

PFO Closure With Implant Tested for Migraine

BY MELINDA TANZOLA
Contributing Writer

ATLANTA — Patent foramen ovale closure with a septal repair implant gave a modest benefit to patients with migraine and PFO, according to preliminary results of a study with 163 patients.

The enrollment phase of the study also showed that right-to-left cardiac shunts occurred in 60% of the patients with migraine who were screened, Dr. Peter Wilmschurst

reported at the annual meeting of the American College of Cardiology.

This prevalence is “very, very high,” commented Dr. David O. Williams, director of interventional cardiology at Rhode Island Hospital in Providence. “The usual prevalence [in the general population] is about 15%-20%,” he said.

Insertion of a STARFlex septal repair implant provided complete migraine relief in 3 of 74 patients (4%) during 6 months of follow-up, the same rate as in the 73 pa-

tients who received a sham procedure. Thus the device, developed by NMT Medical Inc. (which also sponsored the study), failed to achieve the primary end point of complete headache relief.

“However, using more conventional migraine trial end points, significant differences were found,” noted study investigator Dr. Andrew Dowson, a headache specialist at King’s College Hospital in London. Overall, 42% of patients receiving the implant had a 50% reduction in headache

days, compared with 23% of sham-treated patients, a statistically significant difference.

The Migraine Intervention with STARFlex Technology (MIST) trial was a randomized, placebo-controlled, double-blind study that initially screened 432 individuals with migraine. The study was done in 2005 at 13 centers in the United Kingdom. Patients were aged 18-60 years, with a minimum 1-year history of migraine with an age at onset no later than 50 years, frequent migraines (at least 5 days per month but at least 7 headache-free days per month). The study was restricted to those with migraine with aura, because previous studies showed an association between PFO and these types of migraines, Dr. Dowson said.

Contrast transthoracic echocardiograms showed that 72 patients had small shunts (atrial and pulmonary), 22 had large pulmonary shunts, 3 had atrial septal defects, and 163 had large patent foramen ovals (PFOs), for a total of 260 shunts, said Dr. Wilmschurst, a coinvestigator and cardiologist at Royal Shrewsbury (U.K.) Hospital.

The 163 patients with large PFOs were targeted for the study, and after 16 were excluded 147 patients were randomized to receive either PFO closure or a sham operation. Patients underwent a 3-month healing phase after surgery, followed by a 3-month analysis phase in which migraine occurrences were continually monitored.

Patients continued their prophylactic migraine medication, but those who overused migraine medication were excluded from the study. Other exclusion criteria included prior stroke or transient ischemic attack, and cardiac contraindications.

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Van Kerrebroeck et al: A 12-week, double-blind, multicenter, randomized, placebo-controlled study to evaluate the efficacy and tolerability of tolterodine tartrate capsules (4 mg qd) compared with tolterodine tartrate tablets (2 mg bid) and placebo in 1529 patients with overactive bladder (published data from the Registration Study). The primary efficacy variable was the change in the number of incontinence episodes per week from baseline to Week 12.

Landis et al: A post hoc analysis of a 12-week, multinational, randomized, double-blind, placebo-controlled study that compared the efficacy of tolterodine tartrate capsules (4 mg qd) with placebo for overactive bladder in 986 patients with severe urgency incontinence. Severe urgency incontinence was defined as 21 to 168 urgency incontinence episodes/week.

References: 1. Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A, for the Tolterodine Study Group. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology*. 2001;57:414-421. 2. Landis JR, Kaplan S, Swift S, Versi E. Efficacy of antimuscarinic therapy for overactive bladder with varying degrees of incontinence severity. *J Urol*. 2004;171:752-756.

Detrol LA[®]

tolterodine tartrate

extended release capsules

PHARMACIA

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

DETROL LA Capsules are once daily extended release capsules indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

DETROL LA Capsules are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETROL LA is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Risk of Urinary Retention and Gastric Retention: DETROL LA Capsules should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Controlled Narrow-Angle Glaucoma: DETROL LA should be used with caution in patients being treated for narrow-angle glaucoma.

Reduced Hepatic and Renal Function: For patients with significantly reduced hepatic function or renal function, the recommended dose for DETROL LA is 2 mg daily. (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information).

Patients with Congenital or Acquired QT Prolongation:

In a study of the effect of tolterodine immediate release tablets on the QT interval (See **CLINICAL PHARMACOLOGY, Cardiac Electrophysiology** in full prescribing information), the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PMs) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. These observations should be considered in clinical decisions to prescribe DETROL LA for patients with a known history of QT prolongation or patients who are taking Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) antiarrhythmic medications (See **PRECAUTIONS, Drug Interactions**). There has been no association of Torsade de Pointes in the international post-marketing experience with DETROL or DETROL LA.

Information for Patients

Patients should be informed that antimuscarinic agents such as DETROL LA may produce the following effects: blurred vision, dizziness, or drowsiness.

Drug Interactions

CYP3A4 Inhibitors: Ketoconazole, an inhibitor of the drug metabolizing enzyme CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to subjects who were poor metabolizers (see **CLINICAL PHARMACOLOGY, Variability in Metabolism and Drug-Drug Interactions** in full prescribing information). For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as other azole antifungals (eg, itraconazole, miconazole) or macrolide antibiotics (eg, erythromycin, clarithromycin) or cyclosporine or vinblastine, the recommended dose of DETROL LA is 2 mg daily (see **DOSAGE AND ADMINISTRATION**).

Drug-Laboratory-Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tolterodine immediate release were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), AUC values obtained for tolterodine were 355, 291, and 462 µg •h/L, respectively. In comparison, the human AUC value for a 2-mg dose administered twice daily is estimated at 34 µg •h/L. Thus, tolterodine exposure in the carcinogenicity studies was 9- to 14-fold higher than expected in humans. No increase in tumors was found in either mice or rats. No mutagenic effects of tolterodine were detected in a battery of in vitro tests, including bacterial mutation assays (Ames test) in 4 strains of *Salmonella typhimurium* and in 2 strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative in vivo in the bone marrow micronucleus test in the mouse. In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding to AUC value of about 500 µg •h/L), neither effects on reproductive performance or fertility were seen. Based on AUC values, the systemic exposure was about 15-fold higher in animals than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

Pregnancy

Pregnancy Category C. At oral doses of 20 mg/kg/day (approximately 14 times the human exposure), no anomalies or malformations were observed in mice. When given at doses of 30 to 40 mg/kg/day, tolterodine has been shown to be embryolethal and reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification) in mice. At these doses, the AUC values were about 20- to 25-fold higher than in humans. Rabbits treated subcutaneously at a dose of 0.8 mg/kg/day achieved an AUC of 100 µg •h/L, which is about 3-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, DETROL LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

Nursing Mothers

Tolterodine immediate release is excreted into the milk in mice. Offspring of female mice treated with tolterodine 20 mg/kg/day during the lactation period had slightly reduced bodyweight gain. The offspring regained the weight during the maturation phase. It is not known whether tolterodine is excreted in human milk; therefore, DETROL LA should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue DETROL LA in nursing mothers.

Pediatric Use

Efficacy in the pediatric population has not been demonstrated. A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two Phase 3 randomized, placebo-controlled, double-blind, 12-week studies.

The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with DETROL LA compared to 0.9% of children treated with placebo.

Geriatric Use

No overall differences in safety were observed between the older and younger patients treated with tolterodine (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information).

ADVERSE REACTIONS

The Phase 2 and 3 clinical trial program for DETROL LA Capsules included 1073 patients who were treated with DETROL LA (n=537) or placebo (n=536). The patients were treated with 2, 4, 6, or 8 mg/day for up to 15 months. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug 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 DETROL LA 4 mg once daily every morning in 505 patients and to placebo in 507 patients exposed for 12 weeks in the Phase 3, controlled clinical study.

Adverse events were reported in 52% (n=263) of patients receiving DETROL LA and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving DETROL LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with DETROL LA occurring in 23.4% of patients treated with DETROL LA and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving DETROL LA and by 3.6% (n=18) of patients receiving placebo.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with DETROL LA or placebo discontinued treatment due to adverse events. Treatment was discontinued due to adverse events and dry mouth was reported as an adverse event in 2.4% (n=12) of patients treated with DETROL LA and in 1.2% (n=6) of patients treated with placebo.

Table 4 lists the adverse events reported in 1% or more of patients treated with DETROL LA 4 mg once daily in the 12-week study. The adverse events were reported regardless of causality.

Table 4. Incidence* (% of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated with DETROL LA (4 mg daily) in a 12-week, Phase 3 Clinical Trial

Body System	Adverse Event	% DETROL LA n=505	% Placebo n=507
Autonomic Nervous	dry mouth	23	8
	headache	6	4
General	fatigue	2	1
	dizziness	2	1
Central/Peripheral Nervous	constipation	6	4
	abdominal pain	4	2
	dysepisia	3	1
Vision	xerophthalmia	3	2
	vision abnormal	1	0
Psychiatric	somnolence	3	2
	anxiety	1	0
Respiratory	sinusitis	2	1
	urinary	1	0

* in nearest integer.

Postmarketing Surveillance

The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, including angioedema; tachycardia; palpitations; peripheral edema; and hallucinations. Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

OVERDOSAGE

A 27-month-old child who ingested 5 to 7 tolterodine immediate release tablets 2 mg was treated with a suspension of activated charcoal and was hospitalized overnight with symptoms of dry mouth. The child fully recovered.

Management of Overdosage

Overdosage with DETROL LA Capsules can potentially result in severe central anticholinergic effects and should be treated accordingly. ECG monitoring is recommended in the event of overdosage. In dogs, changes in the QT interval (slight prolongation of 10% to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT interval prolongation was not observed with tolterodine immediate release at doses up to 8 mg (4 mg bid) and higher doses were not evaluated. (see **PRECAUTIONS, Patients with Congenital or Acquired QT Prolongation**).

DOSAGE AND ADMINISTRATION

The recommended dose of DETROL LA Capsules are 4 mg daily. DETROL LA should be taken once daily with liquids and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability, however, limited efficacy data is available for DETROL LA 2 mg (see **CLINICAL STUDIES** in full prescribing information). For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of DETROL LA is 2 mg daily (see **CLINICAL PHARMACOLOGY AND PRECAUTIONS, Drug Interactions** in full prescribing information).

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Handheld Device Can Spot Brain Hematomas

An investigational near-infrared imaging technology in a handheld device can detect brain hematomas soon after trauma.

The Infrascanner detects hematomas based on the differential near-infrared light absorption of hemoglobin in the bleeding versus the nonbleeding area of the brain.

“The user-friendly device that maps out the location of the hematoma with graphics on a PDA screen can assist paramedics and emergency room personnel in attending to those injured in traffic and sports accidents, falls, and on the battlefield,” said Banu Onaral, Ph.D., director of the school of biomedical engineering, science, and health systems at Drexel University in Philadelphia.

The scanner unit is a handheld device based on a PDA platform with a wireless probe. The signal from the probe is digitized and transmitted by wireless link to the handheld unit.

Multicenter clinical trials are underway. Pending approval by the Food and Drug Administration, the device could be available by the end of the year.

—Kerri Wachter



Continued from previous page

In addition to the significant reduction in headache days, the implant also provided a significantly greater reduction than did sham in headache burden, a measure that incorporates both the frequency and duration of headaches.

Patients receiving the implant achieved a 37% reduction in headache burden, from 136 at baseline to 86 at last follow-up, whereas those receiving the sham operation improved from 117 at baseline to 96 at the last 6-month follow-up, a 17% reduction. The investigators noted that the difference in the magnitude of the reduc-

tion between the implant and sham groups was statistically significant.

The results send "a little bit of a mixed message" Dr. Williams commented. The low rate of complete headache resolution suggests that PFOs may not have an etiologic role in migraine.

"On the other hand, there was some improvement, and we wonder whether the closure process may not have been complete," he said.



The high prevalence of cardiac shunts in patients with migraine suggests that screening selected patients with transthoracic echocardiography and then performing repairs when indicated may be a good idea.

Significantly more patients with the implant had a 50% reduction in headache days, compared with controls.

DR. DOWSON

skilled hands, the risks of PFO closure are very low. The procedural risk is like that for cardiac catheterization."

"It's something to consider for disabled patients," Dr. Williams said. "In

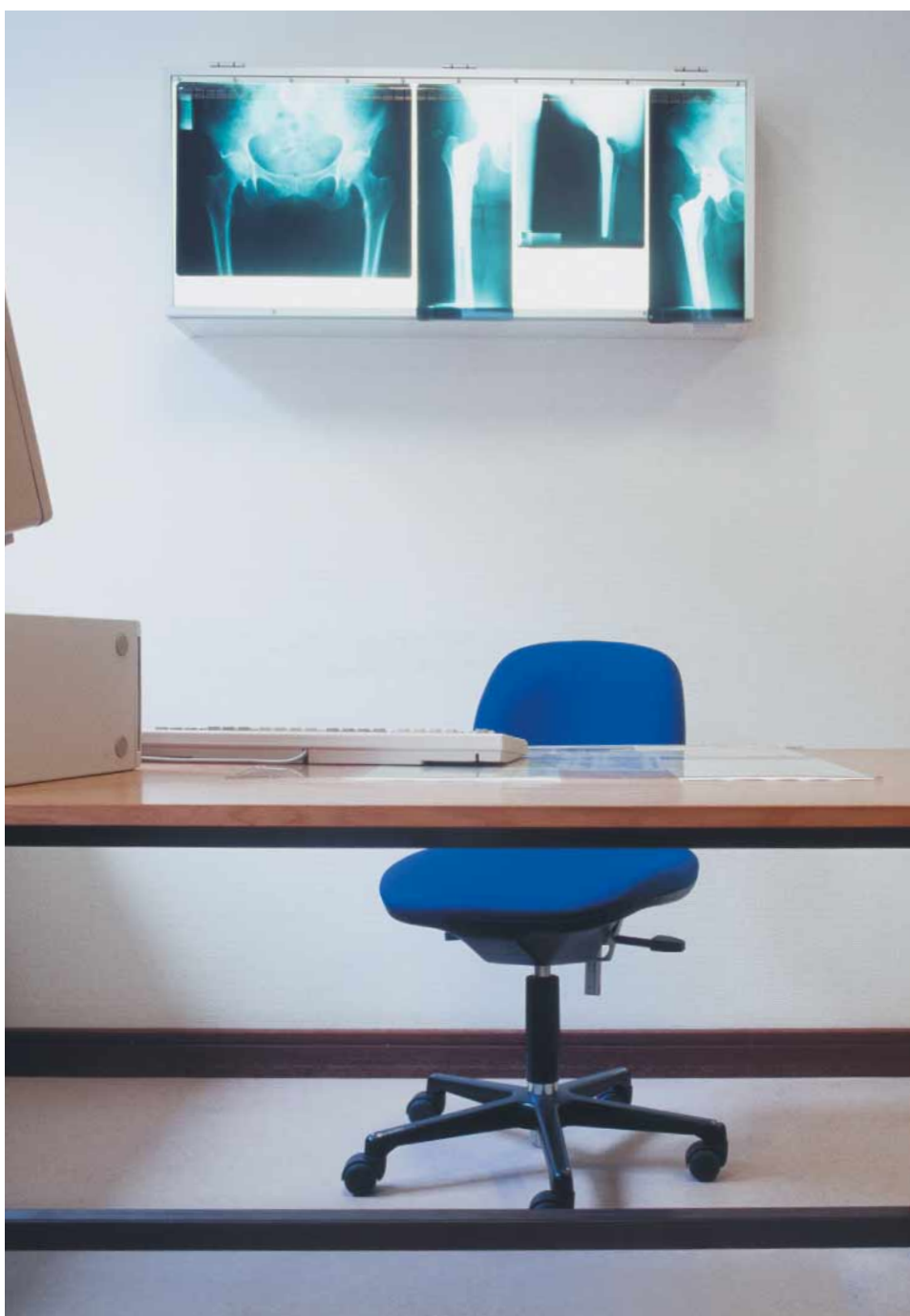
In the implant group, five serious adverse events occurred in one patient each: cardiac tamponade, pericardial effusion, retroperitoneal bleeding, atrial fibrillation, and chest pain. In the sham group, one patient had incision site bleeding, two patients had effects of antiplatelet therapy (anemia, nosebleed), and one patient had a brainstem ischemic stroke 4 months into the follow-up.

The researchers plan to evaluate residual shunting in patients who had repairs. Longer follow-up may show greater benefit from implants, Dr. Dowson noted. ■

Philadelphia bureau chief Mitchel L. Zoler contributed to this report.

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