Esmonol Hcl injection 10mg/ml "Uni Pharma"

Description

Esmonol is a beta adrenergic receptor blocker with a very short duration of action (elimination half-life is approximately 9 minutes). Esmonol is:

• (±)-methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrocinnamate hydrochloride and has the following structure:ch3o2cch2ch2och2chohch2nhch(ch3)2hci

• Esmonol 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.

All esmonol presentations are clear, colorless to light yellow, sterile, nonpyrogenic and administrated by iv infusion.

Clinical pharmacology

Esmonol is a beta1-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, 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. Esmonol inhibits the beta1 receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit beta2 receptors located chiefly in the bronchial and vascular musculature.

Pharmacokinetics

Esmonol 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 esmonol is not limited by the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. Esmonol 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 esmonol for dosages from 50-300 mcg/kg/min are obtained within five minutes. Steady-state is reached in about 30 minutes without the loading dose. Steady-state blood levels of esmonol 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 esmonol can be rapidly altered by increasing or decreasing the infusion rate and rapidly eliminated by discontinuing the infusion. Consistent with the high rate of blood-based metabolism of esmonol, less than 2% of the drug is excreted unchanged in the urine. Within 24 hours of the end of infusion, the acid metabolite of esmonol in urine accounts for approximately 73-88% of the dosage.

Metabolism of esmonol results in the formation of the corresponding free acid and methanol. The acid metabolite has been shown in animals to have negligible activity and in normal volunteers its blood levels do not correspond to 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.

Methanol blood levels, monitored in subjects receiving esmonol for up to 6 hours at 300 mcg/kg/min and 24 hours at 150 mcg/kg/min, approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity. Esmonol has been 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 esmonol, showing reduction in heart rate at rest and during exercise, and attenuation of isoproterenol-induced increases in heart rate. Blood levels of esmonol have been shown to correlate with extent of beta blockade. After termination of infusion,

substantial recovery from beta blockade is observed in 10-20 minutes.

In human electrophysiology studies, esmonol produced effects typical of a beta blocker: a decrease in the 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, esmonol, at dosages of 200 mcg/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, esmonol produced reductions in heart rate, rate pressure product and cardiac index which were also similar to those produced by propranolol, but esmonol produced a significantly larger fall in systolic blood pressure. In patients undergoing cardiac catheterization, the maximum therapeutic dose of 300 mcg/kg/min of esmonol 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 30 minutes after the discontinuation of esmonol infusion, all of the hemodynamic parameters had returned to pretreatment levels.

The relative cardioselectivity of esmonol was demonstrated in 10 mildly asthmatic patients. Infusions of esmonol 100, 200 and 300 mcg/kg/min produced no significant increases in specific airway resistance compared to placebo. At 300 mcg/kg/min, esmonol produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant, and esmonol was well tolerated by all patients. Six of the patients also received intravenous propranolol, and at a dosage of 1 mg, two experienced significant, symptomatic bronchospasm 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 esmonol for

Treatment of supraventricular tachycardia (51 patients) or in perioperative settings (32 patients).

Supraventricular tachycardia

In two multicenter, randomized, double-blind, controlled comparisons of esmonol injection with placebo and propranolol, maintenance doses of 50 to 300 mcg/kg/min of esmonol were found to be more effective than placebo and about as effective as propranolol, 3-6 mg given by bolus injections, in the treatment of supraventricular tachycardia, principally atrial fibrillation and atrial flutter. The majority of these patients developed their arrhythmias postoperatively. About 60-70% of the patients treated with esmonol developed either a 20% reduction in heart rate, a decrease in

Heart rate to less than 100 bpm, or, rarely, conversion to normal sinus rhythm and about 95% of these patients did so at a dosage of 200 mcg/kg/min or less. The average effective dosage of esmonol was approximately 100 mcg/kg/min in the two studies. Other multicenter baseline-controlled studies gave similar results. In the comparison with propranolol, about 50% of patients in both the esmonol and propranolol groups were on concomitant digoxin. Response rates were slightly higher with both beta blockers in the digoxin-treated patients. In all studies significant decreases of blood pressure occurred in 20-50% 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 hyperhidrosis or dizziness) in about 12% of patients, and therapy was discontinued in about 11% of patients, about half of whom were symptomatic. Hypotension was more common with esmonol (53%) than with propranolol (17%). The hypotension was rapidly reversible with decreased infusion rate or after discontinuation of therapy with esmonol. For both esmonol and propranolol, hypotension was reported less frequently in patients receiving concomitant digoxin.

Indications and usage

Esmonol is a beta adrenergic blocker indicated for the short-term treatment of:

- Control of ventricular rate in supraventricular tachycardia including atrial fibrillation and atrial flutter and control of heart rate in noncompensatory sinus tachycardia.
- Control of perioperative tachycardia and hypertension.

Supraventricular tachycardia or noncompensatory sinus tachycardia

Esmonol 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. Esmonol is also indicated in noncompensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention. Esmonol is intended for short-term use.

Intraoperative and postoperative tachycardia and/or hypertension

Esmonol is indicated for the short-term 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 esmonol to prevent such events is not recommended.

Contraindications

Esmonol is contraindicated in patients with:

• severe sinus bradycardia

• heart block greater than first degree

• decompensated heart failure

• cardiogenic shock

Warnings and precautions

Hypotension

Hypotension can occur at any dose but is dose-related. Patients with hemodynamic compromise or on interacting medications are at particular risk. Severe reactions may include loss of consciousness, cardiac arrest, and death. For control of ventricular heart rate, maintenance doses greater than 200 mcg per kg per min are not recommended. Monitor patients closely, especially if pretreatment blood pressure is low. In case of an unacceptable drop in blood pressure, reduce or stop esmonol injection. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

Cardiac failure

Beta blockers, like esmonol injection, can cause depression of myocardial contractility and may precipitate heart failure and cardiogenic shock. At the first sign or symptom of impending cardiac failure, stop esmonol and start supportive therapy

Intraoperative and postoperative tachycardia and/or hypertension

Reactive airways disease

Patients with reactive airways disease should, in general, not receive beta blockers. Because of its relative beta1 selectivity and titratability, titrate esmonol to the lowest possible effective dose. In the event of bronchospasm, stop the infusion immediately; a beta2 stimulating agent may be administered with appropriate monitoring of ventricular rates.

Use in patients with diabetes mellitus and hypoglycemia

In patients with hypoglycemia, or diabetic patients (especially those with labile diabetes) who are receiving insulin or other hypoglycemic agents, beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be masked.

Drug interactions

Concomitant use of esmonol injection with other drugs that can lower blood pressure, reduce myocardial contractility, or interfere with sinus node function or electrical impulse propagation in the myocardium can exaggerate esmonol's effects on blood pressure, contractility, and impulse propagation. Severe interactions with such drugs can result in, for example, severe hypotension, cardiac failure, severe

bradycardia, sinus pause, sinoatrial block, atrioventricular block, and/or cardiac arrest. Esmonol should therefore be used only after careful individual assessment of the risks and expected benefits in patients receiving drugs that can cause these types of pharmacodynamic interactions, including but not limited to:

• digitalis glycosides: concomitant administration of digoxin and esmonol leads to an approximate 10% to 20% increase of digoxin blood levels at some time points. Digoxin does not affect esmonol pharmacokinetics

Nonclinical toxicology

Because of its short term usage no carcinogenicity, mutagenicity, or reproductive performance studies have been conducted with esmonol.

Use in specific populations

Pregnancy

Pregnancy category C.

Esmonol has been shown to produce increased fetal resorptions with minimal maternal toxicity in rabbits when given in doses approximately 8 times the maximum human maintenance dose (300 mcg/kg/min). There are no adequate and well-controlled studies in pregnant women. Esmonol injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Teratogenicity studies in rats at intravenous dosages of esmonol up to 3000 mcg/kg/min (10 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 produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 mcg/kg/min for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 mcg/kg/min produced minimal maternal toxicity and increased fetal resorptions.

Nursing mothers

It is not known whether this drug is excreted in human milk.

Pediatric use

The safety and effectiveness of esmonol in pediatric patients have not been established.

Adverse reactions

The following adverse reaction rates are based on use of esmonol 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

And common adverse effect has been hypotension *[see warnings and precautions].*

Clinical trial adverse reactions (frequency >3%)

System organ class (SOC)	Preferred MedDRA Term	Frequency
Vascular disorders	Hypotension*	
	- Asymptomatic hypotension	25%
	- Symptomatic hypotension (hyperhidrosis, dizziness)	12%
General disorders and Administration site conditions	Infusion site reactions (inflammation and induration)	8%
Gastrointestinal disorders	Nausea	7%
Nervous system disorders	Dizziness	3%
	Somnolence	3%
* Hypotension resolved during esmonol infusion in 63% of patients. In 80% of the remaining patients, hypotension resolved within 30 minutes following discontinuation of infusion.		

Clinical trial adverse reactions (frequency <3%)

Psychiatric disorders

Confusional state and agitation (~2%)

Anxiety, depression and abnormal thinking (<1%)

Nervous system disorders

Headache (~ 2%)

Paresthesia, syncope, speech disorder, and lightheadedness (<1%)

Convulsions (<1%), with one death

Vascular disorders

Peripheral ischemia (~1%)

Pallor and flushing (<1%)

Gastrointestinal disorders

Vomiting (~1%)

Dyspepsia, constipation, dry mouth, and abdominal discomfort (<1%)

Renal and urinary disorders

Urinary retention (<1%)

Overdosage

Dilution errors

Massive accidental overdoses of esmonol have resulted from dilution errors.

Treatment recommendations

Because of its approximately 9-minute elimination half-life, the first step in the management of toxicity should be to discontinue the esmonol infusion. Then, based on the observed clinical effects, consider the following general measures.

Bradycardia

Consider intravenous administration of atropine or another anticholinergic drug or cardiac pacing.

Cardiac failure

Consider intravenous administration of a diuretic or digitalis glycoside. In shock resulting from inadequate cardiac contractility, consider intravenous administration of dopamine, dobutamine, isoproterenol, or inamrinone. Glucagon has been reported to be useful.

Symptomatic hypotension

Consider intravenous administration of fluids or vasopressor agents such as dopamine or norepinephrine.

Bronchospasm

Consider intravenous administration of a beta2 stimulating agent or a theophylline derivative.

Dosage and administration

Esmonol injection is available in concentration of 10mg/ml and ready-to-use vial. The ready-to-use vial may be used to administer a loading dosage by hand-held syringe while the maintenance infusion is being prepared.

Dosing for the treatment of supraventricular tachycardia

Esmonol is administered by continuous intravenous infusion with or without a loading dose.

Additional loading doses and/or titration of the maintenance infusion (step-wise dosing) may be necessary based on desired ventricular response.

Step action

1. optional loading dose (500 mcg per kg over 1 minute), then 50 mcg per kg per min for 4 min
2. optional loading dose if necessary, then 100 mcg per kg per min for 4 min

Intraoperative dosage

The dosage of intraoperative has not been studied. The safety of doses above 300 mcg per kg per minute has not been studied.

Storage

Store at 25°c.

Manufactured for:
Uni Pharma Co., Ltd
8F., No.43, Ln. 115, Sec. 2, Zhongshan n. Rd., Zhongshan Dist., Taipei city 104, Taiwan

Manufactured by:
Genovate Biotechnology Co., Ltd
No.1, Gongye 1st Rd., Hukou Township, Hsinchu County 303, Taiwan