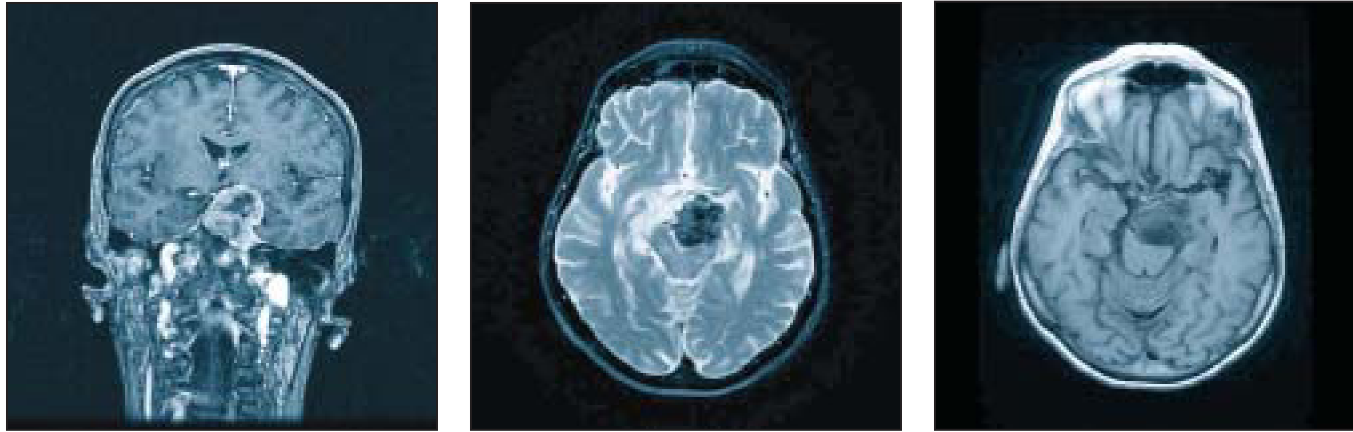

PHOTOS COURTESY DR. M. YASIR HAROON

MRI shows a large lobular mass in the left prepontine region in coronal (left), T2 axial (middle), and T1 axial (right) views.

IMAGE OF THE MONTH

The woman previously had undergone coronary artery bypass graft surgery and resection for colon carcinoma. She also had atrial fibrillation, hypertension, and diverticulosis, according to Dr. M. Yasir Haroon and Dr. Victor Jaramillo of Conemaugh Memorial Medical Center in Johnstown, Pa.

At the time of the incident, she had no associated headache, visual changes, dysarthria or dysphagia, tonic-clonic movements, incontinence, chest pain, palpitations, or shortness of breath.

In the emergency department, the patient was hemodynamically stable, awake, alert, and oriented. An electrocardiogram showed T-wave inversion in the lateral and inferior leads.

The woman was admitted for further evaluation of the syncopal episode and her left jaw pain. A previously performed x-ray of the mandible showed no bony abnormality. A chest x-ray performed at admission showed no acute pulmonary process.

Dr. Haroon and Dr. Jaramillo were consulted for possible trigeminal neuralgia, which may be initially experienced in short, mild attacks that may progress to longer, more frequent bouts of searing pain through the face. It is known to affect women more often than men as well as patients older than 50 years.

The neurologic exam was nonfocal. A brain MRI was performed, which showed a large, multilobular mass suggestive of meningioma in the prepontine region. The mass measured 3.6 cm craniocaudal by 3.2 cm transverse by 2.3 cm anterior-posterior, causing moderate mass effect.

An old infarction also was noted in the right basal ganglia, along with chronic white matter microvascular ischemic changes. An EEG showed slight abnormality with bilateral temporoparietal sharp wave discharges with epileptogenic potential.

A cardiac evaluation also was performed, revealing moderate stenosis of the right internal carotid artery and mild stenosis of the left internal carotid. A stress test was negative and an echocardiogram showed a left ventricular ejection fraction of 58% with no gross valvular abnormalities.

Dr. Haroon and Dr. Jaramillo concluded that the woman had trigeminal neuralgia and that her syncope episode was due to the large prepontine meningioma. Although the patient was referred for neurosurgery, she refused surgical treatment.

Posterior fossa tumors or meningiomas are rarely associated with syncope and trigeminal neuralgia in the literature. There have been very few case reports of trigeminal neuralgia caused by meningiomas located in the cerebellopontine angle and posterior fossa, Dr. Haroon noted. In this patient, the prepontine meningioma ipsilaterally compressed the trigeminal nerve. The doctors suggested that a posterior fossa tumor should be considered a potential cause of trigeminal neuralgia and syncope. ■

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}_{max} 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). The developmental no effect dose was 70 mg/kg/day (0.2 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.

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References: 1. Brodie MJ, Kwan P. Staged approach to epilepsy management. *Neurology*. 2002;58(suppl 5):S2-S8. 2. Buck D, Jacoby A, Baker GA, Chadwick DW. Factors influencing compliance with antiepileptic drug regimes. *Seizure*. 1997;6:87-93. 3. Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. *Epilepsy Behav*. 2002;3:338-342. 4. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA*. 1989;261:3273-3277.

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