DESCRIPTION: Esmolol Hydrochloride Injection, for intravenous administration, is a beta–selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life of approximately 9 minutes). Esmolol hydrochloride is (±)-Methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrochloromethyl ester and has the following structure:

\[
\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{NHCH}_3 + \text{HCl}
\]

C_7H_15NO_3Cl  M.W. 331.8

It has one asymmetric center and exists as an enantiomeric pair.

Esmolol hydrochloride is a white to off-white crystalline powder. It is a relatively hydrophilic compound which is very soluble in water and freely soluble in alcohol. Its partition coefficient (octanol/water) at pH 7.0 is 0.42 compared to 17.0 for propranolol.

Esmolol Hydrochloride Injection is a clear, colorless to light yellow, sterile, non-pyrogenic solution. Each ml contains 10 mg Esmolol Hydrochloride and Water for Injection, buffered with 0.2 M Sodium Acetate Trihydrate and 0.546 mg Glacial Acetic Acid. Sodium Hydroxide and/or Hydrochloric Acid added, as necessary, to adjust pH to 4.5 to 5.5.

CLINICAL PHARMACOLOGY: Esmolol hydrochloride is a beta–selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes. Esmolol hydrochloride inhibits the beta receptors located chiefly in the bronchial and vascular musculature.

The beta adrenergic receptor blocking activity of esmolol hydrochloride is approximately equivalent to the glomerular filtration rate and is excreted in the urine with a clearance of approximately 9 minutes. Esmolol hydrochloride has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. Using an appropriate loading dose, steady-state blood levels of esmolol hydrochloride for dosages from 50 to 300 mcg/kg/min (0.025 to 0.15 mg/kg/min) are obtained within five minutes. (Steady-state is reached in about 30 minutes without the loading dose.) Steady-state blood levels of esmolol hydrochloride increase linearly over this dosage range and elimination kinetics are dose-independent over this range. Steady-state blood levels are maintained during infusion but decrease rapidly after termination of the infusion. Because of its short half-life, blood levels of esmolol hydrochloride can be rapidly altered by increasing or decreasing the infusion rate and rapidly eliminated by discontinuing the infusion.

Pharmacokinetics and Metabolism

Esmolol hydrochloride is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells and not by plasma cholinesterases or red cell membrane acetylcholinesterase. Total body clearance in man was found to be about 20 L/kg/hr, which is greater than cardiac output; thus, the metabolism of esmolol hydrochloride is not limited by the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. Esmolol hydrochloride has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. After termination of the infusion, all of the hemodynamic parameters had returned to pretreatment levels.

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Consistent with the high rate of blood-based metabolism of esmolol hydrochloride, less than 2% of the drug is excreted in the urine within 24 hours of the end of infusion. Approximately 73 to 88% of the dosage has been accounted for in the urine as the acidic metabolite of esmolol hydrochloride.

Metabolism of esmolol hydrochloride results in the formation of the corresponding free acid and methanol. The acid metabolite and methanol are excreted in animals to have about 11500th the activity of esmolol and in normal volunteers its blood levels do not correspond, the level of beta blockade. The acid metabolite has an elimination half-life of about 3.7 hours and is excreted in the urine with a clearance approximately equivalent to the glomerular filtration rate. Excretion of the acid metabolite is significantly decreased in patients with renal disease, with the elimination half-life increased to about ten-fold that of normals, and plasma levels considered elevated.

Methanol blood levels, monitored in subjects receiving esmolol hydrochloride for up to 6 hours at 300 mcg/kg/min (0.3 mg/kg/min) and 24 hours at 150 mcg/kg/min (0.15 mg/kg/min), approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity. Esmolol hydrochloride is shown to be 55% bound to human plasma protein, while the acid metabolite is only 10% bound.

Pharmacodynamics

Clinical pharmacology studies in normal volunteers have confirmed the beta blocking activity of esmolol hydrochloride, showing reduction in heart rate at rest and during exercise, and attenuation of iso-proterenol-induced increases in heart rate. Blood levels of esmolol hydrochloride have been shown to correlate with extent of beta blockade. After termination of infusion, substantial recovery from beta blockade is observed in 10 to 20 minutes.

In human electrophysiology studies, esmolol hydrochloride produced effects typical of a beta blocker; a decrease in heart rate, increase in sinus cycle length, prolongation of the sinus node recovery time, prolongation of the AH interval during normal sinus rhythm and during atrial pacing, and an increase in antegrade Wenckebach cycle length.

In patients undergoing radionuclide angiography, esmolol hydrochloride, at dosages of 200 mcg/kg/min (0.2 mg/kg/min), produced reductions in heart rate, systolic blood pressure, rate pressure product, left and right ventricular ejection fraction and cardiac index at rest, which were similar in magnitude to those produced by intravenous propranolol (4 mg). During exercise, esmolol hydrochloride produced reductions in heart rate, rate pressure product, and cardiac index which were also similar to those produced by propranolol, but produced a significantly larger fall in systolic blood pressure. In patients undergoing exercise testing, the maximum therapeutic dose of 300 mcg/kg/min (0.3 mg/kg/min) of esmolol hydrochloride produced similar effects and, in addition, there were small, clinically insignificant increases in the left ventricular end diastolic pressure and pulmonary capillary wedge pressure. At thirty minutes after the discontinuation of esmolol hydrochloride infusion, all of the hemodynamic parameters had returned to pretreatment levels.

The relative cardioselectivity of esmolol hydrochloride was demonstrated in 10 mildly asthmatic patients. Infusions of esmolol hydrochloride (100, 200 and 300 mcg/kg/min [0.1, 0.2 and 0.3 mg/kg/min]) produced no significant increases in specific airway resistance compared to placebo. At 300 mcg/kg/min (0.3 mg/kg/min), esmolol hydrochloride produced only insignificantly greater bronchoconstriction than placebo, and responses were not significantly different from those produced by methanol. The acid metabolite has been shown in methanol-treated patients requiring bronchodilator treatment. One other propranolol-treated patient also experienced dry air-induced bronchospasm. No adverse pulmonary effects were observed in patients with COPD who received therapeutic dosages of esmolol hydrochloride for treatment of supraventricular tachycardia (51 patients) or in perioperative settings (32 patients).

Supraventricular Tachycardia

In two multicenter, randomized, double-blind, controlled comparisons of esmolol hydrochloride with placebo and propranolol, maintenance doses of 50 to 300 mcg/kg/min (0.05 to 0.3 mg/kg/min) of esmolol hydrochloride were found to be more effective than placebo and about as effective as propranolol, 3 to 6 mg given by bolus injections, in the treatment of supraventricular tachycardia, principally atrial fibrillation and atrial flutter. The majority of these studies were developed in the interventional postoperative period. About 60 to 70% of the patients treated with esmolol hydrochloride had a desired therapeutic effect (either a 20% reduction in heart rate, a decrease in heart rate to less than 100 bpm, or, rarely, conversion to NSR) and about 95% of those who responded did so at a dosage of 200 mcg/kg/min (0.2 mg/kg/min) or less. The average effective dosage of esmolol hydrochloride was approximately 100 to 115 mcg/kg/min (0.1 to 0.15 mg/kg/min) in the studies. In other multicenter baseline-controlled studies gave essentially similar results. In the comparison with propranolol, about 50% of patients in both the esmolol hydrochloride and propranolol groups were converted to sinus rhythm. These patients were slightly higher with both beta blockers in the digoxin-treated patients.

In all studies significant decreases of blood pressure occurred in 20 to 50% of patients, identified either as adverse reaction reports by investigators, or by observation of systolic pressure less than 90 mmHg or diastolic pressure less than 50 mmHg. The hypotension was symptomatic (mainly dizziness or lightheadedness) in about 12% of patients, and hypotensive in about 11% of patients, about half of whom were symptomatic. In comparison to propranolol, hypotension was about three times more frequent with esmolol hydrochloride, 53% vs. 17%. The hypotension was rapidly reversible with decreased infusion rate or discontinuation of therapy with esmolol hydrochloride. For both esmolol hydrochloride and propranolol, hypotension was reported less frequently in patients receiving concomitant digoxin.

INDICATIONS AND USAGE:

Supraventricular Tachycardia

Esmolol Hydrochloride Injection is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter, and/or postoperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable. Esmolol hydrochloride is also indicated in uncompensated sinus tachycardia where, in the physician’s judgment, the rapid heart rate requires specific intervention. Esmolol hydrochloride is not intended for chronic settings where transfer to another agent is anticipated.

Supraventricular Tachycardia and/or Hypertension

Esmolol Hydrochloride Injection 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 postanesthesia period. When the patient’s judgment such specific intervention is considered important.

Use of esmolol hydrochloride to prevent such events is not recommended.

Contraindications

Esmolol hydrochloride is contraindicated in patients with sinus bradycardia, heart block greater than first degree, or aortic stenosis or outflow tract heart failure (see WARNINGS).

WARNINGS:

Hypotension

In clinical trials 20 to 50% of patients treated with esmolol hydrochloride have experienced hypotension at dose levels ranging from less than 90 mmHg and/or diastolic pressure less than 50 mmHg. Hypotension has resulted in about 11%, about half of whom were serious. Hypotension may be severe, associated with syncope, and less common to a variety of allergic reactions may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such reactions may be severe, occasionally associated with a variety of clinical states where vasoconstrictive and inotropic support such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is low. The effect of esmolol hydrochloride on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by esmolol hydrochloride, but the duration of neuromuscular block was prolonged from 5 minutes to 8 minutes. Many of the following adverse effects have been treated with pressors such as dopamine, which may also be reported (see OVERDOSAGE). The use of esmolol hydrochloride for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is complicated by hemo- dynamically 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 esmolol, several cases of cardiac arrest have been reported in complex clinical states where esmolol hydrochloride was presumably being used to control ventricular rate.

Intraoperative and Postoperative Tachycardia and/or Hypertension

Esmolol hydrochloride should not be used as the treatment of hypertension in patients in whom the increased blood pressure is primarily due to the vasocconstriction associated with hypothermia. Bronchospastic Diseases

Patients with bronchospastic diseases. However, since beta selectivity is not warranted but should be used with particular caution as beta blockers may mask tachycardia occurring in about 2%; and fatigue in about 1% of patients. Dyspepsia, constipation, dry mouth, and abdominal discomfort have each occurred in less than 1% of patients. Bronchospasm, wheezing, dyspnea, nasal congestion, rhonchi, and rales have each been reported in less than 1% of patients. Cardiac Failure

Intravenous administration of a bolus dose of 0.5 mg/kg resulted in a decrease of 5 minutes to 8 minutes. Majority of the following adverse effects have been fatal. Patients have recovered completely from overdoses as high as 1.75 g over one minute or doses of 7.5 g over one hour for cardiovascular surgery. The effect of esmolol hydrochloride on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by esmolol hydrochloride, but the duration of neuromuscular block was prolonged from 5 minutes to 8 minutes. Many of the following adverse effects have been treated with pressors such as dopamine, which may also be reported (see OVERDOSAGE). The use of esmolol hydrochloride for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is complicated by hemo- dynamically 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. Two minutes after the 4 minutes of initial maintenance infusion dosing needs to be titrated, using ventricular rate as the guide. A single injection of 0.5 mg/kg infused over a minute period may be repeated, followed by a maintenance infusion of 0.1 mg/kg/min for 4 minutes. Then, depending upon ventricular rate, a bolus dose of 0.5 mg/kg/min infused over a 1 minute period may be administered followed by a maintenance infusion of 0.15 mg/kg/min for 4 minutes of the 0.15 mg/kg/min maintenance infusion. The dose may be increased to a maximum of 0.2 mg/kg/min.

In the absence of loading doses, constant infusion of a single concentration of drug may result in pharmacokinetic and pharmacodynamic steady-state in about 30 minutes. Maintenance infusions (with or without loading doses) may be continued for as long as 24 hours. The following table summarizes the above and assumes that 3 loading doses (the maximum rec-
Immediate Control

For postoperative tachycardia and hypertension, the dosing schedule is the same as that used in supraventricular tachycardia. To initiate treatment, administer a loading dosage infusion of 500 mcg/kg/min of Esmolol Hydrochloride Injection for one minute followed by a four-minute maintenance infusion of 50 mcg/kg/min. If an adequate therapeutic effect is not observed within five minutes, repeat the same loading dosage and follow with a maintenance infusion increased to 100 mcg/kg/min (see above Supraventricular Tachycardia).

Notes:
1. Higher dosages (250 to 300 mcg/kg/min) may be required for adequate control of blood pressure than those required for the treatment of atrial fibrillation, flutter and sinus tachycardia. One third of the postoperative hypertensive patients required these higher doses.

2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Direction for Use

Esmolol Hydrochloride Injection is recommended for intravenous administration. It may be used to administer the appropriate loading dosage infusions by hand-held syringe while the maintenance infusion is being prepared.

Esmolol Hydrochloride Injection has a concentration of 10 mg/mL. When using this concentration, a 1 mg/kg bolus dose 0.5 mg/kg/min over 1 minute period of time, for a 70 kg patient is 3.5 mL.

Compatibility with Commonly Used Intravenous Fluids

Esmolol Hydrochloride Injection was tested for compatibility with 10 commonly used intravenous fluids at a final concentration of 10 mg esmolol hydrochloride per mL. Esmolol Hydrochloride Injection was found to be compatible with the following solutions and was stable for at least 24 hours at controlled room temperature or under refrigeration:

- Dextrose (5%) Injection, USP
- Dextrose (5%) in Lactated Ringer’s Injection
- Dextrose (5%) in Ringer’s Injection
- Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP
- Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
- Lactated Ringer’s Injection
- Potassium Chloride (40 mEq/liter) in Dextrose (5%) Injection, USP
- Sodium Chloride (0.45%) Injection, USP
- Sodium Chloride (0.9%) Injection, USP

Esmolol Hydrochloride Injection is NOT compatible with Sodium Bicarbonate (5%) Injection, USP.

HOW SUPPLIED:

Esmolol Hydrochloride Injection (preservative free) single dose vials are supplied as:

Product NDC No. No. Strength
605210 63323-652-10 100 mg/10 mL (10 mg/mL)

Available in packages of 25.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. PROTECT FROM FREEZING. Avoid excessive heat. Vial stoppers do not contain natural rubber latex.

APP Pharmaceuticals, LLC
Schaumburg, IL 60173

For Product Inquiry: 1-800-551-7176

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