Isuprel™

Name of Medicine
Isoprenaline Hydrochloride 0.2mg/mL Injection

Presentation
A colourless sterile solution of Isoprenaline hydrochloride in a 1mL or 5mL glass ampoule. Each mL of the sterile non pyrogenic 1:5000 solution contains 0.2mg of Isoprenaline hydrochloride and Sodium Lactate, Lactic Acid, Sodium Metabisulphite, Sodium Chloride, Water for Injection and Hydrochloric Acid (for pH adjustment).

Uses

Actions
Isoprenaline is a potent non selective beta-adrenergic agonist with low affinity for alpha-adrenergic receptors.

Isoprenaline acts primarily on the heart and on smooth muscle of bronchi, skeletal muscle vasculature and the gastrointestinal tract.

Isoprenaline increases cardiac output due to its positive inotropic and chronotropic actions and increasing venous return. With usual therapeutic doses, the increase in cardiac output is generally sufficient to maintain or increase systolic blood pressure. Intravenous infusion of isoprenaline also lowers peripheral vascular resistance. The diastolic pressure, therefore, may be expected to fall in normal individuals. Thus the mean pressure may be reduced. The rate of discharge of cardiac pacemakers is increased with isoprenaline.

Isoprenaline relaxes most smooth muscle, the most pronounced effect being on bronchial and gastrointestinal smooth muscle. It produces marked relaxation in the smaller bronchi and may even dilate the trachea and main bronchi past the resting diameter.

In man, isoprenaline causes less hyperglycaemia than does adrenaline. Isoprenaline and adrenaline are equally effective in stimulating the release of free fatty acids and energy production.

Pharmacokinetics
Isoprenaline is readily absorbed when given parenterally.

The half-life of isoprenaline hydrochloride is brief lasting only a few minutes following intravenous administration and up to 2 hours after subcutaneous administration. Isoprenaline is metabolised by catechol-o-methyl transferase primarily in the liver. The major metabolite after intravenous administration is 3-O-methylishoprenaline, which is reported to have weak β-adrenergic blocking activity, and its conjugates. Isoprenaline is a relatively poor substrate for MAO and is not taken up by sympathetic neurons to the same extent as adrenaline and noradrenaline. The duration of action of isoprenaline may therefore be longer than that of adrenaline, but it is still brief. The metabolites are excreted through the kidneys.

Indications
Isuprel™ is indicated for:
1. Mild or transient episodes of heart block that do not require electric shock or pacemaker therapy.
2. Serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia of fibrillation). (See CONTRAINDICATIONS).
3. Use in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, are available. (see CONTRAINDICATIONS).
4. Bronchospasm occurring during anaesthesia.
5. As an adjunct to fluid and electrolyte replacement therapy and the use of other medicines and procedures in the treatment of hypovolaemic and septic shock, low cardiac output (hypoperfusion) states, congestive heart failure, and cardiogenic shock. (See WARNINGS AND PRECAUTIONS).

Dosage and Administration
Isuprel™ can be administered by the intravenous, intramuscular, subcutaneous or intracardiac routes.

Isuprel™ should generally be started at the lowest recommended dose and the rate of administration gradually increased if necessary while carefully monitoring the patient. The usual route of administration is by intravenous infusion or bolus intravenous injection. In dire emergencies, the medicine may be administered by intracardiac injection. If time is not of the utmost importance, initial therapy by intramuscular or subcutaneous injection is preferred.

Elderly patients may be more sensitive to the effects of sympathomimetics and lower doses may be required.

Adults
Recommended Dosage for adults with shock and hypoperfusion states

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Preparation of Dilution+</th>
<th>Infusion Rate++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous infusion</td>
<td>Dilute 5mL (1mg) in 500mL of 5% Glucose Injection, BP</td>
<td>0.5 mcg to 5mcg per minute (0.25mL to 2m5mL) of diluted solution.</td>
</tr>
</tbody>
</table>

+ Concentrations up to 10 times greater have been used when limitation of volume is essential.
++ Rates over 30mcg per minute have been used in advanced stages of shock. The rate of infusion should be adjusted on the basis of heart rate, central venous pressure, systemic blood pressure, and urine flow. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease or temporarily discontinue the infusion.

Recommended dosage for adults with heart block, Adams-Stokes attacks, and cardiac arrest

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Preparation of dilution</th>
<th>Initial dose</th>
<th>Subsequent administration dose range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus intravenous injection</td>
<td>Dilute 1mL of solution 1:5000 (0.2mg) to 10mL with Sodium Chloride Injection BP, or 5% Glucose, Injection, BP</td>
<td>0.02mg to 0.06mg (1mL to 3mL of diluted solution 1:50,000)</td>
<td>0.01mg to 0.2mg (0.5mL to 10mL of diluted solution)</td>
</tr>
<tr>
<td>Intravenous infusion</td>
<td>Dilute 10mL of solution 1:5000 (2mg) in 500mL of 5% Glucose Injection, BP</td>
<td>5mcg/min (1.25mL of diluted solution 1:250,000 per minute)</td>
<td></td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Use Solution 1:5000 undiluted</td>
<td>0.2mg (1mL)</td>
<td>0.02mg to 1mg (0.1mL)</td>
</tr>
</tbody>
</table>
**Recommended dosage for adults with bronchospasm occurring during anaesthesia**

<table>
<thead>
<tr>
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<th>Preparation of Dilution</th>
<th>Initial Dose</th>
<th>Subsequent Dose Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus intravenous injection</td>
<td>Dilute 1mL (0.2mg) to 10mL with sodium chloride injection, BP, or 5% glucose Injection, BP</td>
<td>0.01mg to 0.02mg (0.5mL to 1mL of dilute solution)</td>
<td>The initial dose may be repeated when necessary</td>
</tr>
</tbody>
</table>

*Subsequent dosage and method of administration depend on the ventricular rate and the rapidity with which the cardiac pacemaker can take over when the medicine is gradually withdrawn.

**Children**

There are no well-controlled studies in children to establish appropriate dosing; however, the American Heart Association recommends an initial infusion rate of 0.1mcg/kg/min, with the usual range being 0.1mcg/kg/min to 1.0mcg/kg/min.

Adequacy and safety of intravenous isoprenaline in children are not established. Based on published literature, the initial dose of intravenous isoprenaline used in children is not established. Based on published literature, the initial dose of intravenous isoprenaline used in children (age 7 to 19 years of age) ranges between 0.05 to 0.17mcg/kg/min, which is increased gradually by 0.1 to 0.2mcg/kg/min at intervals of 15 to 20 minutes, titrated to clinical response; a maximum dose ranging between 1.3 to 2.7mcg/kg/min has been used. In children generally, post-operative cardiac patients with bradycardia require lower doses (0.029 ± 0.002mcg/kg/min) of intravenous isoprenaline than asthma patients (0.5 ± 0.21mcg/kg/min).

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Such solution should not be used.

Do not administer unless solution is clear and container is undamaged. Discard unused portion.

**Contraindications**

Use of Isuprel™ is contraindicated in patients with tachyarrhythmias; tachycardia or heart block caused by digitalis intoxication; ventricular arrhythmias which require inotropic therapy; recent myocardial infarction, angina pectoris and previous history of hypersensitivity to isoprenaline.

**Warnings and Precautions**

Isoprenaline injection should generally be started at the lowest recommended dose. This may be gradually increased if necessary while carefully monitoring the patient.

Isoprenaline injection, by increasing myocardial oxygen requirements while decreasing effective coronary perfusion, may have a deleterious effect on the injured or failing heart. Most experts
discourage its use as the initial agent in treating cardiogenic shock following myocardial infarction. However, when a low arterial pressure has been elevated by other means, isoprenaline injection may produce beneficial haemodynamic and metabolic effects.

In a few patients, presumably with organic disease of the A-V node and its branches, isoprenaline has been reported, paradoxically to worsen heart block or precipitate Adams-Stokes seizures during normal sinus rhythm or transient heart block.

Isuprel™ contains sodium metabisulphite, a sulphite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulphite sensitivity in the general population is unknown and probably low. Sulphite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

Particular caution is necessary in administering isoprenaline injection to the elderly and patients with coronary insufficient, ischaemic heart disease, hypertension, aneurysms, diabetes or hyperthyroidism, and in patients sensitive to sympathomimetic amines.

There are case reports of occasional fatal cardiac dysrhythmia and myocardial necrosis at autopsy as a result of intravenous isoprenaline. ECG changes and serum CPK-MB level elevation consistent with transient myocardial ischaemia and abnormal echocardiographic findings suggestive of myocardial dysfunction have been documented with the use of intravenous isoprenaline infusion for the treatment of severe asthma exacerbations in children. Care should be taken to ensure that oxygen is always administered during isoprenaline infusions in patients with asthma. Heart rate, blood pressure, arrhythmias and evidence of myocardial ischaemia by ECG should be monitored. Arterial blood gases should also be monitored carefully and PaO₂ maintained above 60 torr. Where ECG suggests myocardial ischaemia, cardiac enzymes including cardiac-specific CPK-MB isoenzyme levels should be determined.

Adequate filling of the intravascular compartment by suitable volume expanders is of primary importance in most cases of shock, and should precede the administration of vasoactive drugs. In patients with normal cardiac function, determination of central venous pressure is a reliable guide during volume replacement. If evidence of hypoperfusion persists after adequate volume replacement, Isuprel™ may be given.

In addition to the routine monitoring of systemic blood pressure, heart rate, urine flow, and the electrocardiograph, the response to therapy should also be monitored by frequent determinations of the central venous pressure and blood gases. Patients in shock should be closely observed during Isuprel™ administration. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease the infusion rate or temporarily discontinue the infusion.

Determinations of cardiac output and circulation time may also be helpful. Doses of Isuprel™ sufficient to increase the heart rate to a more than 130 beats per minute may induce ventricular arrhythmia. If the cardiac rate increases sharply, patients with angina pectoris may experience anginal pain until the cardiac rate decreases.

If ventricular hyperexcitability (extrasystoles, polymorphic extrasystoles or sustained ventricular tachycardia) should occur, the dosage should be reduced and the electrocardiogram monitored.

Appropriate measures should be taken to ensure adequate ventilation. Careful attention should be paid to acid-base balance and to the correction of electrolyte disturbances.
In cases of shock associated with bacteraemia, suitable antimicrobial therapy is, of course, imperative. Care is required when sympathomimetic agents are given to patients with diabetes mellitus or closed angle glaucoma.

**Use in Pregnancy**

Category A.

Medicines which have been taken by a large number of pregnant women of childbearing age without any proven increase in the frequency of malformation or other direct or indirect harmful effects on the foetus having been observed.

There has been no clinical evidence of teratogenic effects attributable to Isuprel™ in more than 25 years use of the medicine. Isoprenaline may delay the second stage of labour by inhibiting contraction of the uterus. However, before administration of any medicine to pregnant or lactating women, or women of childbearing potential, the expected benefit of the medicine should be carefully weighed against the possible risk to the mother or child.

**Use in Lactation**

It is unknown whether isoprenaline hydrochloride is excreted into breast milk. Caution should be exercised in administering to a nursing mother.

**Paediatric Use**

Dosage has not been established in children (See DOSAGE AND ADMINISTRATION).

**Adverse Effects**

Serious effects to Isuprel™ are infrequent. The following effects, however, have been reported:

**CNS**

Nervousness, headache, dizziness, restlessness, tension, fear of excitement, and rarely, nausea, vomiting, tinnitus, light headedness and asthenia.

**Cardiovascular**

Tachycardia, palpitations, angina, Adams-Stokes attacks, hypertension, hypotension, ventricular arrhythmias, tachyarrhythmias and pulmonary oedema. In a few patients, presumably with organic disease of the AV node and its branches, isoprenaline hydrochloride injection has been reported to precipitate Adams-Stokes seizures during normal sinus rhythm or transient heart block.

**Other**

Hot flashes, flushing of the skin, sweating, mild tremors, weakness. These effects disappear quickly and usually do not require discontinuation of treatment with Isuprel™. No cumulative effects have been reported. Pulmonary oedema has been reported in a patient extremely intolerant to all sympathomimetic drugs.

The following effects to isoprenaline hydrochloride have been reported in healthy adult controls undergoing upright tilt testing:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients (n=15)</th>
<th>Control Gr (n=13)</th>
<th>Control GII (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warmth</td>
<td>87%</td>
<td>93</td>
<td>78</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>87</td>
<td>77</td>
<td>56</td>
</tr>
<tr>
<td>Dizziness</td>
<td>80</td>
<td>77</td>
<td>56</td>
</tr>
</tbody>
</table>

* P=0.03 (difference between patients vs. controls)
<table>
<thead>
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<th>Control GII (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallor</td>
<td>40</td>
<td>69</td>
<td>78</td>
</tr>
<tr>
<td>Visual Blurring*</td>
<td>33</td>
<td>77</td>
<td>56</td>
</tr>
<tr>
<td>Nausea</td>
<td>40</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>Shakiness</td>
<td>20</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Weakness</td>
<td>27</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>33</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>29</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

**Interactions**

**Adrenaline**
Isuprel™ and adrenaline should not be administered simultaneously because both medicines are direct cardiac stimulants and their combined effects may induce serious arrhythmias. The medicines may, however, be administered alternately provided a proper interval has elapsed between doses.

**Anaesthetics**
Isuprel™ should be used with caution, if at all, when potent inhalational anaesthetics such as halothane and cyclopropane are employed because of potential to sensitise the myocardium to effects of sympathomimetic amines.

**Antidepressants, tricyclic or Maprotiline**
Concurrent use may potentiate cardiovascular effects of isoprenaline and phenylephrine, possibly resulting in arrhythmias, tachycardia or severe hypertension or hyperpyrexia.

**Beta-adrenergic blocking agents**
Concurrent use with isoprenaline may result in mutual inhibition of therapeutic effects; beta-blockade may antagonise beta-2-adrenergic bronchodilating effects of isoprenaline; use of a cardioselective beta-2-adrenergic blocker, such as acebutolol, atenolol, or metoprolol, at low doses may reduce antagonism of the bronchodilating effect.

**CNS Stimulants**
Concurrent use with isoprenaline may result in additive CNS stimulation to excessive levels, which may cause unwanted effects such as nervousness, irritability, insomnia, or possibly convulsions or cardiac arrhythmias; close observation is recommended.

**Digitalis Glycosides**
Concurrent use with isoprenaline and phenylephrine may increase the risk of cardiac arrhythmias; caution and electrocardiographic monitoring are very important if concurrent use is necessary.

**Levodopa**
Concurrent use with isoprenaline and phenylephrine may increase the possibility of cardiac arrhythmias; dosage reduction of the sympathomimetic is recommended.

**Nitrates**
Concurrent use with isoprenaline and phenylephrine may reduce the antianginal effects of these medications.
**Sympathomimetics**
Concurrent use may increase the cardiovascular effects of either the other sympathomimetics or isoprenaline and phenylephrine and the potential for side effects.

**Thyroid hormones**
Concurrent use may increase the effects of either these medications or isoprenaline and phenylephrine; thyroid hormones enhance risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease; dosage adjustment is recommended, although problem is reduced in euthyroid patients.

**MAOI’s, Chlorpromazine**
Isoprenaline should not be used with chlorpromazine or monoamine oxidase inhibitors since the effects of isoprenaline may be magnified.

**Xanthines/Corticosteroids**
Caution should be maintained when using continuous intravenous isoprenaline infusions in conjunction with intravenous methyl xanthines (aminophylline, theophylline) and intravenous corticosteroids. The use of isoprenaline with aminophylline and corticosteroids may be additive in cardiotoxic properties and can lead to myocardial necrosis and death. Severe cardiac symptoms of sympathetic overactivation i.e. hypertension, tachycardia, arrhythmias, seizures, myocardial ischaemia, and fatal myocardial necrosis, have been reported.

**Overdosage**
The acute toxicity of isoprenaline in animals is much less than that of adrenaline. Excessive doses in animals or man can cause a striking drop in blood pressure, and repeated large doses in animals may result in cardiac enlargement and focal myocarditis.

In case of accidental overdosage as evidenced mainly by the tachycardia or other arrhythmias, palpitations, angina, hypotension, or hypertension, reduce rate of administration or discontinue Isuprel™ until patients condition stabilises. Blood pressure, pulse, respiration and ECG should be monitored.

Very cautious use of a non-selective beta receptor antagonist should be considered if symptoms are very severe but close monitoring of airway function would be essential.

It is not known whether Isuprel™ is dialysable.

In case of overdose, immediately contact the Poisons Information Centre for advice (in New Zealand call 0800 764 766).

**Pharmaceutical Precautions**
Store at 2°C - 8°C. Refrigerate, do not freeze.

**Medicine Classification**
Prescription Medicine

**Packager Quantities**
Injection, 200 microgram/mL, 1mL ampoules: 25's, 50's; 5mL ampoules: 10's
Further Information
Isoprenaline hydrochloride (also called isoproterenol hydrochloride) is 3,4-Dihydroxy-alpha-(isopropylamino) methyl benzyl alcohol hydrochloride, a synthetic sympathomimetic amine that is structurally related to adrenaline but acts almost exclusively on beta adrenergic receptors.

Toxicity
The oral LD$_{50}$ of isoprenaline in mice is 3,850mg/kg ± 1,190mg/kg of pure drug in solution.

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Date of Preparation
8 January 2010