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Purpose: SP616 was a double-blind, double-dummy investigation of the pharmacokinetics, safety and tolerability of intravenous (iv) lacosamide (LCM) as a replacement of adjunctive oral LCM in adults with partial-onset seizures.

Method: Subjects (n = 60) currently receiving adjunctive, stable, twice daily (bid) doses (200 to 600 mg/day) of oral LCM were randomised 2:1 to receive iv LCM plus oral placebo (PBO) bid or iv PBO plus oral LCM bid for two consecutive days. Subjects (n = 30) in Cohort A received 60-minute infusions. Cohort B subjects (n = 30) received 30-minute infusions. Serial ECGs and vital signs data were collected. Pharmacokinetic sampling was performed for the morning dose on day 2 for both cohorts at predose and hours 0.5, 1, 1.5, 2, 4, 8, and 12.

Results: Fifty-nine subjects completed the trial. No clear differences in AE reports, ECG intervals, blood pressure, or heart rate were observed for iv versus oral dosing.

60- and 30-minute LCM infusions resulted in similar plasma concentration time curves and pharmacokinetic parameters compared with oral administration after normalisation for body weight and dose. The t_{max} most commonly occurred at the end of LCM infusion (eg, 30 min for Group B) and later for oral LCM dosing (eg, 1.5 to 4 hr for 55% of subjects in Group B).

Conclusion: The safety profile following 60- and 30-minute LCM infusions was comparable to oral LCM. In addition, both LCM infusion rates resulted in similar pharmacokinetics to oral dosing. Funding supported by: Schwarz Biosciences, Inc.

045

INCREASED APPARENT ORAL CLEARANCE OF VALPROIC ACID DURING INTAKE OF COMBINED CONTRACEPTIVE STEROIDS IN WOMEN WITH EPILEPSY

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Purpose: Combined contraceptive steroids (CS) stimulate the glucuronidation of paracetamol, some benzodiazepines, and lamotrigine. As a result of this, the serum levels of lamotrigine are considerably higher at the end of a 7-day CS-free interval than during CS intake (*Epilepsia* 2004;45(suppl 7:330). Valproic acid (VPA) undergoes extensive glucuronide conjugation, and a case report suggested that VPA clearance is also increased by CS (*Epilepsia* 2005;46:970–1). We assessed serum VPA concentration in women with epilepsy in relation to a CS intake cycle.

Method: Nine women aged 18–45 years and stabilised on VPA (500–1500 mg/day) in combination with oral or transdermal CS, without associated antiepileptic drugs, were assessed on two randomised occasions: (i) on the last day of CS intake, and (ii) on day 4 to 7 of the CS-free interval. Serum VPA levels were determined by immunoassay.

Results: Mean total VPA concentrations were 21% higher during the CS-free interval than during CS intake (425 ± 184 vs 350 ± 145 (μmol/L respectively, means $\pm$ SD, $p = 0.002$). Unbound, pharmacologically active, VPA levels increased in parallel by 41%, from 39 ± 25 to 55 ± 37 (μmol/L ($p = 0.005$).

Conclusion: Serum VPA concentrations increase during the interval of interruption of CS intake. This is consistent with a stimulating effect of CS on the enzymes responsible for VPA metabolism, presumably due to induction of glucuronosyltransferases by ethinyloestradiol. The magnitude of interaction varies across patients, and may be clinically significant in some cases.

046

PROPHYLACTIC EFFECT OF FOLIC ACID SUPPLEMENTATION ON SPONTANEOUS ABORTION IN WOMEN WITH EPILEPSY UNDERGOING ANTIEPILEPTIC THERAPY

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Purpose: Antiepileptic drugs (AEDs) like phenytoin (PHT), carbamazepine (CBZ), barbiturates and valproic acid (VPA) interfere with folic acid absorption and metabolism, and consequently can elevate risk for adverse pregnancy outcome. Our objective was to study the prophylactic effect of folic acid supplementation with regard to spontaneous abortion in pregnant women receiving AED therapy and compare benefits of most common dosage and pre- and postconceptional commencement.

Method: Retrospective analysis of data from our epilepsy data bank completed with medical records and patients interviews and in some cases prospective examination of 388 pregnancies in 244 patients of the Department of Neurology of Innsbruck University Hospital from 1971 to 2004.

Results: Pregnancies with folic acid supplementation showed a significantly reduced rate of spontaneous abortions. In women without folic acid supplementation spontaneous abortion occurred in 14.5% compared to 6.3% when folic acid had been taken during pregnancy (odds ratio:2.6, 95% CI:1.2–5.3, $p = 0.007$). Supplementation with 5 mg/d had no advantage over 0.4 mg/d. Preconception commencement of supplementation showed no larger benefit. Folate benefits were higher in pregnancies under AED monotherapy than under polytherapy. With regard to monotherapies, only women in the group taking VPA supplementation had a significant benefit. Other examined monotherapies (CBZ, PHT, PB, LTG, and OXC) showed no significant results.

Conclusion: This study confirms the prophylactic effect of folic acid supplementation on spontaneous abortion. Data did not show clear advantage for dosage of 5 mg/day or preconception commencement, but underlined the particular profit for women under AED monotherapy, especially for those who are taking VPA.

047

DRUG INTERACTION BETWEEN PHENPROCOUMON AND VALPROATE: CLINICALLY RELEVANT INCREASE OF INR IN PATIENTS WITH ISCHEMIC STROKE AND SYMPTOMATIC SEIZURES

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Purpose: Cotreatment with the oral anticoagulant phenprocoumon and valproate is common, especially in patients suffering from cardioembolic stroke and symptomatic seizures. There are no reports of clinically relevant interactions between these drugs.

Method: We reviewed the data of all patients of our neurological department within the last 38 months. Two groups of patients were identified: group 1 was treated with valproate in addition to established phenprocoumon therapy, whereas in group 2 phenprocoumon was started either at the same time or in addition to valproate. For group 1, the latest available International Normalized Ratio (INR) values were achieved, mean values calculated and correlated to the maximum INR values shortly after the initiation of valproate. Patients were excluded if the dosage of the drugs during the relevant time was unknown or compliance was insufficient.

Results: 18 patients received a combined treatment with valproate and phenprocoumon. Three patients met exclusion criteria, the remaining patients were divided into group 1 (11 patients) and group 2 (4 patients). Means of INR values in group 1 before treatment with valproate ranged between 1.6 and 3.2 (SD 0.05–1.22) and raised significantly after initiation of valproate (mean +77%, range from +45 to +138%). In group 2, the intended INR values were achieved with unexpectedly low doses of phenprocoumon.

Conclusion: There is a clinically relevant interaction between valproate and phenprocoumon. Patients on valproate need unusually low doses of phenprocoumon for active anticoagulation. In patients receiving valproate with preexisting phenprocoumon a potentially hazardous rise of INR has to be observed.