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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.

Conclusions: This retrospective study demonstrated weight loss in patients treated concurrently with ZNS and VPA. A gender difference in pattern of weight loss was observed. Women tended to continue losing weight at 6–9 months after being maintained on ZNS_{max}. Men's weight loss peaked at 1–3 months on ZNS_{max}. A larger series with better control of dose titration for VPA and ZNS is needed to verify these findings. (Supported by MICNEP Epilepsy Care.)

2.297

CLINICAL EXPERIENCE WITH LEVETIRACETAM MONOTHERAPY IN THE TREATMENT OF EPILEPSY

James P. Valeriano, and Carole L. Lane (Neurology, Allegheny General Hospital, Pittsburgh, PA)

Rationale: Levetiracetam has been approved as adjunctive therapy in the treatment of partial onset seizures in adults. However, in clinical practice we have utilized levetiracetam as monotherapy across a spectrum of multiple seizure types in an adult population with epilepsy. This includes conversion to monotherapy from other anticonvulsants as well as initial drug therapy for newly diagnosed seizure disorder.

Methods: We retrospectively reviewed records in 22 patients in which levetiracetam was used as monotherapy. Seizure types treated included: simple and complex partial seizures with or without secondarily generalization and primary generalized seizures, including myoclonic seizures.

Results: Our patients maintained good to excellent seizure control with levetiracetam monotherapy, allowing us to continue them on a single medication. This degree of seizure control spanned the spectrum of multiple seizure types.

Conclusions: Levetiracetam proved effective as monotherapy in the treatment of various seizure types in an adult epilepsy population. (Supported by UCB Pharma, Inc.)

2.298

CLINICAL SIGNIFICANCE OF A DRUG INTERACTION BETWEEN LAMOTRIGINE AND CYCLIC HORMONAL COMBINATION CONTRACEPTIVE USE IN SELECTED WOMEN WITH SEIZURES: ONE EPILEPSY CENTER's CLINICAL EXPERIENCE

Colleen Vanderkolk, Julie Dagam, George Morris, and Jennifer Burgos (Regional Epilepsy Center, St. Luke's Medical Center, Milwaukee, WI)

Rationale: A potential interaction exists between lamotrigine and hormonal combination contraceptives, including oral combination contraceptives. Patients on lamotrigine and hormonal combination contraceptives may experience decreased lamotrigine blood levels and clinical signs including seizures or side effects.

Most hormonal combination contraceptives provide hormones for 21 of each 28 days. Patients taking lamotrigine and cyclic hormonal combination contraceptives, then, may experience a monthly fluctuation in the interaction resulting in fluctuation of lamotrigine blood levels and clinical signs because the patient takes lamotrigine daily but takes active hormones for only 21 of each 28 day cycle.

As a result, we decided to examine our center's experience with the potential interaction between lamotrigine and cyclic hormonal combination contraceptives, and to characterize the potential clinical significance of this in our patient population.

Methods: Our center developed data collection forms to identify patients taking lamotrigine and cyclic hormonal combination contraceptives and to record blood levels and clinical changes. In Feb 2005, charts of all female patients were reviewed and those taking lamotrigine were identified.

Identified patients were contacted in March 2005 and ongoing. Current medications were verified and patients on both lamotrigine and cyclic oral contraceptives were scheduled for two lamotrigine blood levels: mid-cycle (after active oral contraceptives for 14 days) and end-of-cycle (after no active oral contraceptives for 7 days).

Patients will be contacted mid-cycle and end-of-cycle for clinical data including changes in seizure frequency and side effects. Clinical data will be compared to blood levels changes.

Results: To date, 7 patients agreed to lamotrigine blood levels. By May 2005, end-of-cycle levels are available for 43% (3/7) of patients and 67% (2/3) levels are within the reported reference range while 33% (1/3) is below the reported reference range. Mid-cycle levels are available for 14% (1/7) of patients, and is below the reported reference range. Clinical data is available for one patient, who reported no change in seizure frequency or side effects. All patients were maintained on individualized regimens of antiepileptic medications.

Conclusions: Because patients taking hormonal combination contraceptives and lamotrigine may experience a decrease in their lamotrigine blood level, the end-of-cycle level would be expected to be higher than the mid-cycle level. One of three available end-of-cycle levels is unexpectedly below the reference range, but that patient's mid-cycle level and clinical data are needed for comparison. Data collection is ongoing and our center is continuing to examine our experience and characterize the clinical significance of the interaction in our patient population.

2.299

ESLICARBAZEPINE ACETATE PHARMACOKINETICS AFTER SINGLE AND REPEATED DOSES IN HEALTHY SUBJECTS

Manuel Vaz-da-Silva, Teresa Nunes, Eva Soares, Jose Farancisco Rocha, Susana Tavares, Amilcar Falcao, Luis Almeida, and Patricio Soares-da-Silva (Research & Development, BIAL, S. Mamede do Coronado, Porto, Portugal)

Rationale: The objective was to determine the pharmacokinetics of eslicarbazepine acetate following single and repeated doses.

Methods: Integrated pharmacokinetic results of three double-blind, randomised, placebo-controlled trials. Oral single doses of eslicarbazepine acetate ranging from 20 mg to 2400 mg, and 8-day oral repeated doses ranging from 400 mg to 2400 mg daily were administered to healthy young male subjects (6 subjects per dose).

Results: Previous human studies in which a chiral method has been used in the assay of plasma drug concentrations showed that eslicarbazepine acetate is rapidly and extensively transformed into the active metabolite eslicarbazepine (also known as S-licarbazepine), which represents more than 95% of systemic drug exposure following oral administration of eslicarbazepine acetate. When a non-chiral method is used, which was the case of the current trials, the assay is not able to distinguish between eslicarbazepine and its R-enantiomer (R-licarbazepine), a minor metabolite, and the mixture is reported as BIA 2-005. Eslicarbazepine acetate was extensively metabolized to BIA 2-005. The summary of the main BIA 2-005 pharmacokinetic parameters following repeated (8-day treatment) doses can be found in Tables I. Both the rate and the extent of systemic exposure to BIA 2-005 increased in an approximately dose-proportional manner following repeated administration. The mean observed accumulation (R_O) was 1.4, 1.7, 1.7, 1.5 and 2.1 after once-daily dosing (q.d.) with the 400 mg, 800 mg, 1200 mg, 1800 mg and 2400 mg doses, respectively. Steady-state plasma BIA 2-005 concentrations were attained at 4 to 5 days of once-daily dosing, consistent with an effective elimination half-life ($t_{1/2}$) in the order of 20 h to 24 h. Renal clearance of BIA 2-005 appeared to be constant over the dose range studied.

Conclusions: Eslicarbazepine acetate appeared to be rapidly and extensively metabolized to BIA 2-005 following single and repeated administration to healthy young subjects. Moreover, the dose-proportionality for BIA 2-005 (following single and repeated doses) is in accordance with the concept of linearity regarding its pharmacokinetic behaviour (rate and extent of systemic exposure).

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 $t\frac{1}{2}$ 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)