Steroid Injections Ease Cluster Headaches

BY MARY ANN MOON

FROM THE LANCET

Serial suboccipital injections of steroids rapidly relieve cluster headaches as a transitional treatment while patients wait for long-term prophylactic drugs to take effect, according to a randomized, double-blind, controlled clinical trial.

Compared with placebo injections, cortivazol injections reduced the number of headaches per day during the first 4 days of treatment, decreased the total number of attacks over 15 days while patients waited for verapamil to kick in, and shortened the interval until remission, reported Dr. Elizabeth Leroux of the Emergency Headache Centre, Lariboisière Hospital, Paris, and her associates.

Cluster headache is characterized by attacks of strong periorbital pain with ipsilateral autonomic signs, which recur up to eight times a day. Episodic cluster headaches occur in phases for weeks or months separated by long remissions. In 10% of patients, episodic cluster headaches evolve into chronic cluster headaches.

Most patients are managed with a combination of acute therapy and prophylactic treatment. Transitional treatment is used to suppress attacks at the onset of a cluster while awaiting the delayed efficacy of preventive drugs such as verapamil or lithium. Oral steroids are widely used in this setting, but they can induce rebound attacks when patients are weaned off them and can cause serious adverse effects even when used briefly.

Suboccipital steroid injections have been proposed as an alternative to systemic steroids, but only one small, randomized, controlled trial on this ap-

proach has been published. Dr. Leroux and her colleagues, who have used suboccipital cortivazol injections for 10 years in their clinic, assessed their safety and efficacy when added to usual care. (Cortivazol is not available in the United States.)

During an 8-month period, the investigators enrolled 43 adults who presented to the Emergency Headache Center with frequent daily cluster headaches, including 28 with episodic and 15 with chronic cluster headache. The study subjects were randomly assigned to receive three suboccipital injections containing either cortivazol (21 patients) or saline (22 patients), given singly every 48-72 hours.

The injections were made under the occipital bone at the medial third between the inion and mastoid process, ipsilateral to the attack. Each injection was aimed in three directions: upward, at a 45-degree angle to the left, and at a 45-degree angle to the right.

Acute treatment with sumatriptan or oxygen was given as needed. Patients continued on any prophylactic agents they had been taking before the attack or were started on verapamil.

The study subjects completed daily diaries in which they recorded cluster headache attacks, medication use, and adverse effects for 90 days. All were telephoned after 3-11 months to assess their satisfaction with treatment.

The study's primary end point was to reduce the mean number of daily attacks to two or fewer on the second, third, and fourth days after the final injection. In all, 20 of 21 patients (95%) who received steroid injections reached this end point, compared with 12 of 22 controls (55%) who received placebo injections.

This significant benefit with active injections was the same for both episodic and chronic cluster headaches, reported the investigators (Lancet 2011 Sept. 7 [doi:10.1016/S1474-4422(11)70186-7]).

Patients given steroid injections also had fewer attacks during the first 15 days of the study than did those given placebo, and achieved remission a mean of 7 days earlier. Cortivazol also lowered the need for sumatriptan injections during the first 15 days of the study and reduced the need for verapamil in patients with the episodic type of cluster headache.

In addition, patients' scores of satisfaction with therapy were higher for steroid than for placebo injections.

In a post hoc analysis, 7 of 21 patients (33%) given cortivazol remained pain free from 4 days after the first injection until day 30, while only 2 of 22 control subjects (9%) did. Eleven (52%) in the cortivazol group remained pain free after the last injection to day 30, compared with only 4 (18%) in the control group.

The injections were safe and well tolerated. Adverse events – chiefly neck pain at the injection site and headache other than cluster headache – developed in 18 (86%) of the cortivazol group and 14 (64%) of the control group.

This study received no industry funding. Dr. Leroux and her associates reported ties to numerous industry sources, including Sanofi-Aventis, maker of the prefilled cortivazol syringes used in this study. ■

Table 2 *(continued)*. Incidence of Adverse Reactions in 12-Week RLS Studies Reported in ≥2% of Patients Treated With 600 or 1,200 mg of HORIZANT and Numerically Greater Than Placebo

Body System/ Adverse Reaction	Placebo[a] (N = 245) %	HORIZANT 600 mg/day[b] (N = 163) %	HORIZANT 1,200 mg/day[c] (N = 269) %
General disorders and administration site conditions			
Fatigue	4	6	7
Irritability	1	4	4
Feeling drunk	0	1	3
Feeling abnormal	<1	<1	3
Peripheral edema	1	<1	3
Metabolism and nutritional disorders			
Weight increased	2	2	3
Increased appetite	<1	2	2
Ear and labyrinth disorders			
Vertigo	0	1	3
Psychiatric disorders			
Depression	<1	<1	3
Libido decreased	<1	<1	2

[a] Placebo was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week clinical trials.
[b] The 600-mg dose of HORIZANT was a treatment arm in 2 of the 3 double-blind, placebo-controlled, 12-week clinical trials.
[c] The 1,200-mg dose of HORIZANT was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week clinical trials.

Adverse reactions reported in these three 12-week studies in <2% of patients treated with 600 mg of HORIZANT and numerically greater than placebo were balance disorder, blurred vision, disorientation, feeling drunk, lethargy, and vertigo.

The following adverse reactions were dose-related: somnolence/sedation, dizziness, feeling drunk, libido decreased, depression, headache, peripheral edema, and vertigo.

DRUG INTERACTIONS

Neither gabapentin enacarbil nor gabapentin are substrates, inhibitors, or inducers of the major cytochrome P450 enzymes. Gabapentin enacarbil is neither a substrate nor an inhibitor of P-glycoprotein *in vitro*.

Pharmacokinetic drug-drug interaction studies were conducted to examine the potential for an interaction of gabapentin enacarbil with cimetidine and naproxen. No significant pharmacokinetic interactions were observed. No clinically relevant pharmacokinetic interactions are expected between HORIZANT and other substrates of organic cation transporter type 2 (OCT2) and monocarboxylate transporter type 1 (MCT-1) *[see Clinical Pharmacology (12.3) of full prescribing information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies with HORIZANT in pregnant women. In nonclinical studies in rat and rabbits, administration of gabapentin enacarbil was developmentally toxic when administered to pregnant animals at doses and gabapentin exposures greater than those used clinically. HORIZANT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When pregnant rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or 5,000 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased at the 2 highest doses and fetal body weights were decreased at the high dose. The no-effect dose for embryo-fetal developmental toxicity in rats is approximately 3 times the recommended human dose (RHD) of 600 mg/day on a body surface area (mg/m^2) basis.

When pregnant rabbits were administered gabapentin enacarbil (oral doses of 200, 500, or 2,500 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased and fetal body weights were decreased at the high dose. The no-effect dose for embryo-fetal developmental toxicity in rabbits (500 mg/kg/day) is approximately 16 times the RHD on a mg/m^2 basis.

When female rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or 5,000 mg/kg/day throughout the pregnancy and lactation periods, offspring growth and survival were decreased at the two highest doses. The no-effect dose for pre- and post-natal developmental toxicity in rats is approximately 3 times the RHD on a mg/m^2 basis.

In reproductive and developmental studies of gabapentin, developmental toxicity was observed at all doses tested. Increased incidences of hydroureter and/or hydronephrosis were observed in rat offspring following treatment of pregnant animals in studies of fertility and general reproductive performance, embryo-fetal development, and peri- and post-natal development. Overall, a no-effect dose was not established. In mice, treatment of pregnant animals with gabapentin during the period of organogenesis resulted in delayed fetal skeletal ossification at all but the lowest dose tested. When pregnant rabbits were treated with gabapentin during the period of organogenesis, an increase in embryo-fetal mortality was observed at all doses of gabapentin tested.

In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse formation in a mouse model of synaptic repair. Gabapentin has been shown *in vitro* to interfere with activity of the α2δ subunit of voltage-activated calcium channels, a receptor involved in neuronal synaptogenesis. The clinical significance of these findings is unknown.

Labor and Delivery

The effect of HORIZANT on labor and delivery is unknown.

Nursing Mothers

It is not known whether gabapentin derived from HORIZANT is secreted in human milk; however, gabapentin is secreted into human milk following oral administration of gabapentin products. Because of the potential for adverse reactions in nursing infants from HORIZANT, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of HORIZANT in pediatric patients have not been studied.

Geriatric Use

Of the 515 patients treated with HORIZANT in the 3 double-blind, placebo-controlled, 12-week clinical trials for RLS, 11% were 65 to 74 years of age and 1% were 75 years of age and older. Clinical trials of HORIZANT did not include a sufficient number of patients 65 years and older to determine whether they respond differently from younger individuals.

Gabapentin is known to be almost exclusively 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, the frequency of dosing may need to be adjusted based on calculated creatinine clearance in these patients *[see Dosage and Administration (2.2) of full prescribing information]*.

Renal Impairment

The dose of HORIZANT should be adjusted in patients with renal impairment *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3) of full prescribing information]*.

OVERDOSAGE

Human Overdose Experience

There have been no reports describing individuals who have taken an overdose of HORIZANT. The highest single dose of gabapentin enacarbil administered to date is 6,000 mg in healthy subjects. At this supratherapeutic dose there were no serious adverse events. The incidence of central nervous system adverse reactions, particularly dizziness and somnolence/sedation, is increased with doses greater than 600 mg daily.

Overdosage Management

In the event of an overdose, the patient should be treated supportively with appropriate monitoring as necessary. Gabapentin derived from gabapentin enacarbil can be removed by hemodialysis. Standard hemodialysis procedures result in significant clearance of gabapentin.

Further management should be as clinically indicated or as recommended by a poison control center.

PATIENT COUNSELING INFORMATION

See Medication Guide.

Physicians should instruct their patients to read the Medication Guide before starting therapy with HORIZANT and to reread it upon prescription renewal for new information regarding the use of HORIZANT.

Effects on Driving

Patients should be told that HORIZANT can cause significant driving impairment. Accordingly, they should be advised not to drive a car or until they have gained sufficient experience on HORIZANT to assess whether HORIZANT impairs their ability to drive. Patients should be told that it is not known how long this effect lasts.

Somnolence/Sedation and Dizziness

Patients should be told that HORIZANT can cause significant somnolence and dizziness. This typically resolves within several weeks of initiating treatment. Accordingly, they should be told not to operate dangerous machinery until they have gained sufficient experience on HORIZANT to assess whether HORIZANT impairs their ability to operate dangerous machinery safely.

Suicidal Behavior and Ideation

Patients, their caregivers, and families should be counseled that HORIZANT may increase the risk of suicidal thoughts and behavior, and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Lack of Interchangeability With Gabapentin

Patients should be advised that doses of HORIZANT and other gabapentin products are not interchangeable.

Dosing Instructions

- Patients should be instructed to take HORIZANT only as prescribed.
- HORIZANT should be taken once daily with food at about 5 PM.
- If the dose is not taken at the recommended time, the patient should take the next dose at about 5 PM the following day.
- Tablets should be swallowed whole and should not be cut, crushed, or chewed.

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VIEW ON THE NEWS

Robust, Long-Awaited Data

The study by Dr. Leroux and her colleagues provides "long-awaited evidence in support of" suboccipital steroid injections for cluster headache, said Dr. David W. Dodick.

"Leroux and colleagues have provided the clinical and academic community with the largest and most robust controlled trial to date showing efficacy of suboccipital steroid injections for short-term transitional treatment of cluster headache," he said.

The three-injection strategy used in the study is somewhat cumbersome. It remains to be seen if this strategy could potentially be replaced with a single injection of steroid and local anesthetic, as has been shown in several smaller studies, he noted.

DR. DODICK *is in the department of neurology at the Mayo Clinic, Phoenix. He reported no financial conflicts of interest. These remarks were taken from his commentary accompanying Dr. Leroux's report (Lancet 2011 Sept. 7 [doi:10.1016/S1474-4422(11)70197-1]).*