

Epilepsy

P 3039

Extracellular pharmacokinetics of levetiracetam in rat hippocampus and frontal cortex

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Introduction We have investigated the temporal kinetic inter-relationship of levetiracetam in serum and brain extracellular fluid (frontal cortex and hippocampus) following systemic administration of levetiracetam, a new antiepileptic drug. Concurrent extracellular amino acid concentrations were also determined.

Methods A rat model, which allows serial blood sampling and concurrent brain microdialysis sampling, was used. A catheter was implanted in the jugular vein for blood sampling and microdialysis probes were implanted stereotactically into the hippocampus and frontal cortex. Levetiracetam and amino acid concentrations were measured by HPLC.

Results After administration (40 or 80 mg/kg), levetiracetam rapidly appeared in both serum (T_{max}, 0.4–0.7 h) and extracellular fluid (T_{max}, 2.0–2.5 h) and concentrations rose linearly and dose-dependently, suggesting that transport across the blood-brain barrier is rapid and not rate-limiting. The kinetic profiles for the hippocampus and frontal cortex were indistinguishable suggesting that levetiracetam distribution in the brain is not brain region specific. However, t_{1/2} values were significantly larger than those for serum (mean range, 3.0–3.3 h vs. 2.1–2.3 h) and concentrations did not attain equilibrium with respect to serum. Levetiracetam (80 mg/kg) was associated with a significant reduction in taurine in the hippocampus and frontal cortex. Other amino acids were unaffected.

Conclusion Levetiracetam readily and rapidly enters the brain without regional specificity. Its prolonged efflux from and slow equilibration within the brain may explain, in part, its long duration of action that has been reported clinically. The concurrent changes in taurine may contribute to its mechanism of action.

P 3040

Malignant glioma within the temporal lobe in the rat brain after kainic acid induced chronic epilepsy: Single case

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Injected subcutaneously into the rats kainic acid (KA, 10 mg/kg) induces epileptic activities and neurochemical and histopathological alterations which show similarities to the clinical and histopathological changes observed in human temporal lobe epilepsy. Recurrence of spontaneous seizures have been reported 6 months after the initial KA-induced convulsions and hippocampal lesions reflect a very severe form of atrophy and sclerosis at 6 months of injection (Baran et al., 1988). The GABAergic activity and somatostatin levels in selected brain regions (cortical and basal ganglia areas) were significantly increased and these alterations could be involved in the development and progression of spontaneous seizures activities.

Within KA-treated rats with initial induced convulsions one of KA rat did not develop spontaneous seizures. In this animal a malignant glioma was found within the temporal lobe, mainly located in the amygdala, infiltrating the adjacent entorhinal cortex, the ventral parts of the hippocampus, the claustrum and parts of the striatum. Interestingly, the GABAergic activity was in control range in all analysed brain region, at 6 months after KA. Somatostatin levels were elevated in the hippocampus and a mild increase was found in cingulate and parietal cortices, while in temporal cortex and amygdala/piriform cortex the somatostatin content was markedly decreased. A lack of spontaneous seizures, and a different, moderate pattern of neurochemical alterations observed in the brain of KA rat with a malignant glioma in the temporal lobe would indicate notable network of GABA and somatostatin activities involving seizures development.

P 3041

Analysis of levetiracetam action on calcium channel subtypes of hippocampal neurons

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Introduction The cellular mechanisms of the anti-seizure-activity of new antiepileptic drug levetiracetam (LEV) are not yet identified. We studied, therefore, sensitivity for LEV of different types of voltage-operated Ca²⁺ channels in isolated rat CA1 pyramidal neurons, aiming to discriminate their possible role in the specific action of this substance.

Methods Whole-cell patch clamp recordings of Ca²⁺ channel activity of isolated hippocampal CA1 neurons were performed. For the separation of Ca²⁺ channel subtypes, their selective blockers were used: nifedipine, w-Conotoxin-GVIA, w-Agatoxin and w-Conotoxin-MVIIC for L-, N-, P- and Q-types respectively. HVA Ca²⁺ currents were elicited by shifting the holding potential from –70 mV to depolarising test potentials for 50ms, and LVA from –80 mV to –45mV.

Results In control cells L-type accounted for 25%, N-type for 45.5%, P-type for 16.8% and Q-type for 9.4%. LEV application irreversibly inhibited the evoked currents in all tested cells. IC₅₀ for the inhibition by LEV of HVA Ca²⁺ channels was 14.7μM. The maximum inhibition was observed at 200μM and was about 18%. Application of 200μM LEV in the presence of the corresponding selective blockers further reduced the calcium current amplitude by 17.0%, 15.6% and 17.4% for L-, P- and Q-types respectively. However, LEV was ineffective in the presence of the selective blocker of N-type channels. No inhibitory effect was observed on LVA Ca²⁺ channels.

Conclusions Present study indicates that LEV selectively influences the activity of N-type Ca²⁺ channels of CA1 pyramidal hippocampal neurons with 37% maximal inhibitory efficacy.

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P 3042

Epileptic focus localization with the EEG: The importance of high spatial sampling

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Introduction EEG/MEG source reconstructions have become a valuable technique to non-invasively localize the epileptic focus. However, precise localization depends on the spatial sampling of the electromagnetic field, i.e. on the number of electrodes/sensors. While several studies with large-array MEG systems exist, EEG studies most often use only standard clinical electrode set-up of maximal 32 channels, undersampling the spatial frequency of the electric field. Modern EEG systems now allow fast recordings of high density EEG with more than 100 channels.

Method Interictal epileptiform activity was recorded with 123 electrodes in 14 epileptic patients undergoing presurgical evaluation (5 hippocampal sclerosis, 7 neocortical lesions, 2 non-lesional). All patients became seizure free after operation. Each epileptiform potential was down sampled to 63 and 31 electrodes. A distributed source model (EPIFOCUS) was used to reconstruct the sources in the patient's individual brain with the three different electrode configurations. By calculating the distances from the inverse solution maximum of the individual spikes to the epileptogenic area, the localization accuracy with the three electrode set-ups was assessed.

Results Compared to 31 electrodes, 63 channels led to significantly smaller distances (i.e. better localization) in 9 patients and 123 electrodes to smaller distances in 11 patients. Over all patients the mean distance of the individual spike sources to the epileptogenic area was 16 mm for the 123 channel and 63 channel data and 30 mm for 31 channels.

Conclusion High spatial precision of epileptic source localization can be achieved with the EEG if the electric field is adequately sampled.

P 3043

Incidence of non-epileptic seizures in Georgian inpatient epilepsy population

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Background The incidence of non-epileptic seizures (NES) is significantly higher than clinicians realize. In a number of epidemiological studies conducted, it has been suggested that the incidence of NES is 5–20% and 10–40% in an outpatient and inpatient epilepsy population respectively (Gates J.R.).

Objective To assess the incidence of NES among the patients admitted to the neurological clinic with a preliminary diagnosis of epilepsy.

Methods 344 subjects (all female, aged 18–50, mean age 32.1±1.8) were investigated. All patients were admitted to the Epilepsy Center of Sarajshvili Institute of Neurology and Neurosurgery, Tbilisi, Georgia with a preliminary diagnosis of epilepsy. All subjects were monitored in the clinic over a 2–3 week period. MRI, CT and repeated EEG were performed for all subjects. Patients with pathology discovered by MRI or CT were excluded from the study. In 86 cases EEG-video monitoring was done.

Results For 258 (75%) patients diagnosis of epilepsy was confirmed. In 86 (25%) cases repeated EEG was negative and EEG–video monitoring was performed which revealed 54 (15.7%) cases of NES.

Conclusion The incidence of NES in the Georgian inpatient epilepsy population is comparable to the results of other similar studies (Sigurdardottir KR et al, 1998; Gates 1998). Our findings suggest that in all cases of epileptic seizures when repeated EEG is negative, EEG-video monitoring should be performed in order to exclude NES.

P 3044

Epilepsy in the elderly: A ten years clinical observation in 314 patients

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Objective To individuate in the elderly epilepsy the aetiology and frequent seizure types.

Materials We have analysed in a prospective study 314 epileptic patients 170 males and 144 females, admitted to our Neurologic Department in the last 10 years with epileptic seizures. All patients underwent clinical examination, routine blood laboratory tests, EEG, ECG, brain CT scan and, some of them, angiography and NMR.

Results The causes of epileptic seizures were: 1) acute cerebrovascular disease 110 pts; 2) brain tumour (glioma, meningioma, metastatic) 81 pts; 3) toxic-metabolic 60 pts; 4) dementia 21 pts; 5) head injury 15 pts; 6) marked cerebral atrophy 8 pts; 7) uraemia 4 pts; 8) CNS infection 4 pts; 8) multifactorial aetiology 8 pts; 9) sudden suspension of Lorazepam 3 pts.

Regarding the seizures types 136 pts had generalized tonic-clonic seizures (GTC), 140 simple partial seizures (SPS), 38 partial seizures with secondary generalisation. Regarding the aetiology of the seizures, all toxic-metabolic and due to sudden suspension of Lorazepam had GTC, whereas the majority of the pts. with cerebrovascular disease, brain tumour and head injury had SPS. In the other cases there was an equal distribution between GTC and SPS. Regarding the EEG, 143 pts. showed focal abnormalities, 88 widespread abnormalities and in 83 the EEG was normal. Brain CT scan and MRI was altered in 221 pts. and normal in 93 pts.

Conclusions Epileptic seizures in elderly people are mostly due to focal brain lesions, which must be recognized with suitable, exhaustive investigations.

P 3045

The characteristics of patients with status epilepticus

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Status epilepticus (SE) is common and associated with significant mortality and complications. In this study, we investigated 348 consecutive SE incidents retrospectively to determine the characteristics of the patients, epilepsy, seizure, and SE classifications, etiologic factors for epilepsy and/or SE, therapy, outcome, and the factors affecting morbidity and mortality of SE.

The study group consisted of 273 patients (141 males, 132 females with a mean age of 36) with 348 SE incidents, who were admitted to the neurology clinics between 1989–2001.

The results showed secondarily generalized convulsive SE was the most frequent SE type with a percentage of 80.2. 72.1% of the patients had epilepsy before and over half of these patients (57.3%) had symptomatic partial epilepsy. AED discontinuation and systemic infection were the most frequent etiologic factors for SE in this group. Cerebrovascular accidents were the most frequent factor in the patients presenting with SE as the first seizure. Blood tests showed low level of glucose only in one patient, and 36% of the patients had high levels of glucose. Cranial CT and/or MRI results revealed infarction was the most frequent finding. SE was controlled with one medication in over half of the patients (51%), and only 4.4% needed to have

anaesthesia to control the seizures. Of all the patients 65.2% were discharged without any deficits, 27.3% had neurological deficits, and 7.5% of the patients had died.

Our results revealed old age, generalized convulsive SE, cerebrovascular disease, SE as the first seizure episode were factors rising morbidity and mortality.

P 3046

Levetiracetam in elderly patients with epilepsy

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Rational To evaluate the efficacy and tolerability of levetiracetam (LEV) add on therapy in elderly patients with epilepsy.

Methods Patients ≥ 50 years exposed to LEV in clinical development were analysed. Responder rates ($\geq 50\%$ and 75% seizure reduction) and seizure freedom were calculated and tolerability assessed.

Results 211 patients aged 50–78 years (median 56 years; 14.7% > 65 years; median age at epilepsy onset 24.8 years) were included. Median LEV dose was 3000 mg/day, mean exposure 697 days. 43.6% of the patients took one other AED and 42.7% took two. 43.6% of patients were still receiving treatment at study period end. Treatment was terminated in 19.9% for adverse events (AEs), 15.6% insufficient efficacy, and in 11.8% for study completion. Median seizure reduction from baseline was 43.9% (vs. 39.6% total population) with a decrease of the median seizure frequency from 1.42/week at baseline to 0.84 during LEV. Seizure reductions of either $\geq 50\%$ or $\geq 75\%$ were comparable (37.2% vs. 38.6% and 18.6% vs. 20.1%, respectively). Seizure freedom during the 6 and 12 months prior to final evaluation was greater than in total population (19.0% vs. 11.7% and 15.2% vs. 8.9%, respectively). AEs, mainly CNS-related and mild (e.g. somnolence, asthenia, dizziness), occurred with similar incidence to the total population without increase in effects expected higher in the elderly (e.g. confusion) and no idiosyncratic side effects.

Conclusions In elderly patients, LEV produces higher seizure freedom rates compared to the total population studied, with similar tolerability.

P 3047

Effect of levetiracetam on resistant photosensitivity

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Introduction Photosensitivity is not uncommon in people with uncontrolled primary generalised epilepsy, especially women, and may not respond to conventional anti epileptic treatment (valproate and/or lamotrigine). Levetiracetam (LEV) has previously been shown, in a single dose study, to have a sustained effect on photosensitivity. We report its effect on 20 patients with previously uncontrolled photosensitivity.

Method The notes of 20 patients with uncontrolled photosensitivity in the setting of primary generalised epilepsy and treated, in our department, with LEV were systematically reviewed: all patients had had full photoparoxysmal response assessments before, during and after treatment.

Results All patients treated had either photosensitivity, pattern sensitivity or both: all but one patient completely lost their photoparoxysmal responses: this beneficial result has been sustained on follow-up. 4 patients had eyelid myoclonia, which also responded.

Conclusion LEV appears to be effective in resistant photo and pattern sensitivity. A formal trial of its use in this area is clearly indicated.

P 3048

Effect of Levetiracetam on resistant juvenile myoclonic epilepsy

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Introduction Juvenile Myoclonic Epilepsy (JME) is a common syndrome of early morning myoclonic jerks, absences and tonic clonic seizures, usually treated by sodium valproate or lamotrigine. Not all patients fully respond however, and valproate is relatively contraindicated in women of childbearing potential. Levetiracetam (LEV) is closely related to piracetam, effective in resistant myoclonias, and therefore might be effective in resistant JME. We have been studying its use in this condition in an open study in our department.

Method The notes of 40 patients with resistant JME exposed to treatment with LEV in its usual dose escalation were reviewed for evidence of reduction in seizure frequency and drug-related side effects.

Results 60% of these patients became, and remained, totally seizure free and some have withdrawn from concomitant medication: only 8% had no effect at all. The drug (LEV) seems particularly effective in abolishing myoclonic jerks and concomitant photo or pattern sensitivity. A total daily dose of 4g seems useful in some patients: beneficial results do not fade with the passage of time.

Conclusion This is an impressive result in a group of patients resistant to conventional treatment and suggests that a formal trial of LEV in JME is urgently required.

P 3049

Postischemic stroke epilepsy in the elderly

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Rationale Cerebral ischemia and infarcts are the most frequent cause of epilepsy in the elderly. Seizures occurred in the first week after ischemia (early seizures) corresponds to acute symptomatic seizures, and the late seizures followed about one month after cerebral infarct are included in vascular epilepsy.

Methods This study was performed from January 1999 to January 2002. 139 patients with epileptic seizures and ischemic stroke were identified in our department. The patients were viewed depending on: age, moment of seizure onset, seizures type, recurrence, CT localization of ischemic stroke, atherothrombotic or embolic aetiology, EEG changes.

Results From 139 patients with postischemic stroke epilepsy, 57 presented early seizures (52 patients experienced seizures within 24 hours from the infarction), and 82 patients presented late seizures. Mean age was 67,8 years, 90 patients were men, 49 women. Seizures type were: 49 partial motor, 27 partial motor status, 40 partial motor secondary generalization seizures, 16 tonic-clonic status epilepticus, 7 partial sensitive seizure. The CT localizations of lesions were: 79 cortical, 35 subcortical and thalamic, 25 cortical and subcortical. 33 presented cardioembolic infarcts, 89 patients presented EEG changes, and 20 patients presented recurrent seizures.

Conclusions The incidence of poststroke epilepsy increases with age. The epilepsy risk for men after cerebral infarction is higher than for women. Cortical infarcts (frontal, parietal, occipital) are associated with higher risk for seizures than subcortical infarcts. Cardioembolic cerebral infarcts were risk factors for early seizures.

P 3050

The analysis of electroencephalographic patterns as a predictive factor on post-infarction seizures

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Background and objectives Post-infarction seizures are defined as an ictus that occur following a cerebral infarction in those without a prior seizure history. It is one of the most common causes of epilepsy, particularly in the elderly. There have been only few studies correlating electroencephalographic (EEG) findings to onset of post-infarction seizures. The aim of our study is to analyse EEG patterns that may help to identify those at risk for seizures after an infarction.

Methods Medical records were reviewed on 67 consecutive patients admitted to Pusan National University Hospital (PNUH) from September 2000 to January 2002, with diagnosis of cerebral infarction who had EEG within 2 days of stroke onset. Thirteen patients were identified who subsequently developed new epileptic seizure (post-infarction seizures). We compared EEG abnormalities of the patients with post-infarction seizure and those without seizures. Specific features of EEG patterns; amplitude, persistence, phase relations, morphology, and frequencies were analysed.

Results EEG presence of spike and sharp waves, PLEDs, 2 times high amplitude compare with contralateral lesion side, greater than 60% of abnormal delta wave index, steep ascending phase of slow wave, phase reversal of slow wave on the ipsilateral lesion side correlated with post-infarction seizure onset.

Conclusion This study suggests EEG is helpful in determining the risk for developing epilepsy after cerebral infarction. Risk analysis from baseline EEG shortly after an infarction can be helpful in optimal management.

P 3051

Autoimmune mechanisms in postseizure period in epileptic children

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Epilepsy in 75% of cases begins in childhood. Pathogenic mechanisms of epilepsy development require further analysis.

155 children (75 boys, 80 girls) aging from 3 to 15 were monitored. Along with neurological and EEG examination all patients were subjected to immunological examination in post-seizure period. DNA-antibodies level was determined using immunoenzymatic method on first day after seizure and a month later. The control group included 20 children.

Anamnesis and neurological examination showed that in most cases epilepsy was caused by perinatal brain injury in form of hypoxic-ischemic and traumatic pathology of cerebrum. Seizure pattern in most cases was tonic-clonic and absentia epilepsy state. EEG examination showed epileptic activity in 43.9% and dysfunction of median brain structures in 56.1% cases. Immunological examination showed high anti-DNA level (0.607 ± 0.02 ODU) compared to the control group (0.296 ± 0.002

ODU). Anti-DNA level correlated with seizure frequency and epileptic activity in EEG data. Dynamic monitoring of anti-DNA level a month after the seizure showed its reliable ($p < 0.005$) decrease compared to the first day; however it did not reach the normal value.

High anti-DNA level in post-seizure period and its dynamic decrease approved the presence of an autoimmune process whose intensity tends to diminish with time. Neuron's death leads to releasing of intracellular content and disintegrating of DNA. DNA ejection into extracellular space and its insufficient capture by astroglia causes neuron's death. Induction of specific and nonspecific brain barriers causes apoptosis and immune inflammation. Therefore, appropriate correction is required in post-seizure period in epileptic children.

P 3052

Molecular mechanisms of levetiracetam action on calcium channels in Ca1 hippocampal neurons

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Introduction Previously it was shown that antiepileptic drug levetiracetam (LEV) selectively depress the activity of high voltage activated calcium channels (HVA-CC) in CA1 hippocampal neurons. However the molecular principles of this inhibition are still unknown. Therefore, in the present experiments we studied these mechanisms.

Methods Whole-cell patch clamp and single channel recordings of HVA-CC activity of isolated hippocampal CA1 neurons of rat were performed. A two-pulse protocol was used to study voltage dependence of LEV action on steady-state inactivation, activation of HVA-CC and the time course of recovery from inactivation.

Results We established that in control conditions, the membrane potential at which half-inactivation occurred ($V_{1/2}$) was -10.68 mV and after $200 \mu\text{M}$ LEV application it was -12.24 mV. The slope factor (k) was 8.7 mV and 7.73 mV for control and LEV. Activation characteristics were $V_{1/2} = -6.8$ mV in control and -7.03 mV after LEV application. The k was 9 mV for both cases. The amplitude of tail currents reflecting fraction of calcium channels remaining open at the end of test pulse was not changed by LEV. Usage of depolarising prepulse reversing the possible inhibition of HVA-CC by membrane-delimited action of G-proteins did not reverse the majority of LEV-induced inhibition.

Conclusions We concluded that LEV action slightly depends on extent of channel activation or inactivation and that LEV slightly influences HVA-CC kinetic characteristics. The mechanism of blocking LEV action is not connected with channel deactivation or G-protein pathways underlying LEV-inhibitory effect and presumably depends on direct action on channel molecule. Supported by UCB S.A. Pharma Sector, Belgium.

P 3053

Piracetam (pyramem) in the treatment of cortical myoclonus

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Myoclonus is a rare, disabling symptom arising from a variety of pathologies affecting the nervous system. Involuntary movements can cause severe disability. Conventional treatment with

anticonvulsants such as sodium valproate, clonazepam and primidon often controls the seizures, but not the myoclonus jerks, despite optimum dosage.

The aim of the present study was to assess in an open trial the therapeutic efficacy of Pyramem in patients with cortical myoclonus regardless of its underlying aetiology.

In 10 patients with myoclonic jerks from cortical origin Pyramem was given orally as add-on therapy to valproate and clonazepam. The initial dose of Pyramem was 7.2 g/day increasing every 3 days to maximum 19.2 g/day or until stable clinical benefit was evident. The median daily dose of Pyramem was 15.2 g. Efficacy was assessed using myoclonus rating score (Truong and Fahn, 1988).

A significant improvement with linear dose-effect relation in all patients was observed. Pyramem was well tolerated and essentially free of adverse effects, without drug interaction with the base-line anticonvulsive therapy

P 3054

Causes for drug therapy failure of idiopathic Epilepsies with mixed types of seizures

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Wrong choice of antiepileptic drug (AED) could be the reason for drug therapy failure of idiopathic epilepsies with mixed type of seizures. The aim of our study was to remind and to support this possibility. A total of 28 patients were hospitalised due to refractory of their seizures. The patients were between 12 and 46 years old (20.92±4.54), the onset of the seizures ranged between 5 to 26 years of age (13.25±3.64), while the time duration of the disease was 2 to 25 years (8.89±2.98). The patients were on continuous treatment with carbamazepine, phenobarbiton, phenytoin and primidon, as mono- or polytherapy from the seizure onset until the moment of their hospitalisation.

Careful investigations allowed to revise the diagnosis on the following way: 15 patients suffered from juvenile myoclonus epilepsy (JME), 11 patients from grand mal on waking, 1 from juvenile absence epilepsy (JAE), and 1 patient from phantom absences and grand mal. Previous therapy in all of them was replaced with monotherapy of valproate. At least one year complete control of GTCS was achieved in all patients with JME, in 9 of 11 patients with grand mal on waking and in the other 2 patients.

Carbamazepine, phenobarbiton, phenytoin and primidon appeared to be ineffective AED in our group of patients with mixed types of seizures. Contrary, valproate showed more satisfactory effect.

P 3055

Effect of antiepileptic drug monotherapy on crystalluria in children and young adults

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Introduction Urolithiasis is a rare side effect of antiepileptic drugs (AEDs) in children and young adults. Because crystalluria is frequently associated with urolithiasis, the relationship between AEDs and crystalluria was investigated for the first time.

Methods Urinalysis was retrospectively studied in epilepsy patients treated with AED monotherapy for more than one month. A total of 886 urinary specimens were enrolled from

AED-taking patients aged from five months to 28 years. They were compared with urine samples from 780 age-matched controls and 112 patients before starting AEDs. AEDs administered in this study were: carbamazepine, valproate, phenobarbital, zonisamide (ZNS), sulthiame (STM) and phenytoin.

Results The frequency of crystalluria was higher in patients treated with ZNS ($p<0.0001$) or STM ($p<0.05$) than that in controls, other AEDs and patients before starting AEDs. The age was higher in controls with crystalluria than that in controls without crystalluria ($p<0.001$). There was no such age difference in patients treated with ZNS or STM. The blood concentration of STM was higher in patients with crystalluria than that without crystalluria ($p<0.05$). There was no such difference in ZNS-taking patients. Male patients on ZNS therapy were more likely to have crystalluria than female patients ($p<0.001$). There was no such sex difference in patients on STM therapy.

Conclusions Patients treated with ZNS or STM are likely to have urolithiasis. Male patients on ZNS therapy and high blood concentration of STM are risk factors for urolithiasis.

P 3056

Levetiracetam in combination with other antiepileptic drugs shows enhanced antiepileptic activity in animal models

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Introduction While monotherapy remains the treatment of choice for epilepsy, seizure control is not always achieved and rational polypharmacy is undertaken. The combined action of different antiepileptic drugs (AEDs) is an important subject, not only in reference to seizure control, but also in the context of obviating adverse events. This study utilized a preclinical paradigm to investigate the anticonvulsant effects, pharmacokinetic profile and CNS adverse effects associated with combination therapy using levetiracetam (LEV) and some of the more classical AEDs.

Methods Genetically sound-sensitive male mice ($n=10$ /group) were assessed for protective ED₅₀ determinations of classical AEDs, valproate (VPA), clonazepam (CZP), phenobarbital (PB), carbamazepine (CBZ), and phenytoin (PHT) and for LEV. LEV (fixed dose of 5.5 mg/kg) was combined with the other AEDs and a dose-response curve of protection against clonic convulsions was calculated. Doses inducing CNS adverse effects (TD₅₀) were determined by rotarod impairment and compared with combination therapy. Plasma and brain AED levels were determined by GC/MS, GC/EC, HPLC/UV and FPIA analysis.

Results Co-administration of LEV with VPA, CZP, PB, CBZ and PHT enhanced anticonvulsant potency, resulting in 28-, 23-, 16-, and 2-fold increases, respectively. Conversely, there was no enhancement of the CNS adverse effects. The plasma and brain levels of LEV and the other AEDs were not modified during co-administration.

Discussion The results of this study suggest that co-administration of LEV with VPA, CZP and PB markedly enhances anticonvulsant potency while not increasing CNS adverse effects, suggesting a synergistic pharmacodynamic effect.

P 3057

Pilocarpine-induced status epilepticus: effects of chronic treatment with levetiracetam and valproateH. V. Klitgaard¹, A. C. Matagne, J. Vanneste-Goemaere, D. Margineanu*Preclinical CNS Research, UCB SA Pharma Sector, Braine l'Alleud, BELGIUM*

Introduction Status epilepticus (SE) is a neurological emergency and associated with a high morbidity/mortality rate. The aim of this study was to induce epileptogenesis in rats by administration of pilocarpine (PILO; ip) and to compare the anti-epileptogenic effects of levetiracetam (LEV) and valproate (VPA). **Methods** Male Sprague-Dawley rats were administered PILO (375 mg/kg, ip) and SE terminated after 30 min with diazepam (10 mg/kg; iv). Separate groups were administered either LEV (54 mg/kg; ip) followed by 21 days LEV infusion (50, 150, or 300 mg/kg/d) or VPA (200 mg/kg; ip), followed by 21 days VPA infusion (600 mg/kg/d). The incidence of spontaneous seizure, evoked field potentials (DG and CA1 hippocampal areas), and hippocampal histopathology were examined 3 days after termination of the chronic infusion.

Results The incidence of spontaneous seizures did not differ between groups. LEV treatment dose-dependently reduced the increase in population spike (PS) amplitude in the DG area; while VPA treatment reduced, not significantly, the PS amplitude. Paired-pulse inhibition in the hippocampal CA1 was eliminated in PILO-treated rats, but restored by LEV, but not VPA, treatment. LEV treatment (150, 300 mg/kg/d) reduced, not significantly, the PILO-induced hippocampal necroses; no difference was observed in the VPA-treated animals.

Conclusion LEV treatment (150, 300 mg/kg/d) reduced the epileptogenic effect induced by PILO, as 1) a reduction in amplitude of the PSs, 2) a restoration of paired-pulse inhibition and 3) a modest decrease in neuropathological consequences. VPA (600 mg/kg/d) did not reveal any significant effects on these parameters.

P 3058

Levetiracetam has no measurable binding to, or observed antagonist effect at, metabotropic glutamate receptorsB. A. Lynch¹, A. C. Matagne², H. V. Klitgaard²*¹Cell and Molecular Research, UCB Research, Cambridge, MA, ²Preclinical CNS Research, UCB SA Pharma Sector, Braine l'Alleud, BELGIUM*

Introduction Levetiracetam (LEV) is an antiepileptic drug utilized as adjunctive therapy for partial seizures in adults. Because the exact molecular mechanism of action of LEV is currently unclear, we tested whether LEV might act by modulating metabotropic glutamate receptors (mGluRs). Several mGluR family members have been linked to seizure activity, making this family of receptors attractive as potential sites of LEV action.

Methods We utilized 3H-LEV as a probe to examine the binding of several mGluR ligands at a brain-specific binding site for LEV. To further test this compound, in vivo experiments evaluated the ability of LEV to counteract behavioural changes induced in mice by intracerebroventricular infusion of 1S,3R-ACPD (200 nmol/min).

Results Neither glutamic acid nor any of the subtype specific mGluR ligands (S)-AP-4, quisqualic acid, and (2S, 3S, 4S)-CCG, displaced 3H-LEV in crude rat brain membranes. However, there was a minor displacement observed with the non-specific mGluR agonist 1S,3R-ACPD. In contrast, LEV

(5.4–170 mg/kg; i.p. –60 min) did not significantly prevent the face washing and hind limb scratching induced by 1S,3R-ACPD.

Conclusions Various ligands known to interact with mGluRs did not displace 3H-LEV in crude rat brain membranes. While LEV did cause a modest displacement of the non-specific mGluR agonist, 1S,3R-ACPD, there was no change in the glutamate agonist-induced behaviour. These results suggest that the antiepileptic mechanism of LEV appears to be unrelated to a modulation of mGluRs.

P 3059

Levetiracetam does not alter body weight: analysis of randomised, controlled clinical trials.B. E. Gidal¹, R. D. Sheth¹, L. M. Magnus², A. Herbeuval²*¹University of Wisconsin -Madison, Madison, WI, USA,**²UCB Pharma, Inc., Smyrna, GA, USA*

Introduction Body weight increase is a clinically significant adverse effect of several antiepileptic drugs (AED) including valproate and gabapentin. The objective of this evaluation was to examine the effects of LEV treatment on weight.

Methods We reviewed data from 4 prospective, placebo (PBO)-controlled, clinical trials. The analysis included men and women, >16 years old, who had LEV exposure for ≥ 1 month. Body weight was measured at baseline and final LEV study visit. Data was analysed by gender, body mass index (BMI), duration of LEV exposure and concomitant AED treatment. Data presented is mean values (SD).

Results Analysis included 970 patients (mean 37.5 years, 54% men/46% women); LEV (n=631) PBO (n=339). Mean LEV dose was 2053mg/d (maximum 4000mg/d) and duration was 125 days (max=181 days). Concomitant AED therapy included CBZ=647, GBP=92, LTG=89, PHT=207, VPA=196, PB=77, VGB=75 patients.

Mean body weight at baseline vs final study visit at 1–3 months and >3 months for LEV patients was 74.3 (16.6), 76.6 (17.5) and 75.8 (16.8) kg, respectively (NS). For PBO, 72.4 (15.5), 74.0 (16.8) and 74.6 (16.9) kg (NS). Clinically significant weight change, defined as >7% change from baseline, occurred in 8.8% of LEV patients (4.4% increase/4.4% decrease) vs 9.4% (5.9% increase/3.5% decrease) in PBO. Subgroup analysis revealed that only male patients receiving PBO had modest, yet statistically significant weight change (+0.8–1.0 kg in n=148 with BMI=19–30, p<0.003).

Conclusions We conclude that treatment with LEV was not associated with weight change during controlled clinical trials. LEV appears to be a weight neutral AED.

P 3060

Dose-response relationship of LevetiracetamM. D. Privitera¹, P. Edrich², P. Godfroid³*¹University of Cincinnati, Cincinnati, OH, USA, ²UCB Pharma, Brussels, BELGIUM, ³UCB Pharma, Brussels, BELGIUM*

Objective To evaluate the dose-response relationship (efficacy and tolerability) of levetiracetam (LEV) as adjunctive therapy in adult patients with partial epilepsy.

Methods Pooled data from double-blind, randomised, placebo-controlled trials (n=904) were used to assess the efficacy of LEV at doses of 1000–3000mg/day. Both periods of a cross-over study were analysed and a within-patient (n=93) cross over analysis, comparing LEV 1000 mg and 2000mg, conducted. Tolerability to LEV was also assessed in these trials, including

both cross-over periods, and an additional safety study (n=119), a total of 1023 patients.

Results A dose-response relationship was observed with LEV for $\geq 50\%$ responder rates; increasing from 29% at 1000 mg, 34% at 2000 mg and 41% at 3000 mg. Within patient analysis for 1000 mg and 2000 mg/day LEV showed 2000 mg to increase responder rate by 33–70% and odds of obtaining response by 4.2 compared to 1000 mg (98% CI: 1.0, 17.2). Seizure freedom (the ultimate aim of treatment) also showed a dose-response to LEV; 4.7%, 6.3% and 8.6% at 1000 mg, 2000 mg and 3000 mg doses respectively. There was no evidence for a dose-related adverse effects relationship (asthenia, dizziness and somnolence) at doses of 1000 mg to 3000 mg. At 4000 mg doses, somnolence occurred more frequently. However this group consisted of only 38 patients who started immediately on LEV 4000 mg without dose titration.

Conclusion LEV was effective and well tolerated decreasing seizure frequency in a dose-dependent manner with 3000 mg/day providing the greatest seizure freedom.

P 3061

Interactions of lamotrigine with some antiepileptic drugs – an isobolographic analysis

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The isobolographic analysis distinguishes 3 most important types of interactions, among them the most accepted are: pure additivity, supra-additivity and sub-additivity.

The present study was aimed at determining the exact type of interactions between lamotrigine (LTG) and diphenylhydantoin, carbamazepine, valproate, phenobarbital and topiramate in the maximal electroshock seizure (MES) test in mice. The activity of two-drug mixture, applied in 3 fixed dose ratio combinations, was estimated and expressed as the ED₅₀ values (dose protecting 50% of animals) of these drugs against MES-induced seizures in mice. Moreover, the adverse effects were determined in the chimney test and passive avoidance task in mice.

Interactions between LTG and topiramate or phenobarbital caused a supra-additive interaction as regards their therapeutic activity in the MES test. Simultaneously, the interaction of LTG and topiramate demonstrated a sub-additivity in respect to evoked side effects in the chimney test, whilst the interaction of LTG and phenobarbital in this respect, was supra-additive. Isobolographic analysis revealed the antagonistic interaction between LTG and carbamazepine in the MES test. In contrast, interactions between LTG and diphenylhydantoin or valproate showed a pure additivity, in both MES and chimney tests. Moreover, all combinations of LTG with studied antiepileptics induced no adverse effects, evaluated in the passive avoidance task.

Finally, the isobolographic analysis revealed that LTG combined with topiramate, diphenylhydantoin or valproate generally might result in positive (additive or supra-additive) interactions, in the clinical practice.

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P 3062

Epileptic seizures in children with cerebral paralysis

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Introduction Cerebral paralysis is usually defined as non-progressive disorder with motor disturbances caused by the lesion of the immature brain, which is also a reason of increased excitability and decreased inhibition responsible for the seizures.

Objectives Establish the frequency of the seizures in children suffering from cerebral paralysis and the age at which the attacks are most frequent.

– Most common form of seizures.

– The possibility of controlling the attacks with conventional and new antiepileptics.

Methods A group of 34 patients under 13 years old was analysed (19 males and 15 females) treated in the Krusevac Hospital under the diagnosis of CP in the period of five years.

Results Seizures are recorded in 16 cases (46.5%). In 12/16 patients (75%) the attacks started in the first two years of their life. In 2/16 (12.5%) patients the first seizure happened after the age of 10.

Based on the EEG results we established that the most common type of seizures are partial or secondary generalised seizures.

Epileptiform EEG changes were registered also with children who don't have epilepsy.

Control of the seizures with conventional and new antiepileptics was accomplished in 10/16 (62.5%) patients and incomplete control in 6 patients (37.5%) – with monotherapy in 6/16 (31.24%) and polytherapy in 10/16 (68.76%) patients.

P 3063

Serum thyroid hormones concentrations in postmenopausal women with epilepsy

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Purpose The aim of the study was to evaluate the serum T4, FT4, T3, FT3 and TSH concentrations in postmenopausal epileptic women.

Material and methods 20 postmenopausal women aged 51–65 treated because of epilepsy for 5–49 years were studied. The seizure frequency amounted to several seizures per month and several per year. Fifteen patients received CBZ (3 of them with PHT) and 8 women were treated with PHT (3 of them with CBZ). The control group consisted of 20 healthy women. In all women serum concentrations of T4, FT4, T3, FT3 and TSH were performed by RIA taking blood samples at 8.00.

Results Mean serum T4, FT4, FT3 and TSH concentrations in postmenopausal women with epilepsy were significantly decreased and mean serum T3 concentration was significantly increased as compared with the control group. There were no significant correlations between mean serum hormone concentrations and the aetiology of epilepsy, the seizure type, the seizure frequency and the treatment applied. None of the patients developed symptoms of hypothyroidism.

Conclusions In our patients inducers of the liver microsomal enzymes probably caused an increased metabolism of thyroid hormones – T4, FT4 and FT3. There is also a possibility of decreased hormones synthesis in the thyroid gland. Signifi-

cantly increased serum T3 concentration suggests that CBZ and PHT increase the conversion of T4 to T3. The decreased serum TSH concentration may suggest that the feedback system is not activated.

P 3064

Subacute encephalopathy with seizures in alcoholism (SESA); more common than described?

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SESA syndrome is a very rarely reported dramatic complication of chronic alcoholism first described by Niedermeyer in 1981.

We are presenting cases of three chronic alcohol abusers who developed recurrent seizures and prolonged encephalopathy. Focal neurologic signs were found on examination. The results of neuroimaging and CSF investigations were unremarkable. The EEG changes were, however, severe, with periodic poly-spikes evolving to PLEDs, focal slowing and gradually improving. Two patients developed pneumonia through the course of the disease. All patients eventually recovered.

SESA syndrome consists of prolonged encephalopathy, focal or generalised seizures, focal neurologic signs and prominent focal EEG changes without gross structural lesions. Patients often develop internal medical complications and usually recover.

With our cases we would like to remind clinicians about this severe complication of chronic alcoholism, with relatively good prognosis. According to our observations the SESA syndrome is more common than described.

P 3065

Juvenile myoclonic epilepsy in the elderly

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Juvenile Myoclonic Epilepsy (JME) is an idiopathic generalized epileptic syndrome that has only recently attracted considerable attention. Remarkably, JME is often diagnosed with delay because of physicians involved, including the specialists, are not familiar with a disease whose nature has yet to unfold. JME is believed to be a lifelong epilepsy. However, this view has been debated from time to time. In a total of 37 patients with JME (mean age: 22.5 years) attending our epilepsy out-patients' clinic at the 1st University Department of Neurology, we present two cases where definitive diagnosis of JME was delayed until the age of 60 and 65. The two patients, a male and a female, fulfilled the diagnostic criteria for JME. They presented refractory seizures (myoclonic jerks and tonic-clonic) and were treated with carbamazepine, vigabatrin, phenobarbital, phenytoin and gabapentin. MRA demonstrated multiple gliotic lesions. We conclude that the small percentage of elderly patients with JME in our group of patients with JME suggests that JME is not a lifelong epilepsy. The two cases may represent two non-diagnosed cases in which the delay in diagnosis and the non-appropriate treatment provoked secondary lesions in the brain, which conserved the epilepsy.

P 3066

The role of inherent tendency to febrile seizures

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Objective Recent investigations [1, 2] support the opinion that epilepsy is either an inherent disease or has a genetic tendency. It was found out a tendency to seizure reactions on hyperthermia with age-dependent penetration.

Methods To research the role of inherent factors for appearing of febrile seizures and to define genetic interrelations between febrile seizures and epilepsy we investigated a family history of 33 children with unique episode of febrile seizures and 26 children with recurrent febrile seizures. Age of the children was from 4 to 6 years. EEG was performed for all the children and their relatives.

Results Examination of relatives of the children with febrile seizures demonstrated that 14% of parents, 25% of sibs, 7% of aunts and uncles, 10% of cousins had the same seizures. Incidence of epilepsy among relatives was 10%. Different conditions suggested by many authors as epi-equivalents (headache, enuresis, etc.) occurred in 33% of cases.

Conclusion The febrile seizures appear and repeat with a lower body temperature including a subfebrile one if inherent burdening of epilepsy and/or febrile seizures occurs both in paternal and maternal lines.

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P 3067

Epileptic seizures related to ischemic stroke

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Cerebral ischemias are the largest group of strokes and the most frequent cause of epileptic seizures and vascular epilepsy.

Purpose To study risk factors, clinical polymorphism and morphology of seizures occurred in patients with cerebral ischemic stroke, to find correlations between clinical, biochemical, electrophysiological and neuroimaging findings.

Methods We examined 1162 patients with ischemic stroke hospitalised in Clinic of Neurology of Emergency City Hospital during 1997–2001. 58 of them developed epileptic seizures and underwent: clinical examination, laboratory tests determining fat metabolism and inflammatory markers, EEG, EEG mapping, and cerebral CT or MRI investigations.

Results In our study 58 (4.99%) patients, 34 (58.6%) male and 24 (41.4%) female, with mean age of 58–98 years, developed vascular epileptic seizures. 25 patients (43%) have early seizures, and 33 (57%) late seizures. The morphology of fits was following: 4 cases – generalized absence seizures, 3 cases – status epilepticus, and 51 (87.9%) – partial secondary generalized seizures. In about 60% total cholesterol, LDL cholesterol and beta-lipoproteins were elevated. The localization of focal component was alike that of cerebral infarction. In 70% of patients specific paroxysmal EEG changes were observed. Cerebral CT and MRI revealed ischemic foci with cortical and subcortical involvement.

Conclusion Morphology of post-stroke seizures in majority of cases was represented by partial secondary generalized seizures; localization of focal component was similar with localization of cerebral infarction, CT and MRI revealed cortical involvement. An elevation of total cholesterol and its derivatives is observed in most of the patients.

P 3068

Onset determining factors for post-traumatic epilepsy

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Head traumas (HT) accounts approximately 30–40% of all traumas and represents the major cause of disability in young adults. Post-traumatic epilepsy (PE) is one of the most severe consequences of HT. Occurring in early period of HT post-traumatic seizures are often ignored and not treated specifically in time.

The **aim** of the study was evaluation of risk factors for post-traumatic epilepsy.

Materials and Methods Our study was performed in a group of 84 patients with PE, 58 of whom were males and 28 females. Studied patients were in the age ranges: 20–30 years – 17 persons; 31–40 years – 25 persons; 51–60 years – 10 persons. Patients' personal history was collected in order to evaluate precipitating factors as following: febrile seizures in childhood, enuresis, sleepwalking, family or personal history of inherited epilepsy or psychic disorder, episodic loss of consciousness. The three most important HT forms were: in 37.5% – concussion, in 57.5% – cerebral contusion, and in 5% – opened cranial cerebral trauma. Epileptic seizures occurred at different time periods after HT. Thus the PE incidence is about 17% during first 3 months after HT, 28.5% – during further 3–12 months and 55.5% – after one year following HT.

Results Our study revealed that PE was caused by following factors: cerebral contusion, opened craniocerebral trauma, recurrent HT, loss of consciousness, early post-traumatic seizures.

Conclusions Evaluation of risk factors for PE makes possible early diagnosis of PE, initiation of early specific treatment and prevention of severe disability caused by epilepsy.

P 3069

Does familiarity affect attitude and practice toward epilepsy?

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Social acceptance of epilepsy is a burden for patients and their relatives. The awareness, understanding and attitudes towards epilepsy were evaluated in a pilot study with 250 persons. The survey consisted of 10 questions and was conducted by one-to-one interview. Regarding all subjects 81% had heard about epilepsy; 73% had no objections to social association; 66% believed that epileptics should be employed in equal jobs. Older age and less education showed a non-significant trend to negative attitude. This population has been divided into two strata: those who know someone with epilepsy (FWE) and those who do not (NFWE). Prejudice toward the disease did not differ between groups; 71% of NFWE and 73% of FWE did not object to their children associating with epileptic ones; 70% of NFWE and 67% of FWE objected to their children marrying an epileptic person; 57% of NFWE and 53% of FWE believed that epileptic persons should be employed in jobs like other persons;

36% of NFWE and 13% of FWE group had no opinion about the cause of epilepsy; 28% of NFWE and 6% of FWE responded that they did not know how to help a person having seizure. Knowledge and practice were not different between groups. Familiarity did not improve the attitude toward disease as would be expected. Community health education should attempt to concentrate on first aid measures.

P 3070

Myths and ideas concerning epilepsy among relatives of Portuguese epileptic patients

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Introduction The SPOKE trial showed that Portugal ranks second among countries with the least informed population as far as epilepsy is concerned.

We wanted to know if the relatives of epileptic patients attending our consultation had accurate notions regarding the disease, compared to those of the general population.

Methods We applied a questionnaire to 101 individuals – 45 relatives – R; 56 non-relatives – NR. Statistical analysis used non-parametric tests of *Qui-quadrante* and exact test of Fisher.

Results 84% said epilepsy was a neurological disease (100% of R, 71.4% of NR); 13% a psychiatric disease (23.2% of NR); 1% an infectious disease (1.8% of NR); 2% of another aetiology (3.6% of NR). 81% identified a connection between alcohol, stress and epilepsy (91% of R, 73% of NR). 58% denied connection with mental retardation (47% of R, 68% of NR). 76% admitted hereditary factors (84% of R, 70% of NR). 84% said epileptic patients could have normal lives (87% of R, 82% of NR) and regarding work, family and treatment the answers were similar in both groups. 80% had witnessed a seizure (93% of R, 70% of NR). Regarding what to do during a seizure: R chose removing sharp objects and calling the emergency number (EN); NR chose calling EN and placing an object inside the patients' mouth.

Conclusions Relatives showed good knowledge of the disease, although in general questions the results were similar in both groups. In specific questions and practical issues, the answers were significantly better among relatives.

P 3071

Law regulations, driving ability of patients with epilepsy and traffic safety

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Our Law has draconian regulations: a person having got one single epileptic seizure is forbidden to drive, and the doctors are obliged to report their patients having seizures. The aim of this study was to see how much this law regulation has been respected by the patients and by the doctors.

We have interviewed 99 patients with epilepsy with seizure experience between 3 to 33 year-old (9.85 ± 3.1) for respectability of law regulations. Seventy-five (75.75%) patients did not respect the legal prohibition; 11 of these 75 patients acquired driving licence after the disease onset, the other patients had their driving licence prior to seizure onset.

All patients interviewed had regular antiepileptic therapy. Thirty-three (44%) of these 75 patients did not reach a two-year interval without seizures. Majority of them drove private cars, but nine of them were professional drivers of cars. Nine (12%) of these 75 patients with poor seizures control were participants

in traffic accidents (8 with material damage, and one died, the last one was a doctor). The doctors did not obey their duty to report their patients, but they always informed the patients for the character of the disease and the duties arising from the Law.

It becomes clear that more strict law has not been obeyed by anyone and makes the situation which endangers the lives of the patients as well as the lives of other traffic participants. From here arises the need for its essential change and introduction of more liberal solutions.

P 3072

Prefrontal "cortex" and system of antiepileptic defence: experimental and clinical – neurophysiological investigations.

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P 3073

Cancelled

P 3074

Adjunct anti-primary generalised seizure adjunct therapy for 39 case of refractory PGE (Primary generalised epilepsy)

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P 3075

Primary generalized epileptic seizures and Föhn in Bielsko-Biala

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P 3076

Fuzzy logic based on clinical evaluation of patients with complex partial epilepsy; Case Studies

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P 3077

Fluctuating isolated memory impairment; an unusual case of temporal epilepsy

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P 3078

Our experiences in the use of MRS in children with different types of epilepsy

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