessel length in the CA3 had increased to 27 % of that in controls (P<0.01). Decrease in total vessel length at 2 d correlated with severity of neurodegeneration (r = -0.765, P<0.01). Increase in vessel length was associated with an increase in the number of proliferating endothelial cells with peak at 4 d (10 folds, P<0.001) as compared to controls. As oppose to angiogenesis, neurogenesis was increased at 14 d compared to controls. This finding demonstrates that angiogenesis is one of the components of structural reorganization and is much faster than neurogenesis during epileptogenesis.
P10

Reduced hippocampal injury and epileptogenesis after status epilepticus in mice lacking the pro-apoptotic BH3-only protein Puma

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Introduction: Cortical dysplasia is a disruption in cortical architecture that is associated with epilepsy in both children and adults. Background: We have previously demonstrated focally-evoked limbic status epilepticus activates apoptosis-associated signalling pathways and mice lacking the anti-apoptotic Bcl-2 family gene bcl-w are highly vulnerable to seizure damage. Pro-apoptotic BH3-only proteins may function as upstream effectors in this pathway. Since Puma (p53-upregulated mediator of apoptosis) is among the most potent BH3-only proteins we examined its role in neuronal death and epileptogenesis following experimental status epilepticus. Methods: Adult puma+/+, puma+/-- and puma/-- mice were used. Mice underwent focally-evoked limbic status epilepticus via intramygdaloid microinjection of kainic acid. Brains were harvested 1-72 h later for gene expression and histological analysis. Additional puma+/+ and puma/-- mice were fitted with EEG telemetry units for detecting and quantifying spontaneous seizure occurrence. Results: Puma was largely undetectable in control mouse hippocampus. Hippocampal levels of Puma and the transcription factor p53 were up-regulated within 1 h of status epilepticus and prior to mitochondrial dysfunction (cytochrome c release). Administration of the p53 inhibitor pifithrin blocked Puma induction and attenuated hippocampal injury after status epilepticus. Puma/-- mice displayed significantly less neuronal death in hippocampal CA3 when compared to wild-type and heterozygous mice at 72 h. Video-EEG recordings determined that while both puma+/+ and puma/-- mice developed chronic recurrent seizures, the incidence of epileptic seizures was significantly less in puma/-- mice. Conclusion: The present data suggest Puma may be an apical effector of apoptosis-associated cell death signalling following status epilepticus and targeting Puma may have neuroprotective and anti-epileptogenic effects.

P11

Altersations in Blood-Brain Barrier Integrity in Pentyleneetrazole-Kindled Rats with Cortical Dysplasia

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Introduction: Cortical dysplasia is a disruption in cortical architecture that is associated with epilepsy in both children and adults. The cellular mechanisms underlying epileptogenesis in the setting of CD are still poorly understood. Our aim is to assess BBB permeability and the ultrastructural alterations in rats. Methods: Sprague-Dawley rats and their litters were treated with the protocols that were previously described and modified. On embryonic day 17, the pregnant rats were exposed to gamma-radiation (single dose of 145 cGy). The baby rats were given 30 mg/kg PTZ three times per week intraperitoneally to induce kindling model starting from the 2nd week after birth to the 8th week. The changes in the expression of occludin, which is a tight junction protein in BBB, were shown by using immunohistochemical and Western blot methods in addition to electron microscopy. The experimental protocols were approved by the Ethics Committee of Institute of Experimental Medicine, Istanbul University Results: No increased BBB permeability in PTZ-kindled animals with cortical dysplasia was found although in utero irradiation in rats predisposed to seizures and repeated administration of a subconvulsive dose of PTZ are known to lead to increased susceptibility to seizures. However, acute PTZ-induced seizures in cortical dysplasic plus kindled rats increased BBB permeability to NaFlu. Conclusion: We hereby suggest that cortical dysplasia plus PTZ-kindling could not potentiate seizure-related entry of macromolecules from systemic circulation into brain by compromised BBB integrity, however the induction of acute seizure in these settings induces increase in BBB permeability.

P12

Aggressive behaviors in the lithium-pilocarpine rat models of temporal lobe epilepsy: Resident-Intruder Test

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Purpose: Patients with chronic epilepsy frequently show behavioral problems affecting patients' quality of life. Particularly among the abnormal behaviors, the relationship between aggression and epilepsy is poorly understood, and there have been little data so far in animal models, as well as in humans. In this study, we are to demonstrate the increased level of aggressive behaviors in the lithium-pilocarpine rat models of temporal lobe epilepsy. Method: Adult Sprague-Dawley male rats with spontaneous recurrent seizures (SRS), after lithium-pilocarpine-induced status epilepticus (SE), were subjected to a resident-intruder test to compare the levels of aggression with those for the control group. SRS frequency was assessed before the behavior test by video-EEG monitoring. The behavior test was done between 42 and 56 days after initial SE (chronic SRS phase). Results: Adult male rats with frequent SRS show the higher number of aggressive acts, bites and tail rattles than the control groups. In addition, they spent a greater proportion of the test engaging in non-social behaviors rather than social contact with the intruders. Conclusion: The lithium-pilocarpine rat models of TLE exhibited increased aggressive behaviors and limited social behaviors in
Status epilepticus at infancy and early childhood

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Introduction: Status epilepticus (SE) at infancy is non-rare, but non-completely investigated and sometimes non-well-diagnosed problem. Methods: Were investigated 115 children with debut of SE before the age of three years. The prospective study was done in child neurology department of Russian Children Clinical Hospital at the period 2006-2008. Results: At group of 115 children with debut of SE at infancy and early childhood have been diagnosed: malignant migrating partial seizures in infancy - 12 patients (10,4%), early myoclonic encephalopathy - 11 (9,6%), Ohtahara syndrome (cases with status of cluster tonic spasms and minor motor seizures) - 13 (11,3%), West syndrome (cases with status of infantile spasms clusters) - 26 (22,6%), Dravet syndrome - 7 (6,1%), symptomatic focal forms - 43 (37,4%) and 3 patients (2,6%) with isolated febrile SE. Were marked the following types of SE: status of epileptic spasms clusters and minor motor seizures - 39 patients (33,9%), status of myoclonic seizures - 19 (16,5%), status of GTCS - 13 (11,3%), migrating electro-clinical status of focal seizures - 12 (10,4%), hemicolluvulsive status - 11 (9,6%), versive tonic seizures status - 8 (7%), atypical absences status - 7 (6,1%), hemifacio-pharyngo-oral seizures - 3 (2,6%) and status of generalized tonic seizures - 3 patients (2,6%). Conclusions: The most frequent type of SE at infancy is the status of clusters of epileptic spasms (33,9%). A special type of SE at infantile population is migrating electro-clinical status of focal seizures which is not marked at children of senior age groups and adults.

Effects of 2-chloroadenosine on lithium-pilocarpine status epilepticus elicited in immature rats

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INTRODUCTION: Adenosinergic inhibitory system is able to modulate activity of many brain structures. Agonist of adenosine receptors 2-chloroadenosine was demonstrated to ameliorate pilocarpine status epilepticus in adult rodents. Therefore we studied an action of this agonist on status epilepticus elicited in immature rats. METHODS: Two age groups were used: 12- and 25-day-old rats. Animals pretreated with lithium chloride were 24 h later injected with pilocarpine (40 mg/kg i.p.). Thirty min later 2-chloroadenosine was injected in doses of 1, 5 or 10 mg/kg i.p., controls received saline. Each age and dose group consisted of 8-9 animals. RESULTS: Latency to convulsive seizures was increased by the two lower doses in both age groups. The 10-mg/kg dose of 2-chloroadenosine suppressed completely convulsions, the animals exhibited only epileptic automatisms. Morris water maze as a test of spatial learning and memory was performed in adulthood, i.e. more than two months after status. There was no change in rats undergoing status at the age of 12 days. In contrast, all groups of animals with status at the age of 25 days, performed worse than control animals receiving only lithium chloride. Treatment with 2-chloroadenosine paradoxically even worsened the learning in these animals. CONCLUSION: In spite of less severe convulsions during acute status in 25-day-old rats treated with 2-chloroadenosine effects on spatial memory in adulthood are more serious. This study was supported by a grant No.NR9184/3 of the Ministry of Health of the Czech Republic and by a Research Project AV0Z 50110509.

Febrile infection responsive encephalopathy of school-age (FIRES) with unexpected favorable evolution

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Introduction: Febrile infection responsive encephalopathy of school-age (FIRES), also known as devastating encephalopathy in school-age children (DESC), is a severe encephalopathy that begins with refractory status epilepticus (RSE). After 1 to 3 months, severe epilepsy and cognitive difficulties develop. We report a boy with FIRES, who became seizure free after 5 weeks of RSE, and whose favorable cognitive outcome allowed a return to school. Case Report: An 8.5 year-old boy presented with focal seizures 4 days after a febrile illness. The increasing seizure frequency paralleled a deterioration in his state of consciousness. From day 5 after seizure onset, and during 5 weeks, the patient was in RSE, despite conventional antiepileptic drugs, barbiturate coma, ketogenic diet, steroids, intravenous immunoglobulins, and plasmaphereses. At five weeks, the patient progressively regained consciousness. At three months, he was seizure-free on 3 drugs, and his cognitive examination only revealed mild episodic memory and attention difficulties. Relevant work-up results: CSF (1 day): 17 white cells, proteins 1.04 g/L, absent neurotropic pathogens. EEG (1 week): generalized periodic epileptiform discharges, electrographic seizures; EEG (3 months): normal background, intermittent left temporal slowing. MRI (5 weeks): bilateral hippocampal sclerosis, cortical-subcortical atrophy. Se- rum: negative anti-neuronal antibodies. Discussion: Our report illustrates the fact that the prognosis in FIRES or DESC may not always be as severe as previously thought. Being aware of such a potentially favorable evolution is of importance in a situation which prognosis is invariably considered severe.
The influence of CDP-choline on bicuculline-evoked seizure susceptibility in hyper- and normoglycemic mice exposed to Levin’s model of oligemia/hypoxia

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Introduction: Seizures represent a relatively common complication to transient or permanent ischemia. Preischemic hyperglycemia aggravates brain damage due to transient cerebral ischemia and induces delayed seizures. The aim of the study was to examine the influence of hyperglycemia on seizure susceptibility in mice exposed to oligemic/hypoxic insult. Additionally, the effect of potentially neuroprotective citidine diphosphate choline (CDP-choline) on that parameter was determined. Methods: In this study an experimental Levin’s model of oligemia-hypoxia was adapted to male Albino Swiss mice. Hyperglycemia was induced by oral administration of 40% glucose solution (4g1kg) 30 min before hypoxic insult. Seizures were induced with bicuculline (3.5 mg/kg s.c.) 3 days after the surgery. Animals were treated with CDP-choline (3 x 200mg/kg i.p.: once daily for 3 days after hypoxia, last dose 24 hours before seizure induction). Results: Obtained results indicate that normoglycemic Levin mice displayed increased frequency of clonic bicuculline seizures while prehypoxic hyperglycemia significantly potentiated clonic/tonic seizure activity. Acute treatment with CDP-choline diminished frequency of clonic seizures in normoglycemic Levin mice but did not influence the bicuculline seizure susceptibility in hyperglycemic and sham operated animals. The drug did not change seizure susceptibility in sham operated controls. Conclusion: Transient oligemia/hypoxia in hyperglycemic mice leads to increased susceptibility to bicuculline evoked status epilepticus. CDP-choline had partial potency to prevent the pro-convulsnant effect of the brain oligemia/hypoxia.

Subtle Signs of Different Manifestations of Non-convulsive Status Epilepticus: Diagnostic and Prognostic Challenges

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Introduction: The actual incidence of non-convulsive status epilepticus (NCSE) is about 6 times higher than diagnosed in epidemiological studies. The purpose of this paper is to present the range of different manifestations of NCSE Method-Retrospective series of 18 patient cases. Studied variables include working diagnosis, time to established NCSE diagnosis, outcome, age and etiology. Results: Sample consisted of 10-female and 8-male patients. Mean age was 50.5 years. Total lethality was 33%. In ambulatory patients-10 the ictal symptoms have not yet been recognized 2 -21 day. Working diagnoses were behavioral disturbances, depression and acute confusion, in older patients - over 60 years, dementia and cognitive deterioration. Etiology was: epilepsy - (in 5 cases), brain tumor (2), encephalitis (2), unknown(1). Introduction of antiepileptics resulted in improvement of consciousness, decrease of EEG discharges, improvement of cognitive efficacy, except in one patient who developed dementia. In the intensive care patients consciousness alterations ranged from acute confusion states to coma. Etiology was acute cerebrovascular insult-(4cases), metabolic disorders (1), acute cerebral ischemia after cardiopulmonaryresuscitation (1), terminal renal insufficiency accompanied with metabolic disorders (1) and with sepsis (1). Mortality was 75% in intensive care patients. Two surviving patients were discharged as ambulatory. One surviving patient had metabolic disorder, and the other had a cerebrovascular insult with underlying Wernicke-Korsakoff syndrome and was discharged with severe memory deficit. Conclusion NCSE should be suspected as a possible condition in cases of rapid consciousness alterations and requires EEG changes follow-up. NCSE unrecognized result in more severe cognitive deficit and in intensive care patients it is a sign of poor prognosis and high lethality.

Intravenous Levetiracetam in the Treatment of Status Epilepticus

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Introduction: Status epilepticus (SE) requires a prompt and effective treatment. Levetiracetam (LEV), usually used for refractory partial epilepsy with or without secondary generalisation, has now an intravenous (IV) formulation which relevance for SE treatment is not yet well defined. Methods: We report 3 SE cases treated with intravenous LEV.

Results: Case 1: A 61 years old male with epilepsy since childhood developed a simple partial motor SE. He was treated with IV 1000mg phenytoin followed by IV LEV 1500mg given over 15 minutes with maintenance of seizures. A continuous IV propofol (10cc/h) was then administered successfully. Case 2: A 37 years old male with history of left frontal arteriovenous malformation surgery, started with simple partial SE (aphasia) during video-EEG recording. After IV diazepam, IV clonazepam and IV 1500 mg LEV there was no EEG pattern change. A 1000mg phenytoin perfusion was then tried with no response. A SE resolution was finally obtained after continuous IV propofol (10cc/h). Case 3: A 64 years old male with history of alcoholic cirrhosis developed esophageal bleeding and hepatic encephalopathy. He started with convulsive SE and was treated with 3mg IV clonazepam, 20mg/Kg phenytoin loading dose and intramuscular 200mg phenobarbital. There was no change in seizure frequency. It was
then administered 1500mg IV LEV which ended the seizures. This procedure was repeated twice daily during 3 days. Conclusions: LEV seems to be a possible and safe alternative for SE treatment. However which patients might benefit from it must be clarified.

Febrile infection responsive epileptic (FIRE) encephalopathy in children: A non-encephalitic cause of status epilepticus
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¹Department of Neuropediatrics, University Medical Center Schleswig-Holstein, Campus Kiel, ²Division of Pediatric Neurology, University Hospital RWTH Aachen, ³Epilepsy Centre for Children and Adolescents, Behandlungszentrum Vogtareuth

Introduction: Even though status epilepticus (SE) occurs after simple febrile infection and detection of pathogens in cerebral spinal fluid fails, an encephalitis is generally the presumed cause. Methods: Multicenter case series. Results: From 1997 to 2008, 12 previously healthy children aged 3 – 15 (median 7.5) years presented with SE 3 – 14 (median 5) days after fever onset (8 children with airway infections). An additional 4 children with recurrent seizures instead of SE and 1 without fever were not included. Pathogens were detected in serum or nasopharyngeal aspirate of 4 children (parvovirus B19, rhinovirus, echovirus, Epstein-Barr virus). Cerebral spinal fluid studies revealed 0 – 42 (median 6.5) white cells/µl and no pathogens. Metabolic investigations yielded normal results. EEGs showed bilateral discharges with temporal predilection in 9 children. During acute period, brain MRIs demonstrated slightly increased signal intensity with hippocampal or temporal predilection in 6 children, diffuse edema in 2, and no abnormalities in 4. Anaesthetic barbiturates were used in 8 children and immunotherapy (dexamethasone and/or immunoglobulin) in 4. Brain biopsies were performed in 5 children showing gliosis and no inflammation. One child died, 6 remained in vegetative state, 3 developed refractory epilepsy, 1 had memory and attention deficiency, and 1 was healthy. Conclusion: The similarity between these clinical courses with various prodromic febrile infections followed by SE and the lack of evidence for encephalitis suggest an autoimmune-mediated pathomechanism of a presumed febrile infection responsive epileptic (FIRE) encephalopathy with catastrophic and devastating outcome in most of the previously healthy children.

Experimental study on the protein expression of Erk1/2 in hippocampus and myocardium of epilepsy rats induced by kainic acid.
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Jilin University

Abstract: Background: Epilepsy (especially for status epilepsy) can cause injury not only in the brain, but also in the heart. Erk1/2 belongs to MAPK family, which play an important role on the process of cell injury and protection. The aim of this study is to observe the protein expression of Erk1/2 in hippocampus and myocardium of epilepsy rats. Methods: epilepsy rat models were made by injecting kainic acid into amygdale under stereotactic instrument. 70 male Wistar rats were randomly divided into 7 groups: A the control group; B the false operation group; C-G 0.5h i.q. 1h i.q. 2h i.q. 3h i.q. 4h i.q. 5h i.q. 12h epilepsy group. Erk1/2 protein expression in myocardium of epilepsy rats induced by kainic acid was tested using the method of immunohistochemistry, and the grey values were calculated. Results: The grey value of NMDAR2B and ERK1/2 positive cells in the group A was 15.43±1.32±15.34±1.58 in 1543357±1324±1543215±1356 respectively. The protein expression of NMDAR2B increased from 2h (26.34±2.52) to 24h (23.43±3.31), attain the peak at 6h (27.31±3.02) after kindling. The protein expression of ERK1/2 increased from 0.5h (2634768±2527) to 2h (5230965±3021), then returned to normal level at 6h (1643746±3310). Conclusion: NMDAR2B is involved in the long process of epilepsy brain, and ERK1/2 revolved in the process of epilepsyl’s happen and development.
Introduction/Background: Lacosamide, is a recently-approved anticonvulsant drug for adjunctive treatment for partial-onset seizures in adults. The aim of these experiments was to characterize acute and long-term effects of lacosamide in an animal model for status epilepticus (SE). Methods: Self-sustaining SE was induced in male rats by 10s 20Hz trains of 1ms/30V pulses delivered every 1 minute over 30 minutes. Seizure frequency was assessed by continuous EEG and video monitoring immediately afterwards (acute experiments) and following 16 weeks (long-term experiments). Lacosamide was administered either 10 minutes (early treatment) or 40 minutes (late treatment) following self-sustaining SE onset. Results: In acute experiments, early lacosamide treatment dose-dependently and potently reduced self-sustaining SE; late treatment had less potent effects. Hippocampal damage, assessed 72 hours following SE induction, was greatly reduced following the highest dose tested (50 mg/kg). In long-term experiments, all untreated rats developed spontaneous recurrent seizures following SE. Early lacosamide treatment dose-dependently reduced the number of spontaneous recurrent seizures, with a maximum of 70% reduction with the 50 mg/kg dose. A significant reduction in spikes and cumulative time spent in seizures with lacosamide treatment was observed. Late treatment resulted in a 50% reduction in the frequency of spontaneous recurrent seizures in the highest dose groups (30 and 50mg/kg), and the number of seizure-free animals increased from 0% in the untreated group to 65% in the highest dose groups. Conclusions: In this rat model, lacosamide demonstrated potent effects on acute status epilepticus and showed a potential for disease modification.

The medium-chain triglycerides diet has also been used as an adjunct treatment for astrocytomas. Animal evidence points to a mechanism that one can “force” the body to use fatty acids and ketones as the main sources of energy, while decreasing the utilization of carbohydrates. Careful clinical observation is necessary when starting patients on the ketogenic diet, in order not to worsen pre-existing and undiagnosed conditions e.g. fatty acid oxidation defects. Certain drugs are not advisable to be used simultaneously with the diet. Combining different modalities of treatment including antiepileptic drugs, V.N.S. with the diet has lead to encouraging results. Interest of the ketogenic diet after success in refractory status epilepticus in an adult has been published recently. Based on previous experience in Canada, (see table) we started our ketogenic diet program in King Fahad Medical City, Riyadh, K.S.A. The diet is used mainly in children; but increasing reports for use in adults are there. There are 3 types of the diet: the *classical diet, the medium-chain triglycerides diet, and the nonfasting outpatient protocol. Any type of ketogenic diet is based on the principle that one can “force” the body to use fatty acids and ketones as the main sources of energy, while decreasing the utilization of carbohydrates. Careful clinical observation is necessary when starting patients on the ketogenic diet, in order not to worsen pre-existing and undiagnosed conditions e.g. fatty acid oxidation defects. Certain drugs are not advisable to be used simultaneously with the diet. Combining different modalities of treatment including antiepileptic drugs, V.N.S. with the diet has lead to encouraging results.

### Table: Comparison of Ketogenic Diet (K.D.) and MCT Diet

<table>
<thead>
<tr>
<th>Items</th>
<th>Classic Diet</th>
<th>MCT Diet</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>196</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Lost follow up</td>
<td>6 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Mean age at diet onset</td>
<td>6.9 years</td>
<td>6.86 years</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean age at seizure onset</td>
<td>19 months</td>
<td>25.5 months</td>
<td>0.04</td>
</tr>
<tr>
<td>Range of age at seizure onset</td>
<td>3 weeks-12 years</td>
<td>Birth-11 years</td>
<td>1.0</td>
</tr>
<tr>
<td>Male: female ratio</td>
<td>112:84:1:3.1</td>
<td>16:12:1:3.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Number of patients with single seizure type</td>
<td>47=24%</td>
<td>2=7%</td>
<td>0.79</td>
</tr>
<tr>
<td>Number of patients with 2-6 seizure types</td>
<td>148=75.5%</td>
<td>26=93%</td>
<td>0.15</td>
</tr>
<tr>
<td>Seizure free</td>
<td>26=13%</td>
<td>7=26%</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;90% seizure reduction</td>
<td>51=26%</td>
<td>5=18%</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;50% seizure reduction</td>
<td>57=29%</td>
<td>7=26%</td>
<td>0.15</td>
</tr>
<tr>
<td>Unchanged</td>
<td>55=28%</td>
<td>9=32%</td>
<td>0.04</td>
</tr>
<tr>
<td>Worse</td>
<td>7=3.5%</td>
<td>0=0%</td>
<td>0.04</td>
</tr>
<tr>
<td>At initiation: Nausea &amp; Vomiting</td>
<td>44=22.5%</td>
<td>4=14%</td>
<td>0.46</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>26=13.3%</td>
<td>6=21%</td>
<td>0.25</td>
</tr>
<tr>
<td>During diet: constipation</td>
<td>55=28%</td>
<td>7=26%</td>
<td>0.82</td>
</tr>
<tr>
<td>Increased cholesterol</td>
<td>27=49% (of 55 patients)</td>
<td>3=9.33%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Renal stones</td>
<td>9=75% (of 120 patients)</td>
<td>0=0%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* P value calculated for both groups comparing any response, no response or worse was 0.79 and it was 0.44 when comparing all items together.

* Conclusion: We conclude that MCT Diet efficacy and tolerability is comparable to classic diet and as an alternative, it gives children a wider variety of foods and is more palatable.
INTRODUCTION: We aimed to determine the incidence of seizures and the clinical impact of continuous EEG (cEEG) findings in critically ill children. METHODS: Children in the PICU were prospectively enrolled if they met consensus screening criteria for performing cEEG, including: (1) persisting altered mental status (MS) after a convulsion, (2) altered MS of unclear etiology, or (3) the presence of movements suggestive of subtle seizures. Children underwent at least 24 hours of cEEG. The impact was (1) “decisive” if it led to anti-convulsant medication initiation/adjustment or indicated specific events were not seizures, (2) “contributing” if it ruled out seizures as a cause for MS change, or (3) “no impact”. RESULTS: 34 consecutive children underwent cEEG (median age 1.6 years, range 2 days to 19 years) over 5 months. The primary indications included altered MS with (47%) and without (53%) prior convulsions. Primary conditions included diffuse hypoxic ischemic brain injury (10), encephalitis (4), and status epilepticus (3). Seizures occurred in 62% (21 of 34), constituted SE in 43% (9 of 21), and were entirely non-convulsive in 58% (14 of 21). Non-convulsive seizures were detected in 69% (11 of 16) of patients with altered MS after convulsive seizures. The impact was “decisive” in 76%, “contributing” in 24%, and “no impact” in 0. The most common clinical management change was initiating/adjusting anti-convulsants (21). CONCLUSIONS: Seizures are common in high risk critically ill patients with altered mental status, and are often non-convulsive. In most patients, cEEG has a decisive impact on clinical care.

Stroke as a cause of Status Epilepticus in a hospital based database.

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Stroke is known to be a common cause of status epilepticus. The aims of this study were first to assess the timing and type of SE in stroke patients and second to determine the effects of stroke and the type of SE on the response to treatment and mortality. We retrospectively analyzed 314 episodes over a period of 8 years (January 1998 – December 2006). Eleven episodes were excluded because of missing clinical, EEG or imaging data. A total of 290 patients had 303 episodes. Recurrent episodes (a total of 13) were excluded from further analysis in order to avoid confounding in prognostic data. Among these 72 (49 female, 23 male) cases (25.5%) of stroke SE were identified and evaluated. There were 40 early-onset group, and 31 late-onset SE. There were significantly more patients older than 65 years in the stroke group compared to the non-stroke group (80.6% vs 19.4% p<0.0001). Nonconvulsive SE (NCSE) (56.9%) was more frequent than convulsive SE (CSE) (31.9%) among stroke patients (p: 0.007). However, there was no difference among acute and late onset SE in terms of SE type and mortality. As a conclusion older age and NCSE type seemed to be important risk factors for status epilepticus associated with stroke.

Use of intravenous levetiracetam in the treatment of status epilepticus

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1 Hospital de Bellvitge. Hospitala de Llobregat, 2 Hospital La Fe de Valencia. Valencia, 3 Hospital 12 de Octubre. Madrid, 4 Hospital Josep Trueta. Girona, 5 Hospital CIÀ-nico San Carlos. Madrid

INTRODUCTION: Status epilepticus (SE) is a medical emergency. Early treatment may improve outcome, but the guidelines for the treatment of SE have not changed in decades. Levetiracetam (LEV) is a well tolerated, broad spectrum, highly effective new antiepileptic drug. Intravenous form has become available in Spain last year. The objective of the study is to analyse the efficacy of LEV in treatment of refractory SE. MATERIAL AND METHODS: we retrospectively included patients with SE treated with intravenous LEV from 9 hospitals in Spain. All patients were treated following the accepted worldwide guidelines (benzodiazepines plus phenitoin or valproate). LEV was used as add on therapy, except on those cases that patient had contraindication for classical treatment. Efficacy was defined as seizures cessation in the next 24 hours after starting LEV, with no need of further antiepileptic drug. RESULTS: 31 patients were included, 18 men and 13 women. Mean age was 60 years (range 14-92 years). Most frequent SE type were focal complex in 17 patients. Most frequent etiology was cerebrovascular disease, followed by unknown, tumoral and changes in treatment. Globally LEV was effective in 19 patients (67.7%), in refractory SE the efficacy of LEV was 50% and in patients treated with SE with benzodiacepines the efficacy was 80%. LEV was well tolerated, only 4 patients reported adverse effects, leading to treatment discontinuation in one. CONCLUSION: intravenous LEV is effective in refractory SE, and it could be an alternative in add on therapy.
Use of the Internet to facilitate drug trials in Status Epilepticus.

Peter Bergin1, Tony Ip2, Robert Sheehan2

Introduction: Large multicentre studies comparing antiepileptic drugs could be performed in patients with status epilepticus by using the Internet to recruit patients. Methods: Doctors would log on to a website, and answer several questions regarding the episode of status. What is the type of status? Is the cause known? What drugs is the patient taking? Are any of the study drugs contraindicated? Has the patient had an EEG? Patients could be selected for different studies depending on the aetiology or type of status. If predetermined criteria were met, the patient would be randomised immediately, and explicit instructions given regarding treatment. The on-line form could be completed and a response received within a few minutes. Follow up data would be collected on-line. Results: We have demonstrated in a pilot study that the Internet can be used to recruit patients for randomised controlled trials of anti-epileptic drugs. We established an Internet-based epilepsy-database, and invited neurologists and paediatric neurologists throughout New Zealand to register patients with epilepsy via the Internet whenever they were uncertain of the optimal management. 137 patients were registered in 6 months, of whom 113 were considered suitable for drug trials. We produced an algorithm to select a sub-group of patients who had failed to respond to a single antiepileptic drug. Thirty-five patients who had used a single drug were enrolled, and 14 were randomised on-line to a different drug. Conclusion: This approach could be easily adapted for randomised controlled trials in status. Use of the Internet would greatly facilitate trials.
Clinical case of unprovoked status epilepticus after long term compensation.

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Institute Of Neurology, Psychiatry And Narcology Of AMN Of Ukraine.

Patient P. was born 1954. He had first seizure in 1971. Seizure was diagnosed as complex partial seizure. Beginning of the treatment was in 1972 after 3 complex partial seizures. Starting antiepileptic was Phenobarbital, starting dose was 200 mg/day. Seizures were repeat, usually complex partial, but patient had 1 or 2 complex partial seizures with secondary generalization. EEG dates 1972, 1973 years (interictal) - local epileptic activity in right lobe parietal leads after function loading. From 1974 dose was increase till 400 mg/day and patient had full seizures control. CT and MRT were not done till 1998. From 1994 due long-term remission of epilepsy decreasing dose Phenobarbital was beginning. In 1996 in Phenobarbital dose 100 mg/day, without and provocation status epileptics with complex partial seizures with or without secondary generalization (more after without) was developed. Using of diazepam could not cooped status. Status was cooped only after using combination infusion of diazepam and phenitoin. EEG during status and after showed epileptic activity in right frontal zone. After 1 month after status cooping epileptic activity in interictal EEG remained. MRI showed gliozis zone in right frontal zone. After status cooping patient had stable remission till now. (Valproic Acid and Phenobarbital till 2000, epileptic seizure control from 1998, 2000 till now - Valproic Acid). So if we had the same morphological and EEG epileptic focus decreasing of adequate antiepileptic therapy can he reason of status epileptic.
of antiepileptic drugs and neuroimaging anomalies were significa-
cantly greater in the partial NCSE group. The mean age, number of
elderly individuals, mean episode duration and mortality rate
were significantly greater in the comatose/critically group than
in the ambulatory group. Conversely, a previous history of chronic
epilepsy was significantly more frequent in the ambulatory group.
Conclusion: There are important differences between both gene-
ralised and partial types and ambulatory and comatose forms of
NCSE that justifies its use in the clinical practice. These results
may be useful for developing future definitions and classifica-
tions for this epileptic condition.

A multicenter, open-label trial to assess the safety and
tolerability of a single intravenous loading dose of lacosa-
midé followed by oral maintenance as adjunctive therapy
in subjects with partial-onset seizures: an interim report
Nathan B. Fountain1, Gregory Krauss2, Jouko Isojarvi3, Deanne
Dilley3, Pamela Doty3
7 University Of Virginia, 2 John Hopkins University, 3 Schwarz
Biosciences (a member of the UCB Group)

Purpose To examine the safety and tolerability of a single, 15-mi-
ute IV loading dose of lacosamide followed by oral lacosamide
maintenance treatment in subjects with partial-onset seizures
currently taking 1–2 antiepileptic drugs. Methods: Consecutive
25-subject cohorts were given three progressively increasing do-
ses of lacosamide (200, 300 or 400 mg) administered IV over
15 minutes. Each cohort received the bolus dose followed by the
equivalent daily dose administered orally twice daily for 6.5 days.
The last cohort repeats the highest well tolerated dose to achie-
ve 50 subjects at this dose level. Safety and tolerability of each
cohort was assessed prior to enrollment of subsequent cohorts.
Thus, up to four cohorts are possible. Safety evaluations included
adverse events (AEs), 12-lead ECGs, vital signs and laboratory
parameters. Lacosamide plasma concentrations were measured.
Interim results for completed cohorts are reported. Results: The
first two cohorts have completed enrollment and data analysis is
complete at 200 mg. No serious AEs were reported. Lacosamide
plasma concentrations measured at 12 hours post-infusion and
prior to initial oral dosing were similar to those measured at Days
2 and 8. Enrollment is ongoing in additional cohorts. Conclusi-
ons: This interim evaluation supports the feasibility of a 200mg
IV lacosamide loading dose in patients with partial-onset sei-
zures, and shows that the 200mg IV loading dose provided plasma
concentrations similar to those achieved at steady-state on Day
8. This suggests that 200 mg infusions of lacosamide over 15
minutes are well tolerated and higher dose cohorts should be
assessed.

Evaluation of Seizure Freedom and 75% Responder Rates
with Lacosamide in Subjects with Partial-Onset Seizures in
Phase II/III Clinical Trials
Jacqueline French1, Martin Brodie2, David Hebert3, Jouko Isojarvi3,
Pamela Doty3
1 University Of Pennsylvania, 2 University Department of Medi-
cine and Therapeutics, Western Infirmary, 3 SCHWARZ BIOSCI-
ENCES (a member of the UCB Group)

Purpose: Lacosamide is a new AED approved in the EU and US
for adjunctive treatment of partial-onset seizures in adults. This
presentation summarizes seizure freedom and ≥75% responder
rates in a pooled population from 3 Phase II/III lacosamide clini-
cal trials. Whereas many studies have reported patients seizure
free even if they dropped out due to side effects, this stricter
analysis required completion of maintenance phase. Methods:
Seizure freedom was defined as the proportion of all enrolled
subjects completing the 12 week Maintenance Phase (MP) and
remaining seizure free throughout the MP. The proportion of
subjects experiencing a ≥75% reduction in seizure frequency
from Baseline to the MP was also evaluated. Results: Overall,
subjects achieving seizure freedom were descriptively similar to
the total subject pool. Among total subjects and MP completers,
respectively, a dose-responsive trend for seizure-freedom rates
was observed (2.7%, 3.3%, and 4.8% with increasing lacosamide
dose vs 0.9% placebo). For 75% responder rates, a dose respon-
se was apparent between lacosamide 200 and 400 mg/day but
not between lacosamide 400 and 600 mg/day, possibly due to
the fixed-dose trial design combined with lower tolerability ob-
served at lacosamide doses above 400 mg/day. Conclusions: In
this pooled analysis, seizure freedom was observed even in those
predicted by epidemiological data to have the poorest likelihood
for response. Seizure freedom and ≥75% responder rates gene-
 rally increased with increasing lacosamide dose; however, ability
to show dose response is limited by lower tolerability at doses
>400 mg/day.

Efficacy and safety of Intravenous Levetiracetam in child-
ren with Refractory Status Epilepticus and Acute Repetitive
Seizures
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Lara-Herguedas1, Laura López-Marín1, Anna Duat-Rodríguez2,
Luis G Gutiérrez-Solana1, Mari-Luz Ruiz-Falcó1, María Rodrigo1,
Manuel Leite-Cruzeiro1, Nuria Gutiérrez1
7 University Of Pennsylvania, 2 University Department of Medici-
ne and Therapeutics, Western Infirmary, 3 SCHWARZ BIOSCI-
ENCES (a member of the UCB Group)

Introduction: At present, acute anti-epileptic treatment in children
still has important limitations in the therapeutic arsenal availab-
le and the high rate of adverse effects presented by the most
frequently used antiepileptic drugs (AEDs). The purpose of this
study is to describe the efficacy and safety of intravenous leveti-
racetam (LEV) in children with Status Epilepticus (SE) and acute
repetitive seizures. Methods: Data from 35 consecutive children
aged 14 days to 18 years treated with intravenous LEV were retrospectively analyzed. Medical records of these patients were reviewed for demographic data, underlying neurological disorders, indications, dose, and duration of use of intravenous LEV, seizure control, and adverse events. There was no bolus administration, but in 29 patients we used an attack dose of 30 mg/kg (maximum dose of 1,500 mg). In all patients, the given dose was infused for 10-15 minutes. The frequency of administration was every 8-12 hours. Results: Intravenous LEV was used for control of acute repetitive seizures in 25 patients and for refractory SE in 10 patients. The mean dose used was 50.75 mg/kg/day. All patients received previous treatment with other intravenous AEDs. A symptomatic etiology was found in 30 patients (85%). Twenty-five patients (71%) showed a seizure frequency reduction more than 50%, including thirteen patients (37%) who became seizure-free. Seventeen patients (48%) reported adverse effects being drowsiness the most commonly reported (40%). Conclusions: Our results indicate that intravenous LEV may be an effective and safe alternative in the treatment of acute repetitive seizures and refractory SE in children.

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Perivenous encephalomyelitis as rare cause of status epilepticus

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¹ Ghent University Hospital, Department of Neurology, ² Ghent University Hospital, Department of Pathology

Introduction Main causes of generalized status epilepticus (GSE) are low compliance for anti-epileptic drugs, intracerebral lesions, metabolic causes and withdrawal. However, sometimes the aetiology cannot be found. Methods Two clinical case descriptions with histopathological result. Results Case 1: A 20-year-old woman presented at the ER with a first GSE. Her past medical history was negative. Neurological investigations revealed generalized brain atrophy. An anti-epileptic drug was started, but she was lost to follow-up. In the following months progressive neurological problems developed (cognitive decline, speech and walking difficulties). After a few years she presented at our department. A brain MRI showed diffuse white matter lesions with gadolinium enhancement. Neurological work-up excluded multiple sclerosis, infectious, metabolic and rheumatological diseases, vasculitis and rare coagulopathies. After a stereotactic biopsy histopathological examination showed perivenous encephalomyelitis (PVE). Clinical symptoms and MRI lesions improved after starting steroids with azathioprine. Case 2: A 53-year-old woman presented with a first GSE. Acute investigations (including MR), lumbar puncture, metabolic and infectious screening) yield no diagnosis and she was hospitalized on the ICU. Despite antiepileptic drugs, sedation, antibiotics, antiviral treatment and steroids her situation worsened. The GSE self-sustained, she developed cerebral oedema with subsequent cerebral herniation. After autopsy, histopathological analysis confirmed PVE. Conclusion PVE or disseminated encephalomyelitis (DEM) is a rare form of demyelinating disease of the central nervous system in adults. It usually has an acute and monophasic course, but atypical multiphasic and chronic cases have been described. We demonstrate that DEM should be considered as a possible cause of GSE.

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Clinico-electrographic variants of absence status epilepticus.

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Introduction: As it has been lately revealed, the non-convulsive status epilepticus (NCSE) including absence status epilepticus (ASE) is an important problem not only in childhood, but also with adult and old population. It is considered that clinical and electrographic characteristics of ASE are the same as typical and atypical absences, but with prolonged stupor and slow rhythm at EEG. Method: Clinico-EEG investigation: 12 patients of 6-57 years, night and day sleep monitoring, multistage dipole localization. Results: 10 patients were admitted with different diagnosis: encephalitis, stroke, intoxication and stupor of unknown etiology. Consciousness level was different: stupor, spoor, coma. One girl of 14 was admitted three times with light signs of extrapyramidal disorders, a patient of 57 had light tetraparesis. EEG revealed ASE, all symptoms have disappeared after consciousness and EEG normalization. Next variants of EEG were distinguished: 1. Typical and atypical absence patterns. 2. Interrupted absence pattern: 0,5-1s pauses of epileptic activity . 3. Pattern of regional absence type continued activity . 4. Electrical epileptic status of slow sleep in some patients. Arguments: ASE clinical clear up as stupor, but stupor is not coming to light during sleep; besides valproates the choice of drug is the specific anti-absence medicine ethosuximide. Conclusion: Spike-wave stupor is not obligatory pattern of ASE. Consciousness level and neurological status can be modified. There are at least fore types electroencephalographic variants of ASE.

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Intravenous Lacosamide as treatment for status epilepticus

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Introduction/Background: Treatment of status epilepticus (SE) usually requires intravenous anticonvulsant therapy. Lacosamide (LCM) is a novel anticonvulsant drug that is available as infusion solution. Methods: We identified patients from our hospital database who were admitted because of SE and received at least one dose of intravenous LCM during the course of the treatment. Results: Seven patients (3 female, 4 male) were identified. Median age was 71 years. One patient suffered from generalized convulsive SE, 5 patients had significant reduction of awareness with or without subtle motor symptoms, one patient had an aphasic status. Etiology was acute symptomatic in one patient, and remote symptomatic in 6 patients. LCM was administered after
Seizure characteristics of Dravet syndrome
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1
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Introduction: Severe myoclonic epilepsy in infancy (Dravet syndrome) is one of the most malignant epilepsy syndromes among severe childhood epilepsies. Methods: We investigated 11 children with Dravet syndrome - 7 girls and 4 boys within the age rate from 4 month till 5 years. The study was done in child neurology department of Russian Children Clinical Hospital, Moscow at the period 2005-2008. Results: Febrile debut of seizures was noted at 9 patients (81,8%). Epileptic myoclonic seizures were observed at all 11 patients (100%), hemicolvulsive seizures were noted at 8 (72,7%), focal versive seizures - at 6 (54,5%), generalized tonic-clonic seizures - at 5 (45,5%), pharyngo-oral seizures - at 3 (27,3%), atypical absences with eyelid myoclonus - at 3 (27,3%), tonic spasms - at 2 (18,2 %), atonic seizures - at 1 patient (9,1 %) and affective-respiratory seizures - at 1 girl (9,1%). All at the patients were marked not less than 3 types of seizures, and at 6 patients (54,5%) it was marked 4 and more types of seizures. At all 11 children the delay of cognitive and speech development with formation of non-progressive epileptic encephalopathy was observed. Conclusions: Dravet syndrome is characterized by polymorphism of seizure features. Epileptic myoclonic seizures are obligate seizure type, and frequent seizure types are also hemicolvulsive, focal versive and generalized tonic-clonic seizures. Febrile debut of hemicolvulsive and generalized tonic-clonic seizures is very typical.

Clinical Characteristics and Prognosis in Patients with Status Epilepticus
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Background Although status epilepticus (SE) is a well-recognized neurological emergency with a high mortality, prognostic factors of treatment outcome in SE have not been clearly verified. We performed the present study to document the clinical experience of SE treatment and to identify the prognostic factors. Methods We retrospectively reviewed the medical records of patients who admitted at Seoul National University Hospital for the treatment of SE from July 2003. We analyzed the prognostic value of various clinical and demographic factors which may be associated with the prognosis of SE, including age, sex, SE etiology, seizure semiology, consciousness level at admission, and time to treatment. Results 53 (30 men) patients were recruited. The most commonly encountered etiology was CNS infection (18/53, 34,0%) followed by acute stroke (7/53, 13,2%) and drug withdrawal (16/53, 31,2%). Among 51 patients whose treatment outcome data were available, 4 patients were dead, 26 were alive but substantially impaired relative to baseline clinical condition, and 21 returned to baseline. History of SE (p=0.05), and seizure (p<0.001) was an indicator of favorable treatment outcome, and some etiologies of SE such as large vessel ischemic stroke, acute cerebral infection, and malignant brain tumor (known as potentially fatal etiology) were associated with poor treatment outcome (p<0.001). Conclusion The etiology of SE was diverse. Various demographic and clinical factors were not related with the seizure outcome, but previous history of SE and seizure were related with favorable treatment outcome, and some etiologies were associated with poor treatment outcome.

Safety, tolerability, and pharmacokinetic parameters of 30-, 15-, and 10-minute intravenous lacosamide infusions as short-term replacement therapy in subjects with partial-onset seizures
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Introduction/background: Lacosamide is a newly-approved antiepileptic drug for the adjunctive treatment of partial-onset seizures. Intravenous lacosamide was developed as a short-term replacement for patients in whom oral treatment is temporarily not feasible. Methods: This open-label, inpatient trial (SP757) was conducted to investigate the appropriate infusion duration for IV lacosamide in subjects previously receiving stable doses (200–800mg/day) of oral lacosamide in another open-label extension trial (SP615, SP756 or SP774). Subjects received twice-daily IV infusions over 30, 15, or 10 minutes for 2–5 days. Safety evaluations included adverse events (AEs), ECGs, vital signs, laboratory parameters, and seizure counts. Ten-minute infusions were studied to support the safety of 15-minute infusions. Pharmacokinetic measures included Cmax, Ctrough, and lacosamide metabolite concentrations. Results: A total of 160 subjects were treated with IV lacosamide using 30- (n=40), 15- (n=100) or 10- (n=20) minute infusions. Intravenous lacosamide was generally well tolerated; AE frequency did not increase with days of exposure or shorter infusions. AE incidence was comparable across all groups, with headache (8%, 7%, 5%, for 30-, 15- and 10-minute infusions, respectively) and dizziness (8%, 6%, 5%) most commonly reported. Infusion site-related AEs were infrequent.
and did not result in early discontinuation. Plasma concentrations were dose-proportional and similar across all groups studied. Conclusions: This comprehensive evaluation supports the safety of IV lacosamide (200–600mg/day) as short-term replacement (2–5 days) for oral lacosamide using infusion durations as fast as 10–15 minutes in patients with partial-onset seizures.

Anesthetic agents in the treatment of refractory status epilepticus in children
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Purpose: to evaluate clinical response to the treatment by various anesthetic agents (AAs) in children with refractory status epilepticus (RSE). Methods: RSE was defined as an acute epileptic condition characterized by continuous seizures for at least 60 minutes or by 60 minutes intermittent seizures without full recovery of consciousness between seizures. The drug was effective if the seizure clinically stopped within 20 minutes after its administration without recurrent status epilepticus (SE) within 6 hours. If first and second line drugs for SE failed, midazolam (MDZ), thiopental (THP), propofol and lidocain in continuous intravenous infusion were used. The efficacy of AAs was compared and statistically analyzed by Chit2 test and side effects were observed. Results: The study included 258 episodes (first and recurrent) of RSE in children aged 0.2 -18 years (4.7 ± 4.2). MDZ was used in 242 episodes, thiopental in 36 RSE, and in very resistant cases propofol (4) and lidocain (2). The range of dosage was: MDZ 0.1-1.2 (mean 0.35), THP 3-5 (mean 4.3) mg/kg/h. Mean duration of infusion was 86 (SD=94) hours. MDZ was the most effective with high statistical significance (p=0.0001, ß2=105.6). Side effects were noticed in 40% of RSE treated by MDZ and 60% by THP. Conclusion: Anesthetic agents were used frequently in the treatment for RSE in children. A high dose of MDZ in intravenous continuous infusion was the most effective drug in the treatment for RSE in children. In the cases with prolonged infusion, side effects were noticed in high percentage.

Status epilepticus in NMDA receptor antibody encephalitis
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Introduction: Antibodies to NMDA-type glutamate receptors are associated with a form of encephalitis characterized by neuro-psychiatric prodrome, seizures, and limb, trunk and orofacial jerks and stereotypies. Many patients have been young women with ovarian teratomas. We report 6 cases that required admission to the neurological intensive care unit for management of status epilepticus, decreased level of consciousness and/or hyperkinetic movement disorder. Methods: The patients were admitted to a tertiary centre over a 4 year period. NMDA receptor antibody screening was retrospective in four out of six cases. Results: Four female and two male patients (age range 20-41 years) were positive for anti-NMDA receptor antibodies, accounting for approximately 20% of all patients admitted with a diagnosis of encephalitis. Confusion, agitation or hallucinations were prominent early in the illness. Generalised seizures were documented in 5 patients, and first occurred between 2 days and 3 weeks after symptom onset. All six patients required sedation, tracheal intubation and artificial ventilation, and status epilepticus was the primary indication for ITU admission in 4 cases. EEG monitoring confirmed the later occurrence of non-epileptic jerks and stereotypies, and the movement disorder led to protracted sedation in all 6 cases. Ovarian teratomas were identified in two patients, and no tumour was identified in the other four. Patients were treated with immunomodulation, AEDs and/or surgery, and 3 patients made a good recovery. Conclusions: NMDA receptor antibodies are a common and potentially treatable cause of encephalitis complicated by status epilepticus, neuropsychiatric prodrome and hyperkinetic movement disorder requiring ITU admission.

Effectiveness of topiramate add-on administration in children with refractory status epilepticus
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Background: Refractory status epilepticus (RSE) is a critical condition that requires high level intensive care, and often ends up with poor outcome. However, the optimal guideline of aborting RSE has not been defined yet. This study was aimed to evaluate the effectiveness of topiramate add-on administration in children with RSE. Methods: Seven children were involved in the study and their clinical data were retrospectively analyzed. Topiramate (TPM) was started at 1-2mg/kg/day by nasogastric tube and was titrated to the favorable response every 1-3 days. Results: The age of subjects ranged from 9 month to 14 years (7.5 ± 4.3 years; male 3, female 4). They failed to respond to initial treatment of benzodiazepine, phenytoin, phenobarbital or valproate and midazolam infusion (15.7 ± 4.5 µg/kg/min). The mean dose of TPM was 6.5 ± 3.1 mg/kg/day. One out of them became seizure free, One showed a significant reduction of seizures (greater than 50%), and five showed a fair reduction of seizures (25-50%). No serious adverse events were noted. The time to seizure control ranged from 10 days to 95 days (29.1 ± 30.2 days). One died of sepsis and the remainder experienced the recurrence of seizures after the discharge. Four out of them (50%) were left with cognitive decline or speech/language problem. Conclusion: The results indicate that TPM add-on therapy may be useful in some cases of RSE in children, but further studies are needed to establish the precise role and treatment guideline of TPM in RSE.
Refractory Status epilepticus in a patient with aluminum intoxication

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We report the case of a 28 years old patient with refractory status epilepticus (SE). The patient was admitted to a secondary care hospital due to paresthesia and myoclonic jerks of the face and the left upper limb accompanied by severe agitation and panic attacks. A functional movement disorder was diagnosed and the patient was transferred to a psychiatric ward. She deteriorated showing a massive increase of myoclonic jerks finally leading to intubation and mechanical ventilation. During weaning, convulsive SE was observed and after failure of IV benzodiazepines and IV phenytoin continuous thiopental sedation was initiated. The patient was transferred to our neurological care unit. Valproic acid, levetiracetam and topiramate did not result in termination of SE. The extensive diagnostic workup including infectious, immunemediated, metabolic and paraneoplastic etiologies remained futile. Finally, broad toxicological screening showed a markedly elevated aluminium serum level (485µg/l, normal range 0–75µg/l). Under combined treatment with chelation and hemofiltration, aluminium levels normalized. However the patient only temporarily achieved seizure freedom for a max period of 6 weeks. Hepatic failure and septic complications have led to severe relapses of refractory SE leading to reintubation. With a combined thiopental / ketamin-S nasocosa SE was controlled and the patient was weaned. Under the current treatment with clonazepam, phenytoin and pregabalin the patient has daily myoclonic and focal motor seizures but there is no relapse of SE. We suggest that aluminium-encephalopathy led to SE in our patient although the cause of aluminium intoxication remains undetermined.

The nonconvulsive status epilepticus in palliative care patients – results of a one year prospective investigation

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Introduction: Delirium on admission to a palliative care unit has been described as up to 80% of the patients. However, only rarely nonconvulsive status epilepticus (NCSE) has been considered as its cause and electroencephalographic (EEG) investigation to confirm epileptic activity is not frequently available in these situations. Despite only little data exist, the NCSE has been reported in about 6% of patients with systemic cancer without evidence of CNS involvement and in up to 20% of patients with primary brain tumors or metastases. We report of a prospective evaluation of patients with altered mental status on admission at our palliative care unit. Methods: A total of 290 patients were admitted to our Department of Palliative care in the year 2007. We identified 49 patients with delirium or reduced vigilance. Out of this group 22 patients showed possible clinical signs of NCSE and EEG investigation has been done. Results: In 15 patients epileptic activity could be confirmed in EEG. We managed to treat 10 of them effectively with survival time between 5 and 184 days. Conclusion: We consider NCSE as an important differential diagnosis of patients with altered mental status in a palliative care setting. Treatment should be considered depending on the underlying disease and stage of the disease.

Nonconvulsive status epilepticus in children and elderly patients- differences in etiology, clinical manifestation and prognosis.

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Nonconvulsive status epilepticus (NCSE) represents, according to different reports 5-35% of all SE cases in adults, the data in children is not very sufficient. It’s clinical picture differs through the age of patients. The aim of the study was to assess the type, etiology and prognosis of SE in patients aged over 60 years in comparison to children since these two groups represent the age extremes and require special attention concerning diagnosis and treatment. Methods: The study group consisted of 28 children and 68 elderly patients admitted to the Neurological Departments of Medical University of Gdansk, Institute of Psychiatry and Neurology in Warsaw and Medical University in Poznan during 2004-2008 and diagnosed with NCSE. Repeated routine and Video/EEG monitoring as well as neuroradiological investigations were performed. The statistical analysis was performed. Results: In children group NCSE was mostly due to preexisting epilepsy there were no de novo NCSE whereas in elderly group in 59% of patients. The types of NCSE also differ significantly – in children the majority presented the absence or atypical absence NCSE, in elderly ther were mostly complex partial NCSE. Conclusions: A considerable higher proportion of patients aged over 60 years than of children were admitted to the hospital because of NCSE. De novo NCSE were observed significantly more frequently in patients over 60 years. Vascular etiology of NCSE dominated significantly in patients over 60 years where in children often the NCSE was due to underlying brain malformations causing drug-resistant epilepsies or the etiology was unknown.
Introduction/background Diagnosis of status epilepticus can be wrongly made in several circumstances. This may explain the apparent refractoriness of some status epilepticus. Methods We reviewed the cases of patients who were admitted with a false diagnosis of status epilepticus, either in the Epilepsy Unit, or in the neurological tertiary referred intensive care unit (ICU), at the Pitié-Salpêtrière Hospital. Results Several conditions were found to mimic a status epilepticus. First, nonepileptic pseudoseizures from psychiatric origin can mimic convulsive status epilepticus. Second, post-anoxic encephalopathies and sporadic Creutzfeldt-Jakob disease can be judged as non-convulsive status epilepticus, mainly due to a wrong interpretation of the electroencephalogram (EEG). In these encephalopathies, the existence of non-epileptic myoclonus and the abolition of the EEG abnormalities with the use of a benzodiazepine, without correction of the clinical symptoms, were additional confusing factors, leading to the initial false diagnosis. Conclusion The combined analysis of the clinical data together with the EEG allow, most of the time, to confirm or to reject the diagnosis of status epilepticus. Rectifying the diagnosis results in avoidance of aggressive and unnecessary treatments.

The History of the Treatment of Status Epilepticus

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Introduction: Despite the fact that a condition resembling status epilepticus had been recognised since babylonian times, status epilepticus as a separate clinical phenomenon to epilepsy was largely ignored in the medical literature until the mid nineteenth century. Following the discovery of the bromides as an effective treatment for epilepsy in 1857, treatment options employed for the termination of status epilepticus increased and became more effective as clinical appreciation and understanding of status epilepticus evolved over time. Methods: We reviewed the medical literature on the treatment of status epilepticus from 1870 when the latinised version of the term état de mal status epilepticus was first used in the medical literature until 1973 and the establishment of the bezodiazepines as the mainstay of treatment. Results: Many diverse treatments have been employed and advocated for the termination of status epilepticus, many of which are now largely forgotten as is the rationale for their use. Over 30 major interventions or treatments were identified over this period. Conclusions: Different time periods were dominated by 1-2 treatment options, with treatment becoming generally more aggressive and with earlier intervention advocated over time despite the fact that the gravity of the condition was well recognised since the first clinical descriptions of status epilepticus.

Differential diagnoses of status epilepticus

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Introduction/background Diagnosis of status epilepticus can be wrongly made in several circumstances. This may explain the apparent refractoriness of some status epilepticus. Methods We reviewed the cases of patients who were admitted with a false diagnosis of status epilepticus, either in the Epilepsy Unit, or in the neurological tertiary referred intensive care unit (ICU), at the Pitié-Salpêtrière Hospital. Results Several conditions were found to mimic a status epilepticus. First, nonepileptic pseudoseizures from psychiatric origin can mimic convulsive status epilepticus. Second, post-anoxic encephalopathies and sporadic Creutzfeldt-Jakob disease can be judged as non-convulsive status epilepticus, mainly due to a wrong interpretation of the electroencephalogram (EEG). In these encephalopathies, the existence of non-epileptic myoclonus and the abolition of the EEG abnormalities with the use of a benzodiazepine, without correction of the clinical symptoms, were additional confusing factors, leading to the initial false diagnosis. Conclusion The combined analysis of the clinical data together with the EEG allow, most of the time, to confirm or to reject the diagnosis of status epilepticus. Rectifying the diagnosis results in avoidance of aggressive and unnecessary treatments.

IV Levetiracetam terminates refractory complex-partial status in an infant with migrating partial siezures

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Introduction: Although older generation antiepileptic drugs(AEDs) can terminate status epilepticus(SE) in most cases, a minority of pediatric patients develop medically refractory SE(RSE). The medical treatment options are based only on consensus recommendations or expert opinions. The pharmacological termination of RSE with continuous intravenous(ciV) application of benzodiazepine(MDZ), barbiturates(PB,THIO), (fos)phenytoin(PHT), valproate(VPA) or anesthetics(PRO, KET) bears the risks of potentially life threatening complications. Recent publications describe seizure control in pediatric patients with RSE after intravenous and nasogastral application of Levetiracetam(LEV) and thus suggest a possible role for LEV in treating RSE Case report: We report the case of a 4 months old male infant with underlying MMPSI who was admitted to our pediatric ICU with symptomatic complex-partial status epilepticus after prehospital rectal diazepam(DZP). The rapidly repetitive autonomic seizures with continuous impairment of consciousness were refractory to ivBZP, ivVPA, ivPB and ivPHT but could be terminated after intravenous administration of LEV. No adverse side effects(ASE) occurred and after discontinuation of the ivLEV the infant remained seizure-free for a period of days under oral VPA-LEV comedication Discussion: This case suggests that ivLEV is a useful and safe option for the treatment of RSE in infancy. The LEV pharmacological mechanisms of action seem to be different from other AEDs. The legal questions involved in an off-label use of the new generation AED in young children have not yet been addressed. RCTs of LEV and other newer AEDs as treatment for RSE are necessary Keywords: Intravenous Levetiracetam(ivLEV), refractory status epilepticus(RSE), malignant migrating partial seizures in infancy(MMPSI)

A prospective assessment of refractory status epilepticus

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Background: Status epilepticus (SE) resistant to two AEDs is commonly defined as “refractory” (RSE). In the few available retrospective studies, RSE frequency has been estimated to occur in 31%-43% of patients presenting an SE episode. Almost all seem to require a coma induction for treatment. Methods: Prospective observational study over two years in a tertiary clinical setting, to assess RSE frequency, clinical predictors, and outcome. Clinical data and outcome (mortality and return to baseline clinical conditions) were collected. Univariate and multivariate statistical analyses were applied. Results: In the study period, 128 consecutive SE episodes (118 patients) were recorded. Twenty-seven of these (21%) were refractory to first and second line antiepileptic treatments; there were no recurrent RSE epis-
Malignant status epilepticus: Treatment persistence until when?
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Introduction: Malignant status epilepticus (MSE), with very poor prognosis, is defined by persistent epileptic activity after administration of high doses of anesthetics. The persistence of MSE in a patient with incurable epileptic encephalopathy raised questions of therapeutic approach, in terms of what should be extent of their persistence in such cases? Case report: A 31 years-old man with Lennox-Gastaut syndrome, several different seizures daily, treated with valproic acid, topiramate, lamotrigine, phenytoin and clobazam, was admitted due to increasing number of seizures, progressing to generalized convulsive status epilepticus (GCSE) at day 4. Besides propofol, barbituric coma was induced 3 times, until EEG burst-suppression in 2 and absence of brain electrical activity in 1. During admission, antiepileptic therapy was optimized with benzoalaminopenicin, topiramate in high doses (1200 mg) and intravenous levetiracetam. There were multiple complications, including ventilator-associated pneumonia, atelectasis, cellulites of upper limb, metabolic acidosis and urinary tract infection. Death from septic shock at day 42. Conclusion: Anecdotal cases are reported in literature of reversible MSE related to infection. Death from septic shock at day 42. Conclusion: Anecdotal cases are reported in literature of reversible MSE related to infection.

Seizure duration in focal epilepsies, its correlations and predictors: video-EEG analysis
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Introduction: To assess electroencephalographic seizure duration (eSD), determine its predictors, and explore the relationship of serum AED levels and eSD. Methods: Surface video-EEG recordings of patients with focal epilepsy, admitted to the Video-EEG monitoring Unit (Innsbruck), from January 2006 to March 2008 were retrospectively analysed. Variables (age, duration of the disease, epilepsy syndrome, etiology, localisation of seizure onset, MRI findings, and history of SE or febrile seizures) were evaluated. Corresponding serum AED levels when epileptic seizures occurred were correlated with eSD. Results: We included 1125/1250 uninterrupted seizures (median 4; 1-48) of 159 patients (72 female; 70.3% symptomatic epilepsy; age 34.2±13.2 (13-75); disease duration 15.8±12.4 years (0.1-47)). Analysis showed significant difference of median (per patient) eSD of the different seizure types (p<0.001). FSS lasted significantly shorter (42 s;
Background: Status epilepticus (SE) treatment relies on relatively little evidence, although several guidelines have been published. A recent study (Vignatelli, J Neurol 2008;255:196-204) reported a worse SE prognosis in an urban center compared to a peripheral hospital, postulating better management in the latter. Methods: Over 6 months, we prospectively recorded consecutive adults with SE (5 or more minutes) at the Centre Hospitalier Universitaire Vaudois (CHUV), and in 6 peripheral hospitals (PH) of the same region. Demographical, historical and clinical variables were collected, including SE severity estimation (STESS score) and adherence to Swiss SE treatment guidelines; outcome at discharge was categorized as “good” (return to baseline), or “poor” (persistent neurological sequelae, or death). Results Thirty-six cases from Saudi Arabia and Arab populations. The inclusion criteria were: 1. The age of onset of seizures was between 2-24 months. 2. Normal development before, during and after the onset of seizures. 3. Normal interictal EEG. 4. Normal brain imaging. 5. Good response to treatment. Most of the patients (75%) responded immediately to antiepileptic treatment. The pedigree of three families showed the possibility of benign familial infantile seizures. Conclusions. To our knowledge, this is the first study to document the presence of benign familial and non-familial infantile seizures (Watanabe-Vigevano syndrome) in Saudi Arabia and Arab populations.

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Characteristics of Focal Electrographic Seizures in Awake Vs. Comatose patients.

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Introduction: To compare focal electrographic seizures (EG Sz), in awake and comatose states. Methods: We analyzed EG Sz correlated to clinical and neuroimaging data, depending on the state of the patient. Results: Five EEGs (3 awake & 2 comatose) were evaluated. Mean patient age (+SD) was 38.2(+14.85) yrs. Mean EEG duration was 28 and 55 minutes in awake and comatose. Background was normal in awake and slow/suppressed in comatose. Seizure onset was focal in awake with low amplitude beta, repetitive sharp wave and rhythmic delta activity, while focal & multifocal with repetitive spike-waves in comatose patients. Two awake patients had intermittent discharges lasting <1 minute,
while continuous EgSz seen in remaining 3. EgSz would spread to involve ipsilateral and contralateral hemisphere in comatosed with 1 sec of onset while in awake the time for regional spread was 1-20 secs. Intra-ictally, EgSz in awake would evolve to repetitive spikes, rhythmic alpha–theta and delta activity, while evolution to repetitive spikes/polyspikes was seen in comatosed. Postictally, EEG showed focal slowing and attenuation in 1 awake patient, while generalized and regional suppression was seen in comatosed. Nonlesional epilepsy and stroke was diagnosis in awake while toxic/metabolic (normal imaging in 1 and no imaging in other) etiology in comatosed patients. Conclusion EgSz in comatosed patients were prolonged with intra-ictal evolution to repetitive spike/polyspike waves and rapid spread to involve large/ multiple brain areas. In addition, background slowing and suppression was seen in these patients.

**P59**

Topiramate in Therapy Focal Forms of Epilepsy in Children.
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Purpose: This is a study of clinical efficacy, safety and tolerability of the new antiepileptic drug topiramate (TPM) for treatment different focal forms of epilepsy in children. Methods: Topiramate was used in 31 patients aged from 6 month to 17 years, mean age was 7 years 7 months (14 male and 17 female). All patients received medications for between 4 - 86 months, mean observation time was 35 months. Results: Topiramate in combination with other antiepileptic medications (19(61%) patients) or alternative monotherapy (12(39%) patients) was used in doses 56 - 500 mg/day and 2.5 - 17 mg/kg/day (average 6,6 mg/kg/day). Seizure freedom was achieved in 8/31(26%) patients. Reduction in seizure frequency more than 50 % was observed in 19/31(61%) cases. In general, the positive effect has been reached at 27/31(87%) patients. In 3/31(10%) of patients seizures frequency gradually returning to a baseline 1-3 month after positive effect achievement. Side effects (SE) were detected in 14/31(45%) of all cases. The main of them was salts in urine (9 patients), sleep disorders and hyperactivity. In 2 children was aggravation of frequency of seizures and withdrawal therapy was necessary. Conclusion: Our clinical results show that topiramate is highly effective, well tolerated new antiepileptic drug for treatment of different focal forms of epilepsy in children early age.

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Retrospective analysis of usefulness of phenobarbital in intravenous loading dose for the treatment of status epilepticus
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Rational: Phenobarbital in intravenous loading dose (PB-ILD) is frequently utilized for the treatment of various types and stages of status epilepticus (SE) despite paucity of studies analyzing the issue. Methods: We retrospectively evaluated cases with SE treated with PB-ILD at the Institute of Neurology CCS, Belgrade during 20 years. Patients were identified using prospective SE registry established and administered since 1988. D.S. Results: Among 1359 patients with SE; 273 (20.1%) were treated with PB-ILD (males: 66.3%; median age: 41; range: 13-78 years; 82.2% with generalized convulsive SE). PB-ILD was effective in 235/273 patients (86.1%): in 76/82 (92.7%) as initial, and in 159/273 (83.2%) patients after previous ineffective antistatus drugs. In 235 patients in whom PB-ILD was effective, the median dose was 1100 mg (range: 200-4000 mg), after which SE stopped during first 20 minutes in 195 (83%) patients. Approximately, 50% of responders received more than 15 mg/kg of PB. In 38 patients in whom PB-ILD was ineffective the median dose was 1540 mg (range: 440-3400 mg) (p=0.007). After PB-ILD, 149/273 patients (54.5%) remained in postictal coma lasted 3-214 h (median 14). Coma after PB-ILD lasted significantly longer (p=0.0001) than coma following other antistatus drugs (0.5-123, median 1.1 h). Respiratory depression occurred in 3 (1.1%) patients. 47/273 patients (17%) died: 41 due to underlying disease and 6 due to infective complications of prolonged coma. Conclusion: Although this was uncontrolled study, it appears PB-ILD is very effective drug for the treatment of SE with major disadvantage in potentiating prolonged postictal coma.

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Autonomic Status Epilepticus in Panayiotopoulos Syndrome: neuropsychological assessment
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Background: Panayiotopoulos syndrome is a benign childhood epileptic disorder. Seizure are often prolonged and autonomic status epilepticus occur frequently. The aim of this study is to evaluate the cognitive level of those patients after prolonged seizures, by the administration of a battery of neuropsychological tests. Methods: Children with clinical and EEG feature of Panayiotopoulos syndrome were reviewed. Out of the total number of subjects we selected randomly a group to whom have been administered a battery of age-appropriate tests which tend to explore the global cognitive level (WPPSI, WISC-R, Leiter, Ra-
Intravenous (IV) Levetiracetam in clinical practice – 75 patients reported to an independent registry

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Introduction: Most common clinical studies on antiepileptic drugs do not reflect medical everyday practice due to their strict in- and exclusion criteria and treatment regimen. Here we present a registry with the intention to evaluate the spectrum of application in daily use and the efficacy and tolerability of intravenously given Levetiracetam (LEV iv., Keppra® iv.) over an observation period of 10 days.

Methods: In a national multicenter approach from June until December 2008 LEV iv. treated patients of all ages were reported together with their clinical data (age, seizure and epilepsy type, exclusion criteria and treatment regimen).

Results: From 16 German neurological and (neuro-) pediatric hospitals the data of 90 patients were reported, of which 86 (min 0.7 y, max 90 y of age) could be evaluated: 62 had a diagnosis of epilepsy before LEV iv. In 49 of the patients the reason for initiating LEV iv. treatment was status epilepticus (SE). In 31 % of these cases LEV iv. was used as first-line treatment. The median daily dosage of LEV iv. was about 1000 mg. SE could be terminated in 84%.

Conclusion: The use of LEV iv. exhibited a remarkable good response and tolerability in patients with acute onset seizures (mostly SE) in this registry. Further studies are needed to confirm these findings.

Encephalopathy with Status Epilepticus during Slow Sleep: “The Penelope Syndrome”

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Successful treatment of generalized myoclonus (“myoclonic status epilepticus”) after cardiopulmonary resuscitation does not change the poor prognosis of these patients

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Introduction / background: Generalized myoclonus (GM) after cardiopulmonary resuscitation (CPR) is usually classified as a type convulsive status epilepticus (CSE) and associated with a poor prognosis. There is evidence from single patients that propofol may control GM. Methods: We treated 60 consecutive patients with GM after CPR with propofol. GM occurred within 24
Predictors and prognosis of status epilepticus patients treated with intravenous sodium valproate

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Objective – To analyze factors predicting seizure outcome and prognosis of intravenous sodium valproate use in status epilepticus (SE). Methods – Retrospective analysis of 32 patients diagnosed as SE and received intravenous sodium valproate therapy. Logistic regression analysis with stepwise approach was used to evaluate the predictors of seizure control and death. Results – There were 32 cases met the criteria. Intravenous sodium valproate was prescribed as the first-line therapy in 12 cases and followed the intravenous phenytoin in 20 cases. The first-line therapy of intravenous sodium valproate was the only factor that significantly related to seizure control with adjusted odds ratio [OR] of 5.571; 95% confidence interval [CI] of 1.128-27.523. Initial leukocytosis and hypotension were significantly associated with death (adjusted OR 22.765, 95% CI 1.176-440.640 and adjusted OR 37.591, 95% CI 3.035-465.571, respectively). Conclusion – The first-line therapy of intravenous sodium valproate was the only significant predictor for seizure control in SE. The survival prognosis was associated with initial leukocytosis and hypotension.

Successful Treatment of Status Epilepticus with Lacosamide - the 1st Austrian Case

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Introduction/Background: Status epilepticus (SE) is a potentially life-threatening condition. The evidence-based treatment for SE is not always effective and therefore novel therapeutic approaches are needed especially for patients with pharmacoresistant epilepsy. Lacosamide (Vimpat®) is a novel antiepileptic drug with a new dual mode of action. We report a case of symptomatic generalized epilepsy, whose generalized tonic-clonic SE was successfully controlled with lacosamide. Methods: The 38-year old male patient with 30kg body weight was admitted for a series of complex partial seizures with secondary generalization leading to generalized SE. He had been suffering from epilepsy due to cerebral hypoxia in early infancy with several seizures per month, and was treated with levetiracetem 2x1500mg, clonazepam 2mg, topiramate 200mg. Before arriving at the hospital the patient was given 22.5mg diazepam, 12.5mg etomidate and 5mg midazolam without success. After admission an additional dose of 4mg lorazepam and 1500mg levetiracetam were administered, again without clinical effect. Due to the patient's low body weight, we did not further increase the dose of the antiepileptic drugs, but started treatment with lacosamide (300mg within 2 hours via percutaneous gastric fistula). This resulted in complete clinical remission of the epileptic activity within 30 minutes. Result: Application of lacosamide resulted in cessation of SE and was well tolerated. Conclusion: To our knowledge, this is the first case of successful treatment of SE with lacosamide. Further studies are needed to determine the safety and efficacy of lacosamide in treatment of SE.

Clinical and EEG data in two patients with myoclonic status epilepticus after hypoxic brain injury

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Introduction: It has been suggested that early myoclonic status (MSE) after hypoxic brain injury is usually associated with bad outcome, but there are some reports with good outcome. Different forms of myoclonus may occur in these patients. We report clinical and neurophysiological data in two hypoxic coma patients whom suffered a MSE and had a good outcome. Methods: Patient one presented with early symmetrical spontaneous or triggered by stimuli myoclonus and seizures after cardiorespiratory resuscitation due to an acute asthmatic attack. The other, admit-
Background Efficacy and safety of intravenous sodium valproate has been demonstrated in adults and Western children. Appropriate dosage is yet to be determined in Thai children. Methods: A cross-sectional study was conducted in children aged <15 years at Ramathibodi Hospital from January to December 2008 to evaluate pharmacokinetics and safety of intravenous valproate in Thai children for implication in treatment of status epilepticus. Recruits were children with one of the following: 1) refractory status epilepticus to intravenous loading dose of phenobarbital or phenytoin, 2) repetitive seizures despite being treated with appropriate dose of intravenously phenobarbital and/or phenytoin, 3) history of aromatic drug allergy. Valproate 15-20 mg/kg was intravenously administrated at the rate of 3 mg/kg/min followed by maintenance-dose of 6 mg/kg every 6 hours. Valproate level was determined after initial dose at 30 min, 1, 2, 3, 4, 5, and 6 hours. Complete blood count, ammonia, and liver functions test prior to initial dose and at 6 hours were collected. Results: 11 children (age range 5-15 years, mean age 9.5 years) were recruited. After mean loading dose of 18.4 mg/kg, median maximum concentration was 95.7 mcg/ml (range 67-141). Median volume of distribution (Vd) was 0.21 L/kg (range 0.12-0.45). Two children had seizure recurrence at 5th and 6th hour after initial dose. One child had transient elevation of serum ammonia. Conclusion: Volume of distribution of 0.21 L/kg is appropriate for calculation of intravenous valproate loading dose.

**Is intravenous sodium valproate an effective, safety and well-tolerated drug for status epilepticus?**

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Introduction To evaluate the efficacy, safety and tolerability of the treatment with intravenous sodium valproate (i.v. VPA) in patients with status epilepticus. Methods In this retrospective study, we report our experience with 44 patients (20 males, 24 females) of status epilepticus, who were non-convulsive status epilepticus (NCSE), myoclonic status epilepticus (MSE) or generalized tonic-clonic status epilepticus (GTCSSE) (resistant to conventional drugs such as diazepam or phenytoin) were treated with i.v. VPA. VPA was infused 15 mg/kg in 6-7 minutes and this infusion was continued 1 mg/kg/hour until seizures ceased. If seizures persisted after the loading dose, general anesthesia (barbiturates/prophenofol/midazolam) was administered. Results There were 14 patients of NCSE, 5 of MSE and 25 of GTCSSE. Thirty seven patients (84%) showed clinical improvement and seizures were controlled within 20 minutes-3 hours without any adverse effects. There was no respiratory depression, cardiac arrhythmia or hypotension. These patients remained seizure-free and were then started on oral anticonvulsants. One NCSE, 2 MSE and 4 GTCSSE did not respond to i.v. VPA alone and required an additional other anticonvulsant infusion or general anaesthesia. Conclusion We conclude that i.v. VPA therapy seems to be effective, safety and well tolerated in adult patients with NCSE, MSE and GTCSSE who were contraindicate to conventional anticonvulsants such as diazepam or phenytoin.

**Absence Status Epilepticus caused by Cannabinoids?**

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Because cannabinoids, acting on pre-synaptic CB1 receptors, inhibit the release of neurotransmitters, they may act as brakes in overactive circuits. Abnormalities in the thalamo-cortical circuitry might underlie absence epilepsy. We therefore investigated the influence of a cannabinoid agonist on absence seizures.

We used the genetically epileptic WAG/Rij rat model, which shows spontaneous absence seizures visible in the EEG as “spike-wave discharges” (SWDs). WAG/Rij rats (n=6 per dose) were injected with solvent or with the cannabinoid agonist WIN55,212. EEG’s were recorded.

A single dose of WIN55,212 (3, 6 or 12 mg/kg, ip) reduced the incidence of SWDs during the first 3 hours post-treatment.

**Intravenous Sodium Valproate in Thai Pediatric Patients: Pharmacokinetics and Clinical Application**

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in a dose-dependent way (ED50, 3 mg/kg). After this initial reduction, the incidence of the SWDs returned to baseline level. However, the duration of the reappearing SWDs was markedly changed. Multiple very long SWDs were observed, lasting up to 100 seconds, whereas baseline SWDs rarely last longer than 17 seconds. In the baseline, SWD activity was seen during 2% of the time, whereas in the 6th hour after administering 12 mg WIN55,212, SWD activity was seen during 12% of the time. We will discuss possible mechanisms that underlie these absence-like status epilepticus periods. Clarifying this mechanism may help to answer the intriguing, unsolved question what causes epileptic seizures to stop at all.

Non-Rasmussen, non-vascular epilepsia partialis continua
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Background: EPC comprises entities like Rasmussen and stroke-related EPC. We study cases belonging to neither of these entities. Methods: Inclusion criteria were local continuous irritative motor or sensory symptoms, persistent or recurring in episodes. We analysed age at onset of EPC and epilepsy, time course, syndrome diagnosis, semiology of EPC and concomitant seizure types, localization, findings of EEG and imaging, etiology and response to treatment. Results: 21 cases aged 9 to 66 were identified. Seizures (SF in 19 pats, GTC in 13, CF in 6) had started 1 to 52 years before EPC. 13 patients had EPC of the persistent, and 6 of the recurring type. Twice EPC started episodically and turned persistent later. Semiology was always of the same type as the patient's focal seizures (motor in 11, sensorimotor in 4, somatosensory in 2 and visual in 4). EEG with EPC was unrevealing in 5 cases, showed epileptiform activity in 12 and local slow activity or flattening in 4. Etiology was based on imaging in 16 cases: cortical dysplasia in 5, tumour in 2, atrophic lesion in 2, unspecified morphological lesion in 4, arteriovenous angioma in 1, 7 unclarified. Most patients were resistant to multiple drugs. A positive effect of Topiramate (TPM) was noted in 6 of 11 patients so treated. Conclusions: Our patients are no homogeneous group but may include identifiable subgroups. EPC due to dysontogenetic lesions stood out by their response to TPM. Visual EPC seems to be more common than generally believed.
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Andrea: diagnosed with epilepsy in 1990

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