

Surgery for Cluster Headache: Last Ditch Therapy?

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LAS VEGAS — The medical literature on surgery for cluster headaches is scant, but some patients and their neurologists are willing to chance surgery when all other treatment options have been exhausted, Todd D. Rozen, M.D., said at a symposium sponsored by the American Headache Society.

Even without the reassurance of con-

trolled studies, several surgical techniques seem to have value despite their side effects, said Dr. Rozen of the Michigan Head-Pain and Neurological Institute, Ann Arbor.

For patients with cluster headache to be considered for surgery, they must have exhausted all medical options, or they must have a medical history that precludes the use of typical abortive and preventive medications.

The patients should be psychologically

stable and be judged to have a low proclivity for addiction. Some patients may require opiates for a short period of time after surgery; also, low proclivity for addiction goes with a stable psychology. The surgery is invasive and may have long-term sequelae, so it's best done in patients who are emotionally stable.

A surgical procedure is rarely considered for patients with episodic cluster headaches because they have remission periods sometimes lasting years. These

patients should not be subjected to a procedure that could cause long term side-effects possibly worse than the cluster itself, for example, anesthesia dolorosa.

And it's critical that the headaches be confined entirely to one side of the patient's head. If the patient has ever had an episode on the contralateral side, there will be a high risk of recurrence on the side opposite the site of surgery.

Most surgical approaches have targeted the sensory trigeminal nerve and the cranial parasympathetic system to turn off cluster headaches and their associated autonomic symptoms.

Interrupting the parasympathetic autonomic pathway by sectioning the superficial petrosal nerve, the nervus inter-

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medius, or the sphenopalatine ganglion appears effective in obliterating the autonomic symptoms of cluster headache, such as lacrimation, conjunctival injection, and nasal congestion.

Unfortunately, this surgical approach is far less effective in lessening the pain associated with cluster headaches, resulting in inconsistent pain relief and high recurrence rates.

A number of procedures have been developed that target the sensory trigeminal nerve.

These include alcohol injection into the supraorbital and infraorbital nerves; alcohol injection into the Gasser's ganglion; avulsion of the infraorbital, supraorbital, and supratrochlear nerves; retrogasserian glycerol injection; radiofrequency trigeminal gangliorhizolysis; and trigeminal root section.

Of these, thermocoagulation using radiofrequency energy appears to be the most effective, Dr. Rozen said.

Reviewing a number of small studies on this technique, he said that 50% of patients appear to do very well, 20% have fair-to-good results, and the procedure fails to provide relief in 30%.

The side effects can be severe, however. These include moderate or severe facial dysesthesia, corneal sensory loss, and anesthesia dolorosa ("painful numbness"). Rare but devastating side effects include intracranial hemorrhage, stroke, infection, and motor weakness.

A new and promising surgical approach from Italy involves implanting stimulating electrodes under stereotactic control into the posterior inferior hypothalamus, the possible "cluster generator."

In a report involving seven patients with chronic intractable cluster, five patients have been pain free with no side effects and have needed no additional medication. The pain apparently disappears as soon as the stimulation is turned on, and returns as soon as it is turned off (Neurol. Sci. 2003;24[suppl. 2]:s143-5).

KEPPRA® (levetiracetam) 250 mg, 500 mg and 750 mg tablets and 100 mg/mL oral solution

Brief summary (for full prescribing information, consult package insert)

INDICATIONS AND USAGE: Keppra® (levetiracetam) is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

CONTRAINDICATIONS: This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra® tablets or oral solution.

WARNINGS: Neuropsychiatric Adverse Events: Keppra® use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: 1) somnolence and fatigue, 2) coordination difficulties, and 3) behavioral abnormalities. In controlled trials of patients with epilepsy, 14.8% of Keppra® treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of Keppra® treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence. In controlled trials of patients with epilepsy, 14.7% of treated patients reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced. A total of 3.4% of Keppra® treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients. A total of 0.4% of patients in controlled trials discontinued Keppra® treatment due to ataxia, compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of pre-existing ataxia. Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment. In controlled trials of patients with epilepsy, 5 (0.7%) of Keppra® treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient. Two (0.3%) Keppra® treated patients were hospitalized and their treatment was discontinued. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. Two other events, reported as hallucinations, occurred after 1-5 months and resolved within 2-7 days while the patients remained on treatment. In one patient experiencing psychotic depression occurring within a month, symptoms resolved within 45 days while the patient continued treatment. A total of 13.3% of Keppra® patients experienced other behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability etc.) compared to 6.2% of placebo patients. Approximately half of these patients reported these events within the first 4 weeks. A total of 1.7% of treated patients discontinued treatment due to these events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of treated patients and in 0.5% of placebo patients. A total of 0.8% of treated patients had a serious behavioral event (compared to 0.2% of placebo patients) and were hospitalized. In addition, 4 (0.5%) of treated patients attempted suicide compared to 0% of placebo patients. One of these patients successfully committed suicide. In the other 3 patients, the events did not lead to discontinuation or dose reduction. The events occurred after patients had been treated for between 4 weeks and 6 months. **Withdrawal Seizures:** Antiepileptic drugs, including Keppra®, should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS: Hematologic Abnormalities: Minor, but statistically significant, decreases compared to placebo in total mean RBC count (0.03 x 10¹²/mm³), mean hemoglobin (0.09 g/dL), and mean hematocrit (0.38%), were seen in Keppra® treated patients in controlled trials. A total of 3.2% of treated and 1.8% of placebo patients had at least one possibly significant (≤2.8 x 10¹²/L) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant (≤1.0 x 10⁹/L) decreased neutrophil count. Of the treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts. **Hepatic Abnormalities:** There were no meaningful changes in mean liver function tests (LFT) in controlled trials; lesser LFT abnormalities were similar in drug and placebo treated patients in controlled trials (1.4%). No patients were discontinued from controlled trials for LFT abnormalities except for 1 (0.07%) epilepsy patient receiving open treatment. **Information For Patients:** Patients should be instructed to take Keppra® only as prescribed. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised that Keppra® may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery or engage in other hazardous activities until they have gained sufficient experience on Keppra® to gauge whether it adversely affects their performance of these activities. Physicians should advise patients and caregivers to read the patient information leaflet which appears as the last section of the labeling. **Laboratory Tests:** Although most laboratory tests are not systematically altered with Keppra® treatment, there have been relatively infrequent abnormalities seen in hematologic parameters and liver function tests. **Drug Interactions:** *In vitro* data on metabolic interactions indicate that Keppra® 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 in the placebo-controlled clinical studies in epilepsy patients. **Drug-Drug Interactions Between Keppra® And Other Antiepileptic Drugs (AEDs):** Phenytoin: Keppra® (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: Keppra® (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. Potential drug interactions between Keppra® 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. **Other Drug Interactions:** Oral Contraceptives: Keppra® (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: Keppra® (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: Keppra® (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_{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 Keppra® on probenecid was not studied. **Carcinogenesis, Mutagenesis, Impairment Of Fertility:** Carcinogenesis: Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m² basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a mg/m² or exposure basis). Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied. **Mutagenesis:** Levetiracetam was not mutagenic in the Ames test or in mammalian cells *in vitro* in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an *in vitro* analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an *in vivo* mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (ucb L057) was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay. **Impairment Of Fertility:** No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m² or exposure basis). **Pregnancy: Pregnancy Category C:** In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses. Administration to female rats throughout pregnancy and lactation was associated with 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. Treatment of 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 pregnant rats were treated 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 during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m² basis). There are no adequate and well-controlled studies in pregnant women. Keppra® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Keppra® Pregnancy Registry:** UCB Pharma, Inc. has established the Keppra® Pregnancy Registry to advance scientific knowledge about safety and outcomes associated with pregnant women being treated with Keppra®. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the Keppra® 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® 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®, 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 in patients below the age of 16 have not been established. **Geriatric Use:** Of the total number of subjects in clinical studies of 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 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 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:** Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. 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® and supplemental doses should be given to patients after dialysis (see CLINICAL PHARMACOLOGY in package insert and DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function).

ADVERSE REACTIONS: In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra® in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness. Table 1 lists treatment-emergent adverse events that occurred in at least 1% of patients with epilepsy treated with Keppra® participating in placebo-controlled studies and were numerically more common in patients treated with Keppra® than placebo. In these studies, either Keppra® or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity. The prescriber should be aware that these therapies, obtained when Keppra® was added to concurrent AED therapy, cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied. **Table 1: Incidence (%) Of Treatment-Emergent Adverse Events In Placebo-Controlled, Add-On Studies By Body System (Adverse Events Occurred In At Least 1% Of Keppra® Treated Patients And Occurred More Frequently Than Placebo-Treated Patients).** Keppra® (N=769) vs Placebo (N=439): **Body System/Adverse Event: Body as a Whole:** Asthenia (15% vs 9%); Headache (14% vs 13%); Infection (13% vs 8%); Pain (7% vs 6%). **Digestive System:** Anorexia (3% vs 2%). **Nervous System:** Amnesia (2% vs 1%); Anxiety (2% vs 1%); Ataxia (3% vs 1%); Depression (4% vs 2%); Dizziness (9% vs 4%); Emotional Lability (2% vs 0%); Hostility (2% vs 1%); Nervousness (4% vs 2%); Paresthesia (2% vs 1%); Somnolence (15% vs 8%); Vertigo (3% vs 1%). **Respiratory System:** Cough increased (2% vs 1%); Pharyngitis (6% vs 4%); Rhinitis (4% vs 3%); Sinusitis (2% vs 1%). **Special Senses:** Diplopia (2% vs 1%). Other events reported by 1% or more of patients treated with Keppra® but as or more frequent in the placebo group were: abdominal pain, accidental injury, amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting and weight gain. **Time Course Of Onset Of Adverse Events:** Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first 4 weeks of treatment with Keppra®. **Discontinuation Or Dose Reduction In Well-Controlled Clinical Studies:** In well-controlled clinical studies, 15.0% of patients receiving Keppra® and 11.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. Table 2 lists the most common (>1%) adverse events that resulted in discontinuation or dose reduction. **Table 2: Adverse Events That Most Commonly Resulted In Discontinuation Or Dose Reduction In Placebo-Controlled Studies In Patients With Epilepsy** Keppra® (N=769) vs Placebo (N=439): [Number (%)] Asthenia [10 (1.3%) vs 3 (0.7%)]; Convulsion [23 (3.0%) vs 15 (3.4%)]; Dizziness [11 (1.4%) vs 0]; Somnolence [34 (4.4%) vs 7 (1.6%)]; Rash [0 vs 5 (1.1%)]. **Comparison Of Gender, Age And Race:** The overall adverse experience profile of Keppra® was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race. **Postmarketing Experience:** In addition to the adverse experiences listed above, the following have been reported in patients receiving marketed Keppra® worldwide. The listing is alphabetized: leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases); and thrombocytopenia. Alopecia has been reported with Keppra® use; recovery was observed in the majority of cases where Keppra® was discontinued. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation.

DOSAGE AND ADMINISTRATION: Keppra® is indicated as adjunctive treatment of partial onset seizures in adults with epilepsy. In clinical trials, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice-daily dosing, were shown to be effective. Although in some studies there was a tendency toward greater response with higher dose (see CLINICAL STUDIES in package insert), a consistent increase in response with increased dose has not been shown. Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Doses greater than 3000 mg/day have been used in open-label studies for periods of 6 months and longer. There is no evidence that doses greater than 3000 mg/day confer additional benefit. Keppra® is given orally with or without food. **Patients With Impaired Renal Function:** Keppra® dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose are shown in Table 3. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{Cr}) in mL/min is needed. CL_{Cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$CL_{Cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Table 3: Dosing Adjustment Regimen For Patients With Impaired Renal Function

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	>80	500 to 1,500	Every 12 h
Mild	50 - 80	500 to 1,000	Every 12 h
Moderate	30 - 50	250 to 750	Every 12 h
Severe	<30	250 to 500	Every 12 h
ESRD patients using dialysis	—	500 to 1,000	Every 24 h*

*Following dialysis, a 250 to 500 mg supplemental dose is recommended.

