

Women Wait Longer for Emergency Angioplasty

BY CHRISTINE KILGORE

Contributing Writer

Women who presented to Michigan hospitals with acute ST-segment elevation myocardial infarction waited significantly longer than men to undergo emergency angioplasty—and even men waited too long according to Mauro Moscucci, M.D., the lead, investigator in the study.

“We have an ideal target for quality im-

provement, something we can easily try to correct,” said Dr. Moscucci, who presented the data at the scientific sessions of the American Heart Association and discussed the findings in a later interview. “If we can improve our treatment times, we can substantially reduce the risk of death.”

Dr. Moscucci and his associates analyzed data collected on 1,551 patients who had primary percutaneous coronary intervention for acute ST-segment elevation during a 20-month period ending in June

2004. Patients had the procedure at 1 of the 16 hospitals participating in the regional Blue Cross Blue Shield of Michigan Cardiovascular Consortium.

The investigators found that only 26% of the 442 women who had an emergency angioplasty—and 34% of the 1,069 men—had the procedure within the 90-minute time frame recommended by the American Heart Association and the American College of Cardiology.

On average, women waited more than

118 minutes before treatment began, compared with 106 minutes for men.

Patients of both sexes whose angioplasty began within 90 minutes of arrival at the hospital had a 50% lower risk of dying in the hospital than those who waited longer, said Dr. Moscucci, director of interventional cardiology at the University of Michigan Cardiovascular Center, Ann Arbor.

“Since there’s been such a focus on angioplasty recently, we wondered whether the recommended door-to-balloon time of 90 minutes was still significant in terms of survival,” he said. “We found that it’s still an important predictor of in-hospital mortality, and that perhaps we’re not doing as well as we should.”

Women in the study were more than twice as likely as men to die in the hospital; their mortality rate was about 7%, compared with about 3% in men. When

Only 26% of the 442 women who had emergency angioplasty (and 34% of the 1,069 men) had the procedure within the 90-minute time frame recommended.

the investigators adjusted for the average older age of women and the higher frequency of comorbidities, they still found higher in-hospital mortality rates for women, Dr. Moscucci said.

The gender-difference findings augment a

growing body of research showing that women with heart attacks seek care later, present more often with atypical symptoms and comorbidities such as severe diabetes, and face delays in treatment, he said.

In addition to the greater delays in treatment, the Michigan study showed that it takes longer for women to get to an emergency department in the first place. Women reported that their symptoms started an average of 105 minutes before they got to the emergency department; the average time for men was 85 minutes.

Dr. Moscucci said that hospital procedures for activating cardiac catheterization labs vary significantly. Labs could be activated faster—which, along with faster diagnosis, would help hasten door-to-balloon times—if more ambulances had the capability to automatically read or transmit ECGs and if more hospitals allowed emergency physicians and not just cardiologists to activate the labs directly, he said.

A recent survey of more than 1,000 women older than 35 years showed that only 47% of women who had head, neck, back, and jaw pain—typical heart attack symptoms—would call their doctor, and just 35% would call 911 or visit an emergency department.

“Women and their families still need a great deal of education. Their symptoms can be very atypical—perhaps only weakness, difficulty breathing, or dizziness,” said Michael J. Bresler, M.D., professor of emergency medicine at Stanford (Calif.) University. Women in whom heart attack is diagnosed “should be rushed to the cath lab or quickly given a lytic drug if immediate catheterization isn’t available,” he said. ■

BREVBLOC 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.

BREVBLOC 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.

BREVBLOC 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.

BREVBLOC 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 Brevibloc 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

BREVBLOC (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. BREVBLOC is also indicated in noncompensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention. BREVBLOC is not intended for use in chronic settings where transfer to another agent is anticipated.

Intraoperative and Postoperative Tachycardia and/or Hypertension

BREVBLOC (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 BREVBLOC to prevent such events is not recommended.

CONTRAINDICATIONS

BREVBLOC (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 BREVBLOC (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, BREVBLOC (Esmolol Hydrochloride) should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of BREVBLOC, specific treatment may also be considered (see OVERDOSAGE in full prescribing information). The use of BREVBLOC 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 BREVBLOC, several cases of death have been reported in complex clinical states where BREVBLOC was presumably being used to control ventricular rate.

Intraoperative and Postoperative Tachycardia and/or Hypertension: BREVBLOC (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, BREVBLOC (Esmolol Hydrochloride) may be used with caution in patients with bronchospastic diseases. However, since beta₁ selectivity is not absolute, BREVBLOC 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: BREVBLOC (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 BREVBLOC is primarily excreted unchanged by the kidney, BREVBLOC (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 BREVBLOC 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 BREVBLOC (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 BREVBLOC and warfarin showed that concomitant administration of

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

When digoxin and BREVBLOC 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 BREVBLOC pharmacokinetics. When intravenous morphine and BREVBLOC were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but BREVBLOC steady-state blood levels were increased by 46% in the presence of morphine. No other pharmacokinetic parameters were changed.

The effect of BREVBLOC on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by BREVBLOC, 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, BREVBLOC 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 BREVBLOC and verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVBLOC 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 BREVBLOC (Esmolol Hydrochloride).

Pregnancy Category C

Teratogenicity studies in rats at intravenous dosages of BREVBLOC (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. BREVBLOC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

The following adverse reaction rates are based on use of BREVBLOC (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 BREVBLOC 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 BREVBLOC (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/systole 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

BREVBLOC PREMIXED INJECTION

NDC 10019-055-61, 2500 mg - 250 mL in Ready-to-use 250 mL IntraVia Bags

BREVBLOC PREMIXED INJECTION - DOUBLE STRENGTH

NDC 10019-075-87, 2000 mg - 100 mL in Ready-to-use 100 mL IntraVia Bags

BREVBLOC INJECTION

NDC 10019-015-01, 100 mg - 10 mL Ready-to-use Vials, Package of 25

BREVBLOC 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

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

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

Baxter, Brevibloc 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