

Ultrasound Sister Duet Better for Acute Stroke

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Patients suffering from acute ischemic stroke are significantly more likely to achieve recanalization and/or early or dramatic clinical recovery if thrombolytic therapy is combined with continuous transcranial Doppler sonography, according to a study by Andrei V. Alexandrov, M.D., of the University of Texas, Houston, and colleagues.

Of 63 patients receiving ultrasound combined with tissue plasminogen activator (t-PA), 31 (49%) achieved recanalization and/or clinical recovery within 2 hours, compared with 19 of 63 patients (30%) who received t-PA combined with sham sonography. Within 2 hours, 16 (25%) of the patients in the treatment group experienced both recanalization and clinical recovery, compared with 5 (8%) of the control group. Both differences were statistically significant (N. Engl. J. Med. 2004;351:2170-8).

This phase II study, although not designed to look at clinical outcomes 3 months after treatment, showed that of the 53 patients eligible for follow-up, 22 (42%) had achieved a modified Rankin score of 0 or 1, compared with 4 of the 15 eligible patients (27%) in the control group. Investigators calculated that a phase III study would need just 274 patients in each group to replicate the results with statistical significance.

“At our center, it’s the standard of care right now,” he said. “Both [t-PA and transcranial Doppler sonography] are FDA-approved technologies, and the trial was exempt from investigational new drug status by FDA because these results would not change the labels. Right now in our institution, when we give systemic t-PA within 3 hours [after a stroke], we always put a transcranial Doppler probe on the scalp to help the patient pass the clot faster.”

Nevertheless, “I will not stand here and recommend that everybody else should do the same,” Dr. Alexandrov said. “The reason is that to do it right, you have to pass through a very lengthy and labor-intensive training that is not a routine part of any neurology residency. To do the protocol, you need 1-6 months of daily practicing of this technique under supervision, and that’s something that very few programs can do in the United States.”

Dr. Alexandrov is involved in an effort to design an operator-independent device that would obviate the need for an experienced operator. With such a device, “an emergency department physician could do it, a neurologist could do it, and a nurse could mount the ultrasound machine on the head,” he said.

The mechanism by which transcranial Doppler sonography improves thrombolysis is still unclear. In a commentary accompanying Dr. Alexandrov’s paper, Joseph F. Polak, M.D., of Tufts University, Boston, weighs a number of the possibilities (N. Engl. J. Med. 2004;351:2154-5).

“It’s clear that the mechanism does not involve cavitation, which ultrasound at high energies can cause. It’s also unlikely that the relatively low energies used in transcranial Doppler ultrasound could accelerate thrombolysis by producing heat.”

Dr. Alexandrov believes that the combined treatment works because ultrasound is causing a gentle mechanical pressure wave, which delivers more t-PA molecules to and through the clot.

The study was sparked by an observation, Dr. Alexandrov said. “Patients who were wearing these transducers for diagnostic purposes started to move their paralyzed arms and legs and to talk to us much faster than we ever expected otherwise.”

References: 1. Sandrini G, Fäkkilä M, Burgess G, Forster E, Haughe S, for the ELETriptan Steering Committee. ELETriptan vs sumatriptan: a double-blind, placebo-controlled, multiple migraine attack study. *Neurology*. 2002;59:1210-1217. 2. Mathew NT, Schoenja J, Winner P, Muirhead N, Sikes CR. Comparative efficacy of ELETriptan 40 mg versus sumatriptan 100 mg. *Headache*. 2003;43:214-222.

RELPAQ (elipterian hydrobromide) Tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS: RELPAQ Tablets should not be given to patients with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms, or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease. RELPAQ Tablets should not be given to patients with cerebrovascular syndromes including (but not limited to) strokes of any type as well as transient ischemic attacks (see WARNINGS). RELPAQ Tablets should not be given to patients with peripheral vascular disease including (but not limited to) ischemic bowel disease (see WARNINGS). Because RELPAQ Tablets may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS). RELPAQ Tablets should not be administered to patients with hemiplegic or basilar migraine. RELPAQ Tablets should not be used within 24 hours of treatment with another 5-HT₁ agonist, an ergotamine- or ergotamine-like medication such as dihydroergotamine, or a triptan. RELPAQ Tablets should not be used in patients with known hypersensitivity to elipterian or any of its inactive ingredients. RELPAQ Tablets should not be given to patients with severe hepatic impairment.

WARNINGS: RELPAQ Tablets should be used with caution in patients with a history of migraine because of CYP3A4 inhibitors. ELETriptan should not be used within at least 72 hours of diagnosis with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, tolterodine, clarithromycin, rifabutin, and nefenavir. ELETriptan should not be used within 72 hours of use of any other CYP3A4 inhibitor. ELETriptan should not be used with any of the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, tolterodine, clarithromycin, rifabutin, and nefenavir. ELETriptan should not be given to patients with documented ischemic or vasospastic cardiac disease (see CONTRAINDICATIONS). It is strongly recommended that ELETriptan not be given to patients in whom unrecognized CAD is suspected by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease in patients with coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic, or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, ELETriptan should not be administered (see CONTRAINDICATIONS). For patients who have or who are determined to have a cardiovascular condition that necessitates cardiovascular evaluation, it is strongly recommended that administration of the first dose of elipterian take place in the setting of a physician's office or similarly medicated and equipped facility where the patient has previously received elipterian. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining an oral single-lead electrocardiogram (ECG) during the interval immediately following administration of RELPAQ Tablets. In these patients with risk factors, it is recommended that patients who are intermittent long-term users of 5-HT₁ agonists including RELPAQ Tablets, and who have or require risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use RELPAQ Tablets. The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to elipterian. In addition to the following information associated with 5-HT₁ Agonists, the following information is included: severe allergic reactions, including anaphylaxis and angioedema, and other adverse effects including acute myocardial infarction, life-threatening arrhythmias of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT₁ agonists. Considering the extent of use of 5-HT₁ agonists in patients with migraine, the incidence of these events is extremely low. Framinglingk experience with elipterian, and data from a phase III clinical trial in patients with migraine, the incidence of these events is extremely low. Framinglingk experience with elipterian, and data from a phase III clinical trial in patients with migraine, the incidence of these events is extremely low. Framinglingk experience with elipterian, and data from a phase III clinical trial in patients with migraine, the incidence of these events is extremely low.

ADVERSE REACTIONS: Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT₁ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS). Incidence in Controlled Clinical Trials: Among 1,557 patients in a phase III clinical trial in patients with migraine, the most common adverse effects reported with treatment with RELPAQ were dizziness, nausea, dyspnea, and somnolence. These events appear to be dose related. In long-term open-label studies where patients were allowed to treat multiple migraine attacks (mean 2.08 attacks per patient) with 1 to 2 tablets of RELPAQ Tablets, the most commonly reported adverse events that occurred in the subset of 5,125 migraineurs who received elipterian doses of 20, 40, 60, and 80 mg or placebo in a double-blind placebo-controlled clinical trial, the events cited reflect experience gained under closely monitored conditions. Incidence of adverse effects with elipterian was generally similar to placebo. The 743 adverse events reported in these studies were generally mild to moderate in severity and were self-limiting. The frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Only adverse events that were more frequent in a RELPAQ treatment group compared to the placebo group with an incidence greater than or equal to 2% are listed here.

TABLE 1: Adverse Experience Incidence in Placebo-Controlled Migraine Clinical Trials: Events Reported by ≥ 2% Patients Treated With RELPAQ and More Than Placebo

Adverse Event Type	Placebo (n=588)	RELPAQ 20 mg (n=431)	RELPAQ 40 mg (n=174)	RELPAQ 80 mg (n=130)
ATYPICAL SENSATIONS				
Paresthesia	2%	3%	3%	4%
Warmth	2%	2%	2%	2%
PAIN AND PRESSURE SENSATIONS				
Chest – high/lower/back/pain/pressure	1%	1%	2%	4%
Head – pain/dizziness/stomach pain/cramps/pressure	1%	1%	2%	2%
DIGESTIVE				
Dry mouth	2%	2%	3%	4%
Dyspepsia	1%	1%	1%	2%
Dysphagia – throat tightness/difficulty swallowing	0.2%	1%	2%	2%
Nausea	5%	4%	5%	8%
NEUROLOGICAL				
Dizziness	3%	3%	6%	7%
Somnolence	4%	3%	6%	7%
Headache	3%	4%	4%	4%
OTHER				
Adhenia	3%	4%	5%	10%

RELPAQ is generally well-tolerated. Across all doses, most adverse reactions were mild and transient. The frequency of adverse events in patients with severe hepatic impairment was similar to that in patients with normal hepatic function. The incidence of adverse events in controlled clinical trials was not affected by gender, age, or race of the patients. The incidence of adverse events associated with concomitant use of drugs commonly taken for migraine prophylaxis (e.g., SSRIs, beta blockers, calcium channel blockers, tricyclic antidepressants), estrogen replacement therapy, oral contraceptives, diuretics, and antihypertensives was similar to placebo. Incidence of adverse events in patients with comorbid conditions (e.g., hypertension, diabetes mellitus, asthma, and other chronic conditions) was similar to placebo. Incidence of adverse events in patients with comorbid conditions (e.g., hypertension, diabetes mellitus, asthma, and other chronic conditions) was similar to placebo. Incidence of adverse events in patients with comorbid conditions (e.g., hypertension, diabetes mellitus, asthma, and other chronic conditions) was similar to placebo. Incidence of adverse events in patients with comorbid conditions (e.g., hypertension, diabetes mellitus, asthma, and other chronic conditions) was similar to placebo.

DRUG ABUSE AND DEPENDENCE: Although the abuse potential of RELPAQ has not been assessed, no abuse, tolerance, or physical dependence on drug-seeking behavior was observed in patients who received RELPAQ in clinical trials or their extensions. The CRU₅₀ agonists, as a class, have not been associated with drug abuse.

OVERDOSAGE: No significant overdoses in premarketing clinical trials have been reported. Volunteers (N=21) had received single doses of 120 mg without significant adverse effects. Daily doses of 160 mg were commonly employed in Phase III trials. Based on the pharmacokinetic profile of elipterian, a hypertensive or other more serious cardiovascular symptoms may occur on overdose. The elimination half-life of elipterian is about 4 hours and therefore persistence of patients after overdose with elipterian should continue for at least 20 hours, or longer should symptoms or signs persist. There is no specific antidote to elipterian. In case of severe toxicity or if there is uncertainty as to whether the patient is receiving elipterian, monitoring and maintenance of a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system, if it is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentration of elipterian.

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