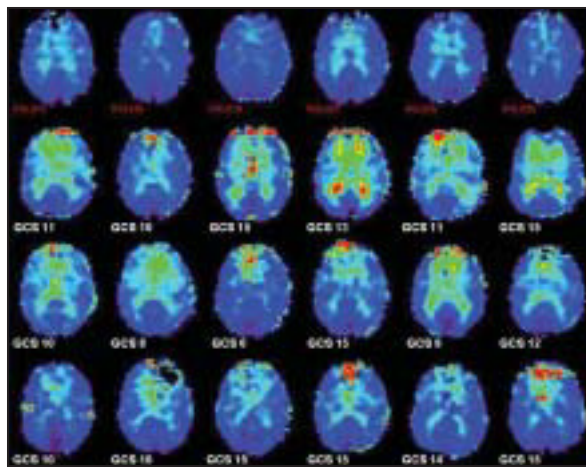


Magnetic resonance spectroscopic imaging of the brains of 18 traumatic brain injury patients (bottom three rows) show widespread alterations in the ratio of choline to N-acetyl aspartate (light blue to green color), unlike the brains of 6 control subjects (top row).



IMAGES COURTESY DR. ANDREW A. MAUDSLEY

Continued from previous page

in the brain. The pilot study compared the average of all measured values from 22 patients who were classified as having mild brain injury with the average values from 67 age-matched controls. MRSI scans took place a median of 21 days after the patients' injuries, which were caused by motor vehicle accidents (17), falls (2), or assault (3).

Assessments of the group averages revealed that brain injury was associated with a significantly decreased level of N-acetylaspartate (a marker of neuronal

and axonal viability), as well as an increased level of choline (a marker of membrane metabolism). The ratio of choline to N-acetylaspartate was the most sensitive marker for injury.

Overall, 90% of the patients had small and well-localized lesions on normal MRI, findings that are typical for mild TBI. But on MRSI, the researchers found widespread metabolite alterations throughout the cerebrum.

The patients' scores on neuropsychological tests were significantly correlated mostly with metabolite changes in the right frontal region. In one patient who underwent follow-up scans, the concentrations of N-acetylaspartate and choline continued to change significantly at 7 and 15 months post injury.

Dr. Maudsley said that he and his team hope to obtain longitudinal assessments of metabolite levels to determine if their short-term levels can predict future outcomes of patients with mild TBI. Outcomes at 6 months in close to half of the patients have shown some correlations between metabolite levels and scores on neuropsychological tests, he said.

"It's my feeling that these metabolites really take several days, if not a couple of weeks, to change. In the one example in which we had a more severe injury, things were actually worse at 6 months than they were at 5 weeks," he added.

The use of the 3-tesla MR scanners that Dr. Maudsley and his associates used in their study is beginning to extend beyond academic medical centers and into regular clinics, especially for brain MRI applications.

Neither Dr. Huang nor Dr. Maudsley had conflicts of interest to report. ■

Table 2: (continued) Incidence (%) Of Treatment-Emergent Adverse Reactions In Placebo-Controlled, Add-On Studies In Adults Experiencing Partial Onset Seizures By Body System (Adverse Reactions Occurred In At Least 1% Of Immediate-Release KEPPRA-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/ Adverse Reaction	Immediate-Release KEPPRA (N=769) %	Placebo (N=439) %
Hostility	2	1
Paresthesia	2	1
Emotional Lability	2	0
Respiratory System		
Pharyngitis	6	4
Rhinitis	4	3
Cough Increased	2	1
Sinusitis	2	1
Special Senses		
Diplopia	2	1

In addition, the following adverse reactions were seen in other well-controlled studies of immediate-release KEPPRA tablets: balance disorder, disturbance in attention, eczema, hyperkinesia, memory impairment, myalgia, personality disorders, pruritus, and vision blurred.

Postmarketing Experience In addition to the adverse reactions listed above for immediate-release KEPPRA tablets [see Adverse Reactions, Clinical Studies Experience], the following adverse events have been identified during postapproval use of immediate-release KEPPRA tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The listing is alphabetized: abnormal liver function test, hepatic failure, hepatitis, leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), suicidal behavior (including completed suicide), thrombocytopenia and weight loss. Alopecia has been reported with immediate-release KEPPRA use; recovery was observed in majority of cases where immediate-release KEPPRA was discontinued.

DRUG INTERACTIONS

General Information *In vitro* data on metabolic interactions indicate that KEPPRA XR is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C_{max} levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, valproate, oral contraceptive, digoxin, warfarin, probenecid) and through pharmacokinetic screening with immediate-release KEPPRA tablets in the placebo-controlled clinical studies in epilepsy patients. The following are the results of these studies. The potential for drug interactions for KEPPRA XR is expected to be essentially the same as that with immediate-release KEPPRA tablets.

Phenytoin Immediate-release KEPPRA tablets (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

Valproate Immediate-release KEPPRA tablets (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057.

Other Antiepileptic Drugs Potential drug interactions between immediate-release KEPPRA tablets and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

Oral Contraceptives Immediate-release KEPPRA tablets (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.

Digoxin Immediate-release KEPPRA tablets (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin Immediate-release KEPPRA tablets (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. C_{ss} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of immediate-release KEPPRA tablets on probenecid was not studied.

USE IN SPECIFIC POPULATIONS

Pregnancy *Pregnancy Category C* There are no adequate and well-controlled studies in pregnant women. In animal studies, levetiracetam produced evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. KEPPRA XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral administration of levetiracetam to female rats throughout pregnancy and lactation led to increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m² basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m² basis). There was no overt maternal toxicity at the doses used in this study. Oral administration of levetiracetam to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥600 mg/kg/day (approximately 4 times MRHD on a mg/m² basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m² basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m² basis). Maternal toxicity was also observed at 1800 mg/kg/day. When levetiracetam was administered orally to pregnant rats during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the MRHD). 1200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study. Treatment of rats with levetiracetam during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at oral doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m² basis). *UCB AED Pregnancy Registry* UCB, Inc. has established the UCB AED Pregnancy Registry to advance scientific knowledge about safety and outcomes in pregnant women being treated with all UCB antiepileptic drugs including KEPPRA XR. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the UCB AED Pregnancy Registry by calling (888) 537-7734 (toll free). Patients may also enroll in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

Labor And Delivery The effect of KEPPRA XR on labor and delivery in humans is unknown.

Nursing Mothers Levetiracetam is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from KEPPRA XR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Safety and effectiveness of KEPPRA XR in patients below the age of 16 years have not been established.

Geriatric Use There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of KEPPRA XR in these patients. It is expected that the safety of KEPPRA XR in elderly patients 65 and over would be comparable to the safety observed in clinical studies of immediate-release KEPPRA tablets. Of the total number of subjects in clinical studies of immediate-release levetiracetam, 347 were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of immediate-release KEPPRA in these patients. A study in 16 elderly subjects (age 61-88 years) with oral administration of single dose and multiple twice-daily doses of immediate-release KEPPRA tablets for 10 days showed no pharmacokinetic differences related to age alone. Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Use In Patients With Impaired Renal Function The effect of KEPPRA XR on renally impaired patients was not assessed in the well-controlled study. However, it is expected that the effect on KEPPRA XR-treated patients would be similar to the effect seen in well-controlled studies of immediate-release KEPPRA tablets. Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing hemodialysis. The dosage should be reduced in patients with impaired renal function receiving KEPPRA XR [see Clinical Pharmacology, Pharmacokinetics and Dosage and Administration Adult Patients With Impaired Renal Function in Full Prescribing Information]. Clearance of immediate-release levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance.

1E 10/2008 KX152-0908

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Corrections

There was an error in the article, "After Methotrexate, Glatiramer Acetate Improves MS Outcomes" that appeared on page 17 of the December 2008 issue of CLINICAL NEUROLOGY NEWS. The treatment described by the investigator involved mitoxantrone, not methotrexate.

There was an error in the caption for the image that appeared in a recent "Neuroscience Today, Neurology Tomorrow" column (November 2008, p. 14). The caption should have said that the neurons and dendrites were located in the dentate gyrus of the mouse's hippocampus, not in the CA1 area.

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