

# New Methods Find TBI Missed by Standard Scans

BY JEFF EVANS  
Senior Writer

WASHINGTON — Advanced imaging methods with MRI and magnetoencephalography may be able to detect mild traumatic brain injury with greater accuracy than can conventional imaging techniques, according to two prospective pilot studies.

Conventional MR and CT neuroimaging

focus on the detection of bleeding, which is only indirectly related to axonal injury. These methods are not able to detect about 70%-80% of mild to moderate traumatic brain injuries (TBIs), according to Mingxiang Huang, Ph.D., of the University of California, San Diego, and his colleagues.

Dr. Huang and his coinvestigators are finding that the combination of diffusion-tensor imaging (DTI) and magne-

toencephalography (MEG) can reveal axonal injury resulting from tissue shearing and stretching, which is a leading cause of persistent postconcussive symptoms in mild TBI patients.

MEG pinpoints the temporal and spatial activation of neurons in the brain based on the tiny magnetic fields created by neuronal currents in cortical gray matter. DTI measures the pattern and direction of the movement of water mol-

ecules through white matter fiber tracts, which become disturbed after a TBI.

Detecting mild TBI is clinically important, Dr. Huang said, because even though roughly 85% of patients with mild TBI will be symptom free by 6 months, the remaining 15% have lingering cognitive and behavioral problems, and have a higher risk for developing epilepsy, severe depression, and dementia.

He and his colleagues studied 18 civilian and military patients with a closed-head injury and mild to moderate symptoms of TBI, along with 17 healthy control patients. None of the patients had visible lesions on conventional MRI or CT. In the patients with TBI symptoms, the researchers found that the location of neurons generating abnormal low-frequency delta waves that were seen on MEG was significantly correlated with the deafferentation of the underlying white matter fiber tracts on DTI. These findings were consistent with the patients' symptoms and the results of neuropsychological exams, and they help to confirm the hypothesis that pathological low-frequency delta waves are caused by the shearing of white matter fiber tracts, Dr. Huang reported at the annual meeting of the Society for Neuroscience.

MEG may be a more sensitive measure for mild TBI than is DTI because in some instances MEG was able to detect pathological low-frequency delta waves when DTI signals in white matter fiber tracts were within normal range, according to Dr. Huang. He also noted that the two modalities could be used to objectively monitor the effect of an intervention and provide prognostic information.

The investigators hope to expand their research by performing a longitudinal study in children that compares their recovery from mild TBI with the recovery of adults. In military personnel, the researchers would like to know how to differentiate the signs and symptoms of mild TBI from those of posttraumatic stress disorder. Both conditions have similar signs and symptoms and coincide in a subpopulation of patients, but the treatments for them are different.

In another study presented at the meeting, Andrew Maudsley, Ph.D., of the University of Miami and his colleagues used magnetic resonance spectroscopic imaging (MRSI) to detect the changes in brain metabolism that are indicative of mild TBI in patients with postconcussive symptoms.

The researchers used a volumetric acquisition method to obtain data on the whole brain rather than on just a single area, which is beneficial in imaging diffuse brain injury, according to Dr. Maudsley.

"If you used a conventional MRS method, which is a single voxel method, you have to [focus on] one brain region. You could very clearly choose a brain region, especially with mild injury, that actually looks normal on spectroscopy," he said in an interview.

The investigators measured levels of N-acetylaspartate, creatine, and choline

Continued on following page

## BETASERON®

(INTERFERON BETA-1b) IP 55  
INJECTION

10011479

### Brief Summary of Full Prescribing Information

#### INDICATIONS AND USAGE

Betaseron (Interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

#### CONTRAINDICATIONS

Betaseron is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, Albumin (Human), USP, or any other component of the formulation.

#### WARNINGS

##### Depression and Suicide

Betaseron (Interferon beta-1b) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression and suicide have been reported to occur with increased frequency in patients receiving interferon compounds, including Betaseron. Patients treated with Betaseron should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, cessation of Betaseron therapy should be considered.

In the four randomized controlled studies there were three suicides and eight suicide attempts among the 1532 patients in the Betaseron treated groups compared to one suicide and four suicide attempts among the 965 patients in the placebo groups.

##### Injection Site Necrosis

Injection site necrosis (ISN) has been reported in 4% of patients in controlled clinical trials (see ADVERSE REACTIONS). Typically, injection site necrosis occurs within the first four months of therapy, although post-marketing reports have been received of ISN occurring over one year after initiation of therapy. Necrosis may occur at a single or multiple injection sites. The necrotic lesions are typically three cm or less in diameter, but larger areas have been reported. Generally the necrosis has extended only to subcutaneous fat. However, there are also reports of necrosis extending to and including fascia overlying muscle. In some lesions where biopsy results are available, vasculitis has been reported. For some lesions debridement and, infrequently, skin grafting have been required.

As with any open lesion, it is important to avoid infection and, if it occurs, to treat the infection. Time to healing was varied depending on the severity of the necrosis at the time treatment was begun. In most cases healing was associated with scarring.

Some patients have experienced healing of necrotic skin lesions while Betaseron therapy continued; others have not. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with Betaseron after injection site necrosis has occurred, Betaseron should not be administered into the affected area until it is fully healed. If multiple lesions occur, therapy should be discontinued until healing occurs.

Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated, particularly if injection site necrosis has occurred.

##### Anaphylaxis

Anaphylaxis has been reported as a rare complication of Betaseron use. Other allergic reactions have included dyspnea, bronchospasm, tongue edema, skin rash and urticaria (see ADVERSE REACTIONS).

##### Albumin (Human), USP

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

#### PRECAUTIONS

##### Information for Patients

All patients should be instructed to carefully read the supplied Betaseron Medication Guide. Patients should be cautioned not to change the dose or schedule of administration without medical consultation.

Patients should be made aware that serious adverse reactions during the use of Betaseron have been reported, including depression and suicidal ideation, injection site necrosis, and anaphylaxis (see WARNINGS). Patients should be advised of the symptoms of depression or suicidal ideation and be told to report them immediately to their physician. Patients should also be advised of the symptoms of allergic reactions and anaphylaxis.

Patients should be advised to promptly report any break in the skin, which may be associated with blue-black discoloration, swelling, or drainage of fluid from the injection site, prior to continuing their Betaseron therapy.

Patients should be informed that flu-like symptoms are common following initiation of therapy with Betaseron. In the controlled clinical trials, antipyretics and analgesics were permitted for relief of these symptoms. In addition, gradual dose titration during initiation of Betaseron treatment may reduce flu-like symptoms.

Female patients should be cautioned about the abortifacient potential of Betaseron (see PRECAUTIONS, Pregnancy-Teratogenic Effects).

##### Instruction on Self-Injection Technique and Procedures

Patients should be instructed in the use of aseptic technique when administering Betaseron. Appropriate instruction for reconstitution of Betaseron and methods of self-injection should be provided, including careful review of the Betaseron Medication Guide. The first injection should be performed under the supervision of an appropriately qualified health care professional.

Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of full containers. Patients should be advised of the importance of rotating areas of injection with each dose, to minimize the likelihood of severe injection site reactions, including necrosis or localized infection.

##### Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests, are recommended at regular intervals (one, three, and six months) following introduction of Betaseron therapy, and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every six months in patients with a history of thyroid dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

##### Drug Interactions

No formal drug interaction studies have been conducted with Betaseron. In the placebo controlled studies in MS, corticosteroids or ACTH were administered for treatment of relapses for periods of up to 28 days in patients (N=664) receiving Betaseron.

##### Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: Interferon beta-1b has not been tested for its carcinogenic potential in animals. Mutagenesis: Betaseron was not mutagenic when assayed for genotoxicity in the Ames bacterial test in the presence or absence of metabolic activation. Interferon beta-1b was not mutagenic to human peripheral blood lymphocytes in vitro, in the presence or absence of metabolic inactivation. Betaseron treatment of mouse BALBc-3T3 cells did not result in increased transformation frequency in an in vitro model of tumor transformation.

Impairment of fertility: Studies in normally cycling, female rhesus monkeys at doses up to 0.33 mg/kg/day (32 times the recommended human dose based on body surface area, body surface dose based on 70 kg female) had no apparent adverse effects on either menstrual cycle duration or associated hormonal profiles (progesterone and estradiol) when administered over three consecutive menstrual cycles. The validity of extrapolating doses used in animal studies to human doses is not known. Effects of Betaseron on normally cycling human females are not known.

##### Pregnancy-Teratogenic Effects

Pregnancy Category C: Betaseron was not teratogenic at doses up to 0.42 mg/kg/day when given to pregnant female rhesus monkeys on gestation days 20 to 70. However, a dose related abortifacient activity was observed in these monkeys when Interferon beta-1b was administered at doses ranging from 0.028 mg/kg/day to 0.42 mg/kg/day (2.8 to 40 times the recommended human dose based on body surface area comparison). The validity of extrapolating doses used in animal studies to human doses is not known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reported in patients (n=4) who participated in the Betaseron RRMS clinical trial. Betaseron given to rhesus monkeys on gestation days 20 to 70 did not cause teratogenic effects; however, it is not known if teratogenic effects exist in humans. There are no adequate and well-controlled studies in pregnant women. If the patient becomes pregnant or plans to become pregnant while taking Betaseron, the patient should be apprised of the potential hazard to the fetus and it should be recommended that the patient discontinue therapy.

##### Nursing Mothers

It is not known whether Betaseron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Betaseron, a decision should be made to either discontinue nursing or discontinue the drug, taking into account the importance of drug to the mother.

##### Pediatric Use

Safety and efficacy in pediatric patients have not been established.

##### Geriatric Use

Clinical studies of Betaseron did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

#### ADVERSE REACTIONS

In all studies, the most serious adverse reactions with Betaseron were depression, suicidal ideation and injection site necrosis (see WARNINGS). The incidence of depression of any severity was approximately 30% in both Betaseron-treated patients and placebo-treated patients. Anaphylaxis and other allergic reactions have been reported in patients using Betaseron (see WARNINGS). The most commonly reported adverse reactions were lymphopenia (lymphocytes<1500/mm<sup>3</sup>), injection site reaction, asthenia, flu-like symptom complex, headache, and pain. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Betaseron, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were depression, flu-like symptom complex, injection site reactions, leukopenia, increased liver enzymes, asthenia, hypertension, and myasthenia.

Because clinical trials are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical trials of Betaseron cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to Betaseron in the four placebo controlled trials of 1407 patients with MS treated with 0.25 mg or 0.16 mg/rf, including 1261 exposed for greater than one year. The population encompassed an age range from 18-65 years. Sixty-four percent (64%) of the patients were female. The percentages of Caucasian, Black, Asian, and Hispanic patients were 94.8%, 3.5%, 0.1%, and 0.7%, respectively.

The safety profiles for Betaseron-treated patients with SPMS and RRMS were similar. Clinical experience with Betaseron in other populations (patients with cancer, HIV positive patients, etc.) provides additional data regarding adverse reactions; however, experience in non-MS populations may not be fully applicable to the MS population.

Table 1 enumerates adverse events and laboratory abnormalities that occurred among all patients treated with 0.25 mg or 0.16 mg/rf Betaseron every other day for periods of up to three years in the four placebo controlled trials (Study 1-4) at an incidence that was at least 2.0% more than that observed in the placebo patients (System Organ Class, MedDRA v. 8.0).

Table 1: Adverse Reactions and Laboratory Abnormalities		
System Organ Class MedDRA v. 8.0 <sup>†</sup> Adverse Reaction	Placebo (n=965)	Betaseron (n=1407)
<b>Blood and lymphatic system disorders</b>		
Lymphocytes count decreased (<1500/mm <sup>3</sup> ) <sup>*</sup>	66%	86%
Absolute neutrophil count decreased (<1500/mm <sup>3</sup> ) <sup>*</sup>	5%	13%
White blood cell count decreased (<3000/mm <sup>3</sup> ) <sup>*</sup>	4%	13%
Lymphadenopathy	3%	6%
<b>Nervous system disorders</b>		
Headache	43%	50%
Insomnia	16%	21%
Incoordination	15%	17%
<b>Vascular disorders</b>		
Hypertension	4%	6%
<b>Respiratory, thoracic and mediastinal disorders</b>		
Dyspnea	3%	6%
<b>Gastrointestinal disorders</b>		
Abdominal pain	11%	16%
<b>Hepatobiliary disorders</b>		
Alanine aminotransferase increased (SGPT > 5 times baseline) <sup>*</sup>	4%	12%
Aspartate aminotransferase increased (SGOT > 5 times baseline) <sup>*</sup>	1%	4%
<b>Skin and subcutaneous tissue disorders</b>		
Rash	15%	21%
Skin disorder	8%	10%
<b>Musculoskeletal and connective tissue disorders</b>		
Hypertonia	33%	40%
Myalgia	14%	23%
<b>Renal and urinary disorders</b>		
Urinary urgency	8%	11%
<b>Reproductive system and breast disorders</b>		
Menstrorrhagia <sup>*</sup>	7%	9%
Impotence <sup>*</sup>	6%	8%
<b>General disorders and administration site conditions</b>		
Injection site reaction (various kinds) <sup>o</sup>	26%	78%
Asthenia	48%	53%
Flu-like symptoms (complex) <sup>§</sup>	37%	57%
Pain	35%	42%
Fever	19%	31%
Chills	9%	21%
Peripheral edema	10%	12%
Chest pain	6%	9%
Malaise	3%	6%
Injection site necrosis	0%	4%

<sup>#</sup> except for "injection site reaction (various kinds)" and "flu-like symptom complex" the most appropriate MedDRA term is used to describe a certain reaction and its symptoms and related conditions.

<sup>x</sup> laboratory abnormality

<sup>\*</sup> pre-menopausal women  
<sup>\*\*</sup> men

<sup>o</sup> "injection site reaction (various kinds)" comprises all adverse events occurring at the injection site (except injection site necrosis), i.e. the following terms: injection site reaction, injection site hemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site pain, injection site edema and injection site atrophy.

<sup>§</sup> "Flu-like symptom complex" denotes flu syndrome and/or a combination of at least two AEs from fever, chills, myalgia, malaise, sweating.

##### Injection Site Reactions

In four controlled clinical trials, injection site reactions occurred in 78% of patients receiving Betaseron with injection site necrosis in 4%. Injection site inflammation (42%), injection site pain (16%), injection site hypersensitivity (4%), injection site necrosis (4%), injection site mass (2%), injection site edema (2%) and non-specific reactions were significantly associated with Betaseron treatment (see WARNINGS and PRECAUTIONS). The incidence of injection site reactions tended to decrease over time. Approximately 69% of patients experienced the event during the first three months of treatment, compared to approximately 40% at the end of the studies.

##### Flu-Like Symptom Complex

The rate of flu-like symptom complex was approximately 57% in the four controlled clinical trials. The incidence decreased over time, with only 10% of patients reporting flu-like symptom complex at the end of the studies. For patients who experienced a flu-like symptom complex in Study 1, the median duration was 7.5 days.

##### Laboratory Abnormalities

In the four clinical trials, leukopenia was reported in 18% and 6% [of patients in Betaseron- and placebo-treated groups, respectively]. No patients were withdrawn or dose reduced for neutropenia in Study 1. Three percent (3%) of patients in Studies 2 and 3 experienced leukopenia and were dose-reduced. Other abnormalities included increase of SGPT to greater than five times baseline value (12%), and increase of SGOT to greater than five times baseline value (4%). In Study 1, two patients were dose reduced for increased hepatic enzymes; one continued on treatment and one was ultimately withdrawn. In Studies 2 and 3, 1.5% of Betaseron patients were dose-reduced or interrupted treatment for increased hepatic enzymes. In Study 4, 1.7% of patients were withdrawn from treatment due to increased hepatic enzymes, two of them after a dose reduction. In Studies 1-4, nine (0.6%) patients were withdrawn from treatment with Betaseron for any laboratory abnormality, including four (0.3%) patients following dose reduction. (see PRECAUTIONS, Laboratory tests).

##### Menstrual Irregularities

In the four clinical trials, 97 (12%) of the 783 pre-menopausal females treated with Betaseron and 79 (15%) of the 528 pre-menopausal females treated with placebo reported menstrual disorders. One event was reported as severe, all other reports were mild to moderate severity. No patients withdrew from the studies due to menstrual irregularities.

##### Postmarketing Experience

As with all therapeutic products, there is a potential for immunogenicity. Serum samples were monitored for the development of antibodies to Betaseron during Study 1. In patients receiving 0.25 mg every other day 56/124 (45%) were found to have serum neutralizing activity at one or more of the time points tested. In Study 4, neutralizing activity was measured every 6 months and at end of study. All individual visits after start of therapy, activity was observed in 16.5% up to 25.2% of the Betaseron treated patients. Such neutralizing activity was measured at least once in 75 (29.9%) out of 251 Betaseron patients who provided samples during treatment phase; of these, 17 (22.7%) converted to negative status later in the study.

Based on all the available evidence, the relationship between antibody formation and clinical safety or efficacy is not known.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Betaseron using a biological neutralization assay that measures the ability of immune sera to inhibit the production of the interferon-inducible protein, MxA. Neutralization assays are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Betaseron with the incidence of antibodies to other products may be misleading.

Anaphylactic reactions have rarely been reported with the use of Betaseron.

#### DRUG ABUSE AND DEPENDENCE

No evidence or experience suggests that abuse or dependence occurs with Betaseron therapy; however, the risk of dependence has not been systematically evaluated.

#### OVERDOSAGE

Safety of doses higher than 0.25 mg every other day has not been adequately evaluated. The maximum amount of Betaseron that can be safely administered has not been determined.

#### Rx Only.

#### REFERENCES

References furnished upon request.

U.S. Patent No. 4,588,585; 4,961,969; 5,702,699; 6,994,847

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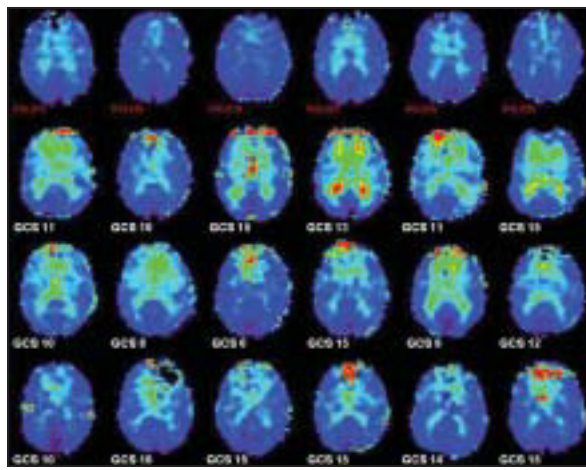
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**Magnetic resonance spectroscopic imaging of the brains of 18 traumatic brain injury patients (bottom three rows) show widespread alterations in the ratio of choline to N-acetyl aspartate (light blue to green color), unlike the brains of 6 control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



IMAGES COURTESY DR. ANDREW A. MAUDSLEY

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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-acetyl aspartate (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-acetyl aspartate 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-acetyl aspartate 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
<b>Respiratory System</b>		
Pharyngitis	6	4
Rhinitis	4	3
Cough Increased	2	1
Sinusitis	2	1
<b>Special Senses</b>		
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<sub>max</sub> 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<sub>ss</sub> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m<sup>2</sup> 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/m<sup>2</sup> 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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**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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