

Uses for Drug-Eluting Stents Are Rising Rapidly

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Despite their higher cost, and despite recent concerns about late thrombosis, drug-eluting stents now dominate.

In the final 3 months of 2004, drug-eluting stents were estimated to have been used for 87% of all interventional coronary procedures in the United States, Martin B. Leon, M.D., said last November at the

American Heart Association's scientific sessions in New Orleans. Less than 2 years earlier, not a single drug-eluting stent had been used in the United States outside of a clinical trial. The Food and Drug Administration first approved a drug-eluting stent in April 2003.

"We have not yet identified any subsets of patients who don't benefit from receiving drug-eluting stents [by having less restenosis] compared with bare metal stents," said David J. Cohen, M.D., associ-

ate director of interventional cardiology at Beth Israel Deaconess Medical Center in Boston. "De facto practice in the United States today is to use drug-eluting stents whenever the available stent lengths and diameters fit. At Beth Israel Deaconess, most of the time when patients [who are undergoing coronary stenting] don't receive drug-eluting stents it's because the vessel is too small or too large to accommodate available stent sizes," he told this newspaper.

They are so widespread that medicole-

gal concerns may now drive their use even more than purely clinical factors. "When the risk of restenosis is low, operators must balance the need for drug-eluting stents with the medicolegal risk of avoiding what has become the de facto standard of care for all patients," said Herbert D. Aronow, M.D., director of the cardiac catheterization laboratories at the Veterans Affairs Medical Center in Philadelphia.

According to one study, in 2003, about a third of all sirolimus-eluting (Cypher) stents used in the United States were for off-label coronary artery indications (CARDIOLOGY NEWS, February 2005, p. 15).

As of early this year, no cardiology society had issued formal recommendations on the appropriate uses of drug-eluting stents, although these are expected soon. In the meantime, some experts have given their personal opinions.

One set of standards was laid out by Gregg W. Stone, M.D., in a talk at the AHA scientific session. "In workhorse lesions, in patients undergoing elective coronary interventions with de novo lesions up to 46 mm in length and in vessels with reference diameters of 2.5-3.75 mm without acute coronary syndrome or acute MI, in general the safety and efficacy of two drug-eluting stents, Cypher and Taxus [paclitaxel-eluting], has been proved," said Dr. Stone, an interventional cardiologist at Columbia University in New York. "Using drug-eluting stents over bare metal stents in these lesions is the appropriate thing to do."

But, he added, "we desperately need more data regarding the safety and efficacy of drug-eluting stents in unapproved and high-risk indications before their use should be considered routine. . . . You need to be aware of the evidence so you know what you are doing."

A step was taken this past March to better define the safety and efficacy of drug-eluting stents in more complex vessels and lesions, with reports from two studies at the annual meeting of the American College of Cardiology. A Danish study with 322 patients compared sirolimus-eluting with bare-metal stents in patients with total occlusions, lesions at bifurcations, ostial lesions, and lesions in angulated arteries. Patients who received drug-eluting stents had better angiographic and clinical outcomes. A second report involved more than 1,100 patients who were treated with either paclitaxel-eluting or bare metal stents. The results showed that the drug-eluting stents were superior in coronaries narrower than 2.25 mm and in wide arteries.

According to Dr. Stone last November, there are also grounds for using a single drug-eluting stent to treat in-stent restenosis within a bare metal stent. But he cautioned physicians to "think twice" about using drug-eluting stents outside of a study for unprotected left main disease, in-stent restenosis following failed brachytherapy, and in patients with acute myocardial infarction. There is even less evidence on using drug-eluting stents for V-stenting of a bifurcation, and it is completely unclear how cardiologists should manage restenosis within a drug-eluting stent. ■

BREVIBLOC 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.

BREVIBLOC 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.

BREVIBLOC INJECTION

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

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

Intraoperative and Postoperative Tachycardia and/or Hypertension
BREVIBLOC (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 BREVIBLOC to prevent such events is not recommended.

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

Intraoperative and Postoperative Tachycardia and/or Hypertension: BREVIBLOC (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, BREVIBLOC (Esmolol Hydrochloride) may be used with caution in patients with bronchospastic diseases. However, since beta₂ selectivity is not absolute, BREVIBLOC 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: BREVIBLOC (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 BREVIBLOC is primarily excreted unchanged by the kidney, BREVIBLOC (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 BREVIBLOC 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 BREVIBLOC (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 BREVIBLOC and warfarin showed that concomitant administration of

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

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

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

Pregnancy Category C

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

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

The following adverse reaction rates are based on use of BREVIBLOC (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 BREVIBLOC 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 2%; and fatigue in about 1% of patients. Parosmia, 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

BREVIBLOC PREMIXED INJECTION
NDC 10019-055-61, 2500 mg - 250 mL in Ready-to-use 250 mL IntraVia Bags
BREVIBLOC PREMIXED INJECTION - DOUBLE STRENGTH
NDC 10019-075-87, 2000 mg - 100 mL in Ready-to-use 100 mL IntraVia Bags
BREVIBLOC INJECTION
NDC 10019-015-01, 100 mg - 10 mL Ready-to-use Vials, Package of 25
BREVIBLOC 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
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