

Thoracic Endograft Safer Than Surgery at 2 Years

BY BRUCE JANCIN
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SAN FRANCISCO — Use of the Gore TAG thoracic endograft markedly reduced morbidity and mortality, compared with open repair through 2 years of follow-up, R. Scott Mitchell, M.D., said at the annual meeting of the American Association for Thoracic Surgery.

Earlier this year, the catheter-delivered Gore TAG device was approved as the first

stent graft for treating descending thoracic aortic aneurysms. It consists of a Teflon tube covered by a nitinol exoskeleton. Although several endovascular devices for treatment of abdominal aortic aneurysms are on the market, endoprotheses for the less frequent thoracic aortic aneurysms has been slower to develop. The Gore TAG was the first such device to enter clinical trials, which were halted for 2 years upon discovery that it was prone to asymptomatic stent fractures along the graft spine.

The 17-center prospective nonrandomized trial compared outcomes in 140 patients with endovascular repair using the Gore TAG and a historical control group of 94 patients with a conventional open repair.

Mean estimated procedural blood loss was 472 mL in the Gore TAG group vs. 2,402 mL with open surgery. Temporary or permanent paraplegia occurred within 30 days in 3% of the Gore TAG group and 14% of controls. Early mortality in the Gore TAG group was 2%, compared with 6% in

controls. The 3.5% perioperative stroke rate in the Gore TAG group was significantly lower than in controls. Rates of renal dysfunction and cardiac complications were also lower. ICU time and hospital length of stay were markedly shorter in the Gore TAG patients, who were able to return to normal activities in an average of 30 days, vs. 78 days in the open-surgery patients.

The rate of 2-year freedom from aneurysm-related mortality was 98% in the stent group and 91% in controls. However, all-cause mortality was similar in the two groups, at about 25%, according to Dr. Mitchell, professor of cardiovascular surgery at Stanford (Calif.) University and co-principal investigator in the trial.

Over 2 years of follow-up, 15% of Gore TAG-treated patients had an endoleak, for which four underwent endovascular revision; one required an open conversion.

During follow-up, the aneurysm sac decreased in size by more than 5 mm in 24

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(Esmolol Hydrochloride) 250 mL Ready-to-use Bags

Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride
FOR INTRAVENOUS USE. CAN BE USED FOR DIRECT INTRAVENOUS USE.
Esmolol Hydrochloride concentration = 10 milligrams/mL (10,000 micrograms/mL)
Single Patient Use Only. No Preservative Added.

BREVILOC DOUBLE STRENGTH PREMIXED INJECTION

(Esmolol Hydrochloride) 100 mL Ready-to-use Bags

Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride
FOR INTRAVENOUS USE. CAN BE USED FOR DIRECT INTRAVENOUS USE.
Esmolol Hydrochloride concentration = 20 milligrams/mL (20,000 micrograms/mL)
Single Patient Use Only. No Preservative Added.

BREVILOC INJECTION

(Esmolol Hydrochloride) 10 mL Ready-to-use Vials

Iso-Osmotic Solution of Esmolol Hydrochloride in Sodium Chloride
FOR INTRAVENOUS USE. CAN BE USED FOR DIRECT INTRAVENOUS USE.
Esmolol Hydrochloride concentration = 10 milligrams/mL (10,000 micrograms/mL)
Single Patient Use Only. No Preservative Added.

BREVILOC CONCENTRATE

(Esmolol Hydrochloride) 10 mL Ampuls for Dilution

NOT FOR DIRECT INTRAVENOUS INJECTION.
Esmolol Hydrochloride concentration = 250 milligrams/mL (250,000 micrograms/mL)
AMPULS MUST BE DILUTED PRIOR TO ITS INFUSION - SEE DOSAGE AND ADMINISTRATION, Directions for Use of the Brevilloc Concentrate 10 mL Ampul (250 milligrams/mL) in full prescribing information.

BRIEF SUMMARY. FOR FULL PRESCRIBING INFORMATION SEE PRODUCT INSERT.

INDICATIONS AND USAGE

Supraventricular Tachycardia

BREVILOC (Esmolol Hydrochloride) is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable. BREVILOC is also indicated in noncompensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention. BREVILOC is not intended for use in chronic settings where transfer to another agent is anticipated.

Intraoperative and Postoperative Tachycardia and/or Hypertension

BREVILOC (Esmolol Hydrochloride) is indicated for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, or emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated. Use of BREVILOC to prevent such events is not recommended.

CONTRAINDICATIONS

BREVILOC (Esmolol Hydrochloride) is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure (see WARNINGS).

WARNINGS

Hypotension: In clinical trials 20-50% of patients treated with BREVILOC (Esmolol Hydrochloride) have experienced hypotension, generally defined as systolic pressure less than 90 mmHg and/or diastolic pressure less than 50 mmHg. About 12% of the patients have been symptomatic (mainly diaphoresis or dizziness). Hypotension can occur at any dose but is dose-related so that doses beyond 200 mcg/kg/min (0.2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, BREVILOC (Esmolol Hydrochloride) should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of BREVILOC, specific treatment may also be considered (see OVERDOSAGE in full prescribing information). The use of BREVILOC for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of the effects of BREVILOC, several cases of death have been reported in complex clinical states where BREVILOC was presumably being used to control ventricular rate.

Intraoperative and Postoperative Tachycardia and/or Hypertension: BREVILOC (Esmolol Hydrochloride) should not be used as the treatment for hypertension in patients in whom the increased blood pressure is primarily due to the vasoconstriction associated with hypothermia.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity and titratability, BREVILOC (Esmolol Hydrochloride) may be used with caution in patients with bronchospastic diseases. However, since beta₂ selectivity is not absolute, BREVILOC should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately; a beta₂ stimulating agent may be administered if conditions warrant but should be used with particular caution as patients already have rapid ventricular rates.

Diabetes Mellitus and Hypoglycemia: BREVILOC (Esmolol Hydrochloride) should be used with caution in diabetic patients requiring a beta blocking agent. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

PRECAUTIONS

General

Infusion concentrations of 20 mg/mL were associated with more serious venous irritation, including thrombophlebitis, than concentrations of 10 mg/mL. Extravasation of 20 mg/mL may lead to a serious local reaction and possible skin necrosis. Concentrations greater than 10 mg/mL or infusion into small veins or through a butterfly catheter should be avoided.

Because the acid metabolite of BREVILOC is primarily excreted unchanged by the kidney, BREVILOC (Esmolol Hydrochloride) should be administered with caution to patients with impaired renal function. The elimination half-life of the acid metabolite was prolonged ten-fold and the plasma level was considerably elevated in patients with end-stage renal disease.

Care should be taken in the intravenous administration of BREVILOC as sloughing of the skin and necrosis have been reported in association with infiltration and extravasation of intravenous infusions.

Drug Interactions

Catecholamine-depleting drugs, e.g., reserpine, may have an additive effect when given with beta blocking agents. Patients treated concurrently with BREVILOC (Esmolol Hydrochloride) and a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

A study of interaction between BREVILOC and warfarin showed that concomitant administration of

BREVILOC and warfarin does not alter warfarin plasma levels. BREVILOC concentrations were equivalently higher when given with warfarin, but this is not likely to be clinically important.

When digoxin and BREVILOC were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. Digoxin did not affect BREVILOC pharmacokinetics. When intravenous morphine and BREVILOC were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but BREVILOC steady-state blood levels were increased by 46% in the presence of morphine. No other pharmacokinetic parameters were changed.

The effect of BREVILOC on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by BREVILOC, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes.

Although the interactions observed in these studies do not appear to be of major clinical importance, BREVILOC should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Caution should be exercised when considering the use of BREVILOC and verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVILOC should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with BREVILOC (Esmolol Hydrochloride).

Pregnancy Category C

Teratogenicity studies in rats at intravenous dosages of BREVILOC (Esmolol Hydrochloride) up to 3000 mcg/kg/min (3 mg/kg/min) (ten times the maximum human maintenance dosage) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while a dosage of 10,000 mcg/kg/min (10 mg/kg/min) produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 mcg/kg/min (1 mg/kg/min) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 mcg/kg/min (2.5 mg/kg/min) produced minimal maternal toxicity and increased fetal resorptions.

Although there are no adequate and well-controlled studies in pregnant women, use of esmolol in the last trimester of pregnancy or during labor or delivery has been reported to cause fetal bradycardia, which continued after termination of drug infusion. BREVILOC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether BREVILOC (Esmolol Hydrochloride) is excreted in human milk; however, caution should be exercised when BREVILOC is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of BREVILOC (Esmolol Hydrochloride) in pediatric patients have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on use of BREVILOC (Esmolol Hydrochloride) in clinical trials involving 369 patients with supraventricular tachycardia and over 600 intraoperative and postoperative patients enrolled in clinical trials. Most adverse effects observed in controlled clinical trial settings have been mild and transient. The most important adverse effect has been hypotension (see WARNINGS). Deaths have been reported in post-marketing experience occurring during complex clinical states where BREVILOC was presumably being used simply to control ventricular rate (see WARNINGS, Cardiac Failure).

Cardiovascular—Symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients, and therapy was discontinued in about 11%, about half of whom were symptomatic. Asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during BREVILOC (Esmolol Hydrochloride) infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Diaphoresis accompanied hypotension in 10% of patients. Peripheral ischemia occurred in approximately 1% of patients. Pallor, flushing, bradycardia (heart rate less than 50 beats per minute), chest pain, syncope, pulmonary edema and heart block have each been reported in less than 1% of patients. In two patients without supraventricular tachycardia but with serious coronary artery disease (post inferior myocardial infarction or unstable angina), severe bradycardia/sinus pause/asystole has developed, reversible in both cases with discontinuation of treatment.

Central Nervous System—Dizziness has occurred in 3% of patients; somnolence in 3%; confusion, headache, and agitation in about 2%; and fatigue in about 1% of patients. Paresthesia, asthenia, depression, abnormal thinking, anxiety, anorexia, and lightheadedness were reported in less than 1% of patients. Seizures were also reported in less than 1% of patients, with one death.

Respiratory—Bronchospasm, wheezing, dyspnea, nasal congestion, rhonchi, and rales have each been reported in less than 1% of patients.

Gastrointestinal—Nausea was reported in 7% of patients. Vomiting has occurred in about 1% of patients. Dyspepsia, constipation, dry mouth, and abdominal discomfort have each occurred in less than 1% of patients. Taste perversion has also been reported.

Skin (Infusion Site)—Infusion site reactions including inflammation and induration were reported in about 8% of patients. Edema, erythema, skin discoloration, burning at the infusion site, thrombophlebitis, and local skin necrosis from extravasation have each occurred in less than 1% of patients.

Miscellaneous—Each of the following has been reported in less than 1% of patients: Urinary retention, speech disorder, abnormal vision, midscapular pain, rigors, and fever.

HOW SUPPLIED

BREVILOC PREMIXED INJECTION
NDC 10019-055-61, 2500 mg - 250 mL in Ready-to-use 250 mL IntraVia Bags
BREVILOC PREMIXED INJECTION - DOUBLE STRENGTH
NDC 10019-075-87, 2000 mg - 100 mL in Ready-to-use 100 mL IntraVia Bags
BREVILOC INJECTION
NDC 10019-015-01, 100 mg - 10 mL Ready-to-use Vials, Package of 25
BREVILOC CONCENTRATE
NDC 10019-025-18, 2500 mg - 10 mL Ampuls for Dilution, Package of 10

Store at 25°C (77°F). Excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.] PROTECT FROM FREEZING. Avoid excessive heat.

Baxter

Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA

BREVILOC INJECTION and BREVILOC CONCENTRATE manufactured by Paulding Puerto Rico, Inc.
P.O. Box 471 Aguadilla, PR 00604 USA

BREVILOC PREMIXED INJECTION and BREVILOC PREMIXED INJECTION - DOUBLE STRENGTH manufactured by Baxter Healthcare Corporation
Deerfield, IL 60015 USA

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For Product Inquiry 1 800 ANA DRUG (1-800-262-3784)

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DR. MITCHELL

patients and grew by more than 5 mm in 11 patients. There have been no late aneurysm ruptures.

"I think these complications will be ongoing. Hopefully they'll be decreasing with time. But we don't know that, so these patients will require lifelong follow-up," the surgeon stressed.

The device is not for everyone. It requires access vessels that allow passage of a 20-24 French sheath. The patient must have a minimum 2-cm landing zone of normal thoracic aorta free of thrombus or calcification proximal and distal to the aneurysm. Patients with Marfan syndrome and other connective tissue disorders were excluded from the trial, and Dr. Mitchell urged that the same policy be followed in clinical practice because the device is unlikely to be effective in that population.

Roughly 10,000-15,000 thoracic aortic aneurysms are diagnosed annually, often in elderly patients who are not good surgical candidates. The Gore TAG device, which spares patients the large chest incision and prolonged aortic clamping entailed in open surgery, could expand the pool of patients who can undergo repair.

Recognizing this, discussant Joseph S. Coselli, M.D., of Baylor College of Medicine in Houston, predicted, "this technology will forever alter how we approach descending thoracic aortic aneurysm pathology." He added, however, that many participants in the control group for this trial were retrospectively acquired.

"It's not the best control group. We admit that," said Dr. Mitchell. "But I think all of us are aware of the difficulties in trying to get a very aware public to enroll in a randomized trial."

He is a consultant to W.L. Gore & Associates Inc., the study sponsor. ■