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Annual Meeting of the American Epilepsy Society

December 3, 2005
Investigators' Workshop
2:30 p.m.–5:45 p.m.

MIW.001
Seizures Beget Seizures
Yehezkel Ben-Ari (INMED Institute, Marseilles, France)

Seizures produce long lasting alterations of the networks that lead to a reduction of the threshold of further seizures. In adults, the underlying mechanisms have been extensively investigated in particular in temporal lobe epilepsies. Seizures notably produced by kainate or pilocarpine induce cell death in vulnerable regions of the hippocampus. This is followed by sprouting and the formation of novel glutamatergic synapses –notably mossy fibres of CA3 pyramidal neurons. These new synapses are functional as attested by the massive rise of glutamatergic EPSCs in target epileptic neurons. Interestingly also recordings from temporal lobe epileptic animals, reveal that these synapses are aberrant since control granule cells use only AMPA receptors mediated synapses whereas after the formation of novel synapses, most EPScs are purely kainate receptor mediated. This implies directly that the sprouting has induced the formation of novel synapses that operate differently from the control ones. Other studies have shown also that the inaugurating status epilepticus induced by the injections of the convulsive agent triggers a cascade of events associated with the activation of hundreds of genes in the hours –days that follow the seizures that are responsible for the sprouting and neo-synapse formation. The period of roughly 3 weeks that follows the seizures is a "silent" period during which seizures are not generally generated and spontaneous events do not take place. Ed Dudek will deal with the events that occur at that stage. One additional basic issue concerns the generation by thalamo- cortical connections of fst oscillations and the role of GABAergic synapses in that event. Mircea Steriade will summarize these events and explain how seizures are generated in the neocortex and how they can affect the network. Finally, relying on the triple chamber that accommodate the intact neonatal hippocampi and their connections, Y Ben-Ari will describe the mechanisms of seizures beget seizures during development. In essence, the questions here are which seizures beget seizures and produce long lasting alterations and which do not. This has important implications as to the determination of the mechanisms at work but also may be useful in a clinical perspective to evaluate potentially deleterious seizures.

MIW.002
Fly, Fish and Worm Models of Epilepsy
[3]Guy Caldwell, [2]Mark Tanouye, and [1]Scott C. Baraban ([1]Neurological Surgery, UCSF, San Francisco, CA; [2]Environmental Science, UC Berkeley, Berkeley, CA; and [3]Biological Sciences, University of Alabama, Tuscaloosa, AL)

Rodent models of experimental epilepsy have been an especially valuable aid in understanding fundamental aspects of human seizure disorders. While there are distinct advantages to using a rodent model of a human neurological disorder, there is no rationale to support our almost exclusive reliance on this species. Indeed, fundamental research related to genetic modifiers of epilepsy, high-throughput anticonvulsant drug screening and forward-genetic screening strategies to uncover novel epilepsy genes are better suited to simpler systems. Exciting new discoveries in the general field of neurobiology have begun to exploit the experimental advantages of simpler organisms such as C. elegans (worms), Drosophila melanogaster (fruit flies) and Danio rerio (zebrafish). Similar discoveries could be possible in the epilepsy field. To highlight recent advances, an Investigator Workshop is planned to present the current state of knowledge in these systems (and provide a forum to discuss where we can, or should, go from here). Guy Caldwell (University of Alabama) will discuss his work with C.elegans lissencephaly mutants. Using a pentylenetetrazole exposure paradigm, they have uncovered a convulsive phenotype that correlated with interesting intraneuronal deficits in presynaptic GABA vesicle trafficking. This suggests it may be possible to separate the intrinsic neuronal deficits leading to LIS1-dependent epilepsy from the more overt cortical defects associated with neuronal migration. Mark Tanouye (UC Berkeley) will present studies on mutant and wild-type Drosophila tested in a stimulation-induced seizure protocol. Using this approach they have identified "epilepsy" mutants that are especially prone to seizures when compared with normal flies and have begun to explore seizure-suppressor and seizure-enhancer mutations. Scott C. Baraban (UCSF) will discuss his work with zebrafish larvae. Using a PTZ exposure protocol, they have described the electrophysiological, behavioral, pharmacological and molecular aspects of a novel simple vertebrate seizure model. Screening a colony of over 6300 ENU-mutagenized zebrafish, seizure-resistant larvae were identified and are now undergoing further characterization and gene mapping. Jeffrey L. Noebels (Baylor) will act as moderator for a lively discussion of these topics.

MIW.003
Imaging Excitatory Neurotransmission
[1]Jonathan Wetherington, [2]Ognen Petroff, and [3]Matthias Koepp ([1]Dept of Pharmacology, Emory University, Atlanta, AL; [2]Dept of Neurology, Yale University, New Haven, CT; and [3]Dept of Clinical and Experimental Epilepsy, Institute of Neurology, UCL, London, United Kingdom)

The N-methyl-D-aspartate (NMDA) ion channel plays a role in neuroprotection, neurodegeneration, long-term potentiation, memory, and cognition. It is implicated in the pathophysiology of several neurological and neuropsychiatric conditions. The development of effective radiotracers for the study of NMDA receptors is critical for our understanding of their function, and their modulation by endogenous substances or therapeutic drugs. The intrachannel PCP binding site has attracted most attention, as it is only accessible when the channel is in the active and "open" state", but not when it is in the inactive or "closed" state. The physical location of the NMDA/PCP receptor not only makes it an important theoretical imaging target, but also complicates the development of suitable PET and SPECT radiotracers for this site and attempts to quantify in-vivo binding. An intimate understanding of the biochemical, pharmacological, physiological and behavioral processes associated with the NMDA ion channel is essential to develop improved imaging agents and interpret in-vivo measurements.

This workshop will focus on the development of creative approaches to the study of excitatory neurotransmission in patients with epilepsy using MRI/MRS, PET or SPECT. It will provide participants with an understanding of the biochemical, pharmacological, physiological and behavioral processes associated with the NMDA ion channel and an insight into the difficulties and complexities of imaging excitatory neurotransmission in vivo. The participants of this workshop will discuss the animal and pharmacological models used for in-vitro and in vivo assessment of NMDA receptor functions.

The multi-disciplinary nature of this workshop provides opportunities for interactions between participants and faculty with diverse backgrounds including paediatric and adult neurology/epileptology, basic neuroscience, pharmacology, neurophysiology, neuroradiology and nuclear medicine.

2.325

RELATIVE BIOAVAILABILITY AND BIOEQUIVALENCE OF THREE DIFFERENT ORAL FORMULATIONS OF ESLICARBAZEPINE ACETATE

[1]Teresa Nunes, [1]Amilcar Falcao, [1]Luis Almeida, [1]Ricardo Lima, [1]Susana Tavares, [2]Carla Neta, [2]Carlos Fontes-Ribeiro, [2]Tice Macedo, and [1]Patricio Soares-da-Silva ([1]Research & Development, BIAL, S. Mamede do Coronado, Porto, Portugal; and [2]CEB, AIBILI, Coimbra, Coimbra, Portugal)

Rationale: To investigate the bioavailability and bioequivalence of three formulations of eslicarbazepine acetate: 50 mg/mL oral suspension (Test 1), 200 mg tablets (Test 2) and 800 mg tablets (Reference).

Methods: This was a single-centre, open-label, randomised, 3-way crossover study in 18 healthy subjects. Each subject received a 800 mg single-dose of eslicarbazepine acetate in three different occasions: either 16 mL of oral suspension 50 mg/mL, 4 tablets 200 mg or 1 tablet 800 mg. Single-doses were separated by a washout period of 7 days or more.

Results: Eslicarbazepine acetate was rapidly and extensively metabolised to BIA 2-005. Figure 1 displays mean BIA 2-005 plasma concentration-time profiles and Table I presents the main pharmacokinetic parameters**:** maximum plasma drug concentrations (C_{max}), time to its occurrence (t_{max}), area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), and the apparent terminal half-life ($t_{1/2}$). Point estimate (PE) and 90% confidence intervals (90%CI) were calculated for the $AUC_{0-\infty}$ and C_{max} geometric means. PE and 90%CI for $AUC_{0-\infty}$ Test 1/Reference ratio were 1.09 and 1.01–1.15; for C_{max} ratio, PE and 90% CI were 1.07 and 0.97–1.15. When Test 2 and Reference formulations were compared, the PE and 90%CI were 0.99 and 0.94–1.07 for the $AUC_{0-\infty}$ ratio, and 0.94 and 0.86–1.02 for the C_{max} ratio. Bioequivalence of Test versus Reference formulations is accepted for both $AUC_{0-\infty}$ and C_{max} because the 90%CI lie within the acceptance range of 0.80–1.25.

Conclusions: The pharmacokinetic profiles of three different formulations of eslicarbazepine acetate (oral suspension 50 mg/mL, 200 mg tablet and 800 mg tablet) were similar and these formulations can be considered bioequivalent.

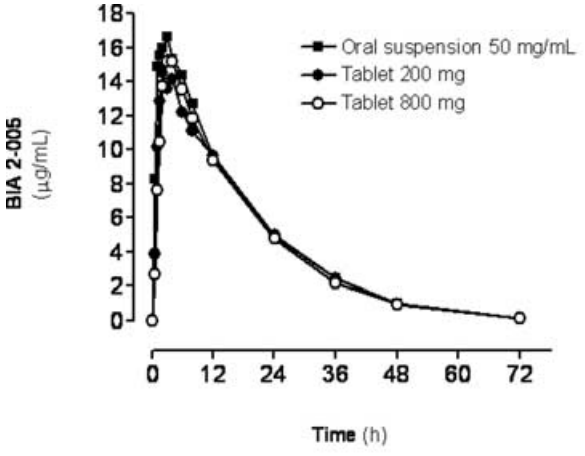

Figure 1. Mean plasma BIA 2-005 concentration-time profiles following administration of 800 mg of eslicarbazepine acetate in three different oral formulations (n=18).

Main BIA 2-005 pharmacokinetic parameters following last dose of an 8-day repeated dose regimen of eslicarbazepine acetate (n = 6 per dose group)

Dose	Mean Cmax µg/mL (%CV)	Median tmax h (range)	Mean AUC0-24h µg.h/mL (%CV)	Mean apparent $t^1/_2$ h (%CV)
400 mg q.d.	8.8 (16.0)	3 (0.5–7)	126.3 (11.7)	9.50 (18.8)
800 mg q.d.	18.7 (14.0)	3.5 (1–7)	268.4 (10.3)	12.3 (22.9)
1200 mg q.d.	25.5 (10.8)	3 (0.5–6)	423.0 (10.9)	13.1 (20.1)
1800 mg q.d.	47.7 (23.3)	2 (0.5–4)	740.3 (19.6)	11.3 (28.8)
2400 mg q.d.	56.5 (20.0)	2 (1.5–8)	905.9 (12.8)	10.4 (24.1)

2.326

USE OF TOPIRAMATE IN VERY YOUNG CHILDREN WITH REFRACTORY INFANTILE SPASMS OR REFRACTORY EPILEPSY

[1]Tracy A. Glauser, [2]Nathan Watemberg, [3]Yann Mikaeloff, and [4]Jeffrey S. Nye ([1]Neurology, Children's Hospital Medical Center, Cincinnati, OH; [2]Pediatric Neurology, Wolfson Medical Center, Holon, Israel; [3]Pediatric Neurology, Centre Hospitalier Universitaire Bicetre, Paris, France; and [4]Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, NJ)

Rationale: Epilepsy in very young children (e.g. <2 yrs old) is especially difficult to manage. Not only is the nature of epilepsy different in this age group, pharmacokinetics and toxicity may have age-related differences. We report on findings from topiramate (TPM) use in very young children (≤2 yrs old).

Methods: Data from 3 studies involving 57 children ≤2 yrs old with refractory infantile spasms or refractory epilepsy were analyzed. Open-label TPM was added to existing therapy at 1 mg/kg/day and titrated to an optimal dosage.

Results: In Study 1, TPM pharmacokinetics were evaluated in 8 young children (0.8–1.8 yrs) receiving TPM twice a day (7.0–8.9 mg/kg/day). At steady state, apparent oral clearance was 30.5–60.2 ml/hr/kg and half-life was 7.4–9.9 hrs in patients receiving non-enzyme-inducing AEDs; in those receiving enzyme-inducing AEDs, oral clearance and half life were 76.8–121 ml/hr/kg and 4.4–5.0 hrs, respectively. In Study 2, 21 children with infantile spasms (median age, 8.8 months; range, 0.8–25.8 months) were treated with a median dose of 17.3 mg/kg/day TPM. Monthly rates of spasms and other seizures appeared to decline over time with TPM treatment; 11 patients were spasm-free ≥7 days. In Study 3, 7 of 8 children with infantile spasms had a clinically significant response (≥50% seizure reduction). Among children with other forms of refractory epilepsy, seizures were reduced ≥50% in 8/20 patients. Overall, few patients in these 3 studies experienced treatment-limiting adverse events (4/57 discontinued). The most common adverse event was irritability, a common occurrence in children with infantile spasms.

Conclusions: Children ≤2 yrs old with refractory epilepsy or infantile spasms who were treated with open-label TPM had fewer spasms and other seizure types. Because TPM clearance is higher in infants than in older children, higher mg/kg doses may be needed, especially in those also taking enzyme-inducing AEDs. (Supported by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. and Janssen-Cilag.)

2.327

LOADING OF LEVETIRACETAM OVER 24 TO 48 HOURS IS WELL TOLERATED IN PEDIATRIC EPILEPSY PATIENTS

Kevin M. Rathke, John D. Wooten, and Traci E. Irwin (Pediatric Neurology, Raleigh Neurology Associates, Raleigh, NC)

Rationale: Rapid administration of anti-epileptic drugs (AEDs) is often necessary in the treatment of pediatric patients with intractable seizures but significant and often prolonged adverse reactions can occur. Levetiracetam (*Keppra*) is a well-tolerated oral AED with few significant adverse effects even at high doses. Levetiracetam may be a safe, well-tolerated option when enteral AED loading is indicated.

Methods: The records of 9 patients ages 3–16 years old with intractable seizures (generalized or partial) were reviewed. All were on other AEDs, clinically conscious and interactive, and monitored