

Abciximab During PCI Seems No Aid to Diabetics

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW ORLEANS — Treatment with abciximab failed to improve the outcomes of patients with diabetes who underwent elective percutaneous coronary interventions in a randomized study with 701 patients.

All patients in the study received a loading dose of 600 mg of the antiplatelet drug clopidogrel at least 2 hours before their

percutaneous coronary intervention (PCI), which suggested that clopidogrel treatment “may obviate the need for abciximab during elective PCI in patients at low to intermediate risk,” Julinda Mehilli, M.D., reported at the annual scientific sessions of the American Heart Association.

But the results from this German study, which was not sponsored by a pharmaceutical company, cannot be considered the last word on using a glycoprotein IIb/IIIa platelet inhibitor in patients with

diabetes undergoing PCI, said some experts at the meeting.

One limitation is that the current study excluded patients with acute coronary syndrome, an acute myocardial infarction, or visible thrombus. “These patients have been the sweet spot for abciximab and other IIb/IIIa inhibitors,” commented Gregg W. Stone, M.D., director of cardiovascular research and education at the Cardiovascular Research Foundation of Lenox Hill Hospital in New York.

Other shortcomings of the study included its enrollment of a relatively small number of insulin-dependent diabetics, and the fact that it was underpowered to prove that patients did just as well without abciximab as they did with the drug, commented Eric R. Bates, M.D., a professor of medicine at the University of Michigan, Ann Arbor.

The study was designed as a superiority trial, to prove that abciximab-treated patients fared better than those who didn't get the drug. Dr. Bates was also skeptical that physicians who now use abciximab to treat diabetic patients undergoing elective PCI would be persuaded to change their practice based on the results of a single study.

The study was done at three German hospitals from January 2001 to October 2003. Patients were enrolled if they were on active treatment with either insulin or an oral hypoglycemic agent and were scheduled to undergo an elective PCI in a native coronary vessel. The study's primary end point was the incidence of death or MI during the first 12 months following the procedure.

All patients received a loading dose of clopidogrel plus 500 mg aspirin. Following randomization, patients in the abciximab group received a 0.25-mg/kg bolus followed by a 0.125-mcg/kg per minute infusion for 12 hours, along with 70 U/kg of unfractionated heparin.

Patients in the placebo group received a placebo bolus and infusion, along with a 140-U/kg bolus of heparin. Following their procedure, all patients received a 200-mg daily aspirin dosage that was continued indefinitely. Patients also received 75 mg clopidogrel b.i.d. until discharge or for a maximum of 3 days, and then continued on 75 mg clopidogrel daily for at least 6 months. Patients received other medications as indicated.

After 1 year of follow-up, the incidence of death or MI was essentially identical in the two groups: 8.3% among the 351 patients treated with abciximab, and 8.6% among those treated with placebo, reported Dr. Mehilli of the German Heart Center in Munich.

The secondary end point of the study was the incidence of angiographic restenosis at follow-up. By this criterion, the abciximab group did better: Angiographic restenosis occurred in 28.9% of the patients in the abciximab group, compared with 37.8% of placebo patients, a statistically significant difference.

But this result is already outdated because the study was done largely before the advent of drug-eluting stents. Only 10% of the patients received drug-eluting stents; in this small subgroup, treatment with abciximab conferred no significant advantage over placebo.

The edge in restenosis conferred by abciximab “would have been a very important finding 2 years ago, but now it's too little too late,” said Dr. Stone. “Drug-eluting stents are clearly the treatment of choice to reduce restenosis in patients with diabetes, and no drug has been shown to reduce restenosis when used on top of drug-eluting stents,” he said. ■

BREVILOC PREMIXED INJECTION

(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, on 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 23°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 Faulding 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

Baxter, Brevilloc and IntraVia are trademarks of Baxter International Inc.
U.S. Pat. Nos. 5,849,843; 5,998,019; Pat. Pending.

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

Revised: March 2003 748522 2003-04