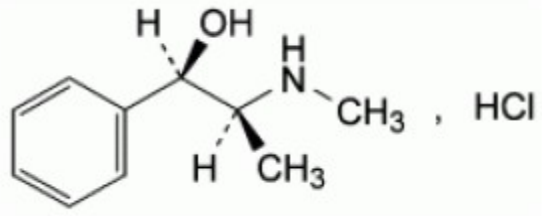
Ephedrine Hydrochloride SXP Injection

PRODUCT INFORMATION

Name of the medicine

Ephedrine hydrochloride.
Chemical name is (1*R*,2*S*)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride. Its structural formula is:



$C_{10}H_{16}ClNO$ Molecular weight: 201.7 CAS No.: 50-98-6

Description

Ephedrine hydrochloride is a white to almost white crystalline powder or colourless crystals. It is freely soluble in water and soluble in ethanol (96%).

Ephedrine hydrochloride injection comes in one strength containing 30 mg/ mL. The injection also contains water for injections. The mass of ephedrine in one ampoule is 24.6 mg.

Pharmacology

Ephedrine is a sympathomimetic which stimulates both alpha and beta adrenergic receptors, and also releases noradrenaline from storage site. The main effects of therapeutic doses of ephedrine are relaxation of bronchial smooth muscle, cardiac stimulation and increased systolic and usually diastolic blood pressure via an increase in cardiac output and peripheral vasoconstriction. Ephedrine also decreases intestinal tone and motility, relaxes the bladder wall, contracts the sphincter muscle, relaxes the detrusor muscle, and decreases uterine activity. Ephedrine also has central nervous system stimulant effects. Tachyphylaxis to the effects of ephedrine may also occur after use for a short while possibly due to the depletion of noradrenaline stores.

Pharmacokinetics

The duration of pressor and cardiac responses to ephedrine is 1 hour after intravenous administration of 10 to 25 mg Small quantities of ephedrine are metabolised in the liver, but the majority of ephedrine is excreted unchanged in the urine. The plasma half-life of ephedrine is 3 to 6 hours. Elimination of ephedrine is increased (and hence the half- life is decreased) with decreasing pH of the urine. Ephedrine is presumed to cross the placenta, and to be excreted into breast milk.

Clinical trials

The supporting evidence for the use of ephedrine in the treatment of hypotension secondary to spinal anaesthesia is based on published literature, predominantly in patients undergoing spinal anaesthesia for caesarean section. In one study the frequency of reactive hypertension was 0% in the patients receiving 10mg ephedrine, and 13.3% and 46.7% respectively in patients receiving a 15mg or 20mg bolus. In a second study reactive hypertension was observed in 5% of patient receiving 10 mg ephedrine, and 25% and 45%, respectively, in patient receiving a 20mg or30 mg bolus. Overall the body of literature evidence supports the use of ephedrine in the treatment of hypotension secondary to spinal anaesthesia administered as an IV bolus dose with additional incremental rescue boluses as required

Indications

Ephedrine Hydrochloride Injection is indicated in the treatment of hypotension secondary to spinal anaesthesia.

Contraindications

Ephedrine Hydrochloride Injection is contraindicated in closed angle glaucoma, since ephedrine may exacerbate the condition.

Ephedrine hydrochloride is contraindicated in patients with pheochromocytoma, since severe hypertension may result.

Ephedrine hydrochloride is contraindicated in patients with asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis) since the obstruction may increase as myocardial contractility improves.

Ephedrine hydrochloride is contraindicated in patients undergoing therapy with monoamine oxidase inhibitors (MAO inhibitors), or within 14 days of ceasing such therapy, since MAO inhibitors may prolong and intensify the cardiac and pressor effects of ephedrine.

Ephedrine hydrochloride is contraindicated in patients undergoing general anaesthesia with cyclopropane or halothane or other halogenated hydrocarbons, since anaesthesia may increase cardiac irritability which may lead to arrhythmias.

Ephedrine hydrochloride is contraindicated in patients with tachyarrhythmias coronary thrombosis or ventricular fibrillation, since exacerbation of these conditions may occur.

Ephedrine hydrochloride is also contraindicated in patients with hypersensitivity to ephedrine and in patients with psychoneurosis.

Ephedrine is contraindicated in patients using linezolid.

Precautions

The use of ephedrine as a pressor agent is not a substitute for replacement of blood, plasma, fluids and/or electrolytes. Blood volume depletion should be corrected as fully as possible before ephedrine therapy is instituted. In an emergency, ephedrine may be used as an adjunct to fluid volume replacement or as a temporary supportive measure to maintain coronary and cerebral artery perfusion until volume replacement therapy can be completed, but ephedrine must not be used as sole therapy in hypovolaemic patients.

Ephedrine may deplete noradrenaline stores in sympathetic nerve endings resulting in reduced cardiac and pressor effects of the drug. Consequently, it may be necessary to administer noradrenaline to replace tissue stores for restoration of the pressor effects of ephedrine.

Caution should be exercised if a dose greater than the maximum recommended bolus is administered as this may lead to undesirable hypertension.

Prolonged administration of pressor agents has been associated with oedema, haemorrhage, focal myocarditis, subpericardial haemorrhage, necrosis of the intestine and hepatic and renal necrosis. Since these effects have generally been observed in patients with severe shock and it is not clear if the drug or the shock state itself was responsible, they should therefore be taken into consideration before ephedrine hydrochloride is used.

Hypoxia, hypercapnia and acidosis may also reduce the effectiveness or increase the incidence of adverse effects of ephedrine, and should be identified and corrected prior to or concurrently with administration of the drug.

Ephedrine hydrochloride should be used with caution, if at all, in patients with hypertension or hyperthyroidism, since there is an increased risk of adverse effects in these patients.

Ephedrine hydrochloride should also be used with caution in geriatric males, especially those with prostatic hyportrophy, since ephedrine may cause acute urinary retention.

Ephedrine hydrochloride should also be used with caution in diabetic patients since drug induced hyperglycaemia may result in loss of diabetic control.

Ephedrine hydrochloride should also be used with caution in patients with cardiovascular disease including angina, cardiac arrhythmia and coronary insufficiency, since the cardiovascular effects of ephedrine may exacerbate these conditions. Ephedrine may intensify the ischaemia in myocardial infarction by increasing myocardial oxygen demands.

Patient monitoring
Cardiovascular parameters, including blood pressure should be monitored during therapy with ephedrine. Urinary output should also be monitored.

Use in pregnancy (Category A[1])

Ephedrine Hydrochloride Injection may accelerate the foetal heart rate when used to control maternal hypotension during spinal anaesthesia for delivery. Ephedrine Hydrochloride Injection should not be used if the maternal blood pressure is greater than 130/80 mmHg.

Ephedrine has been shown to cross the placenta and undergo early metabolism and/or redistribution in the foetus. Ephedrine has been associated with an increased risk of mild metabolic acidosis with increased umbilical plasma concentrations of lactate, glucose, epinephrine, and norepinephrine and greater UV PCO2.
Despite the transplacental passage of ephedrine and notable effects on the cord blood pH; it is uncertain whether this has the potential to affect clinical outcome on the neonate. Other studies have not demonstrated significant effects on neonatal outcomes.

Effects on fertility

The effects of ephedrine hydrochloride on male and female fertility have not been investigated in animal studies.

Use in lactation
Ephedrine hydrochloride is distributed into breast milk, and therefore Ephedrine Hydrochloride Injection is not recommended for use during lactation because of the risk of adverse effects in the infant.

Paediatric use
Ephedrine hydrochloride SXP Injection is not approved for use in this patient population.

Genotoxicity

Ephedrine sulfate was not mutagenic in four strains of Salmonella typhimurium (TA100, TA1535, TA97, or TA98) with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 activation. Ephedrine sulfate did not induce sister-chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells

Carcinogenicity

Carcinogenesis studies of ephedrine were conducted by administering 0, 125, or 250 ppm of ephedrine sulfate to groups of rats and mice for 103 weeks. Neoplasms that occurred in these studies were not considered to be related to administration of the drug. Two high dose female mice had ovarian granulose cell tumours, and luteomas were found in one low dose and one high dose female mouse. Because of the low incidence, these uncommon, benign tumours could not be clearly related to ephedrine sulfate administration.
Under the conditions of these studies, there was no evidence of carcinogenicity for rats or mice of either sex receiving 125 or 250 ppm ephedrine sulfate in the diet for 2 years.

[1] Drugs which have been taken by a large number of pregnant women and women of childbearing age without

any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed

Interactions with other medicines

Alpha blockers
Alpha blockers may decrease the vasopressor effect of ephedrine.

Atropine sulphate
Atropine sulfate may increase the vasopressor effect of ephedrine.

Beta blockers
Beta blockers may inhibit the cardiac and brochodilator effects of ephedrine.

Cardiac glycosides
Concurrent use of cardiac glycosides and ephedrine may increase the risk of arrhythmias.

Ergotamine, ergometrine, methylergometrine, oxytocin
Concurrent use of these drugs with ephedrine hydrochloride may result in a potentiation of the pressor effect of ephedrine. Concurrent use of ergotamine and ephedrine sulfate may also produce peripheral vascular ischaemia and gangrene.

Guanethidine
Ephedrine hydrochloride may decrease the antihypertensive effect of guanethidine.

Hydrocarbon inhalation anaesthetics, such as cyclopropane, halothane
These drugs may increase cardiac irritability, and concurrent use with ephedrine hydrochloride may lead to increased risk of arrhythmia (see **CONTRAINDICATIONS**).

Indirect sympathomimetic agents (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate)
Risk of vasoconstriction and/or of acute episodes of hypertension

Methyldopa
Concurrent use of methyldopa with ephedrine hydrochloride may result in a reduced pressor effect.

Moclobemide
Risk of headache and palpitations, and/or hypertension.

Monoamine Oxidase (MAO) inhibitors
Concurrent use of MAO inhibitors and ephedrine sulphate may result in potentiation of the cardiac and pressor effects of ephedrine (see **CONTRAINDICATIONS**).

Noradrenergic-serotoninergic antidepressants (minalcipran, venlafaxine)
Paroxysmal hypertension with possibility of arrhythmia (inhibition of adrenaline or noradrenaline entry in sympathetic fibres).

Linezolid
By extrapolation from non-selective MAO inhibitors.

Reserpine
Concurrent use of reserpine with ephedrine hydrochloride may result in a reduced pressor effect.

Sympathomimetic agents
Concurrent use of ephedrine hydrochloride and other sympathomimetics may result in increased cardiovascular and pressor effects and an increased risk of adverse effects.

Tricyclic antidepressants
Concurrent use of tricyclic antidepressant and ephedrine may result in potentiation of the cardiovascular and pressor effects of ephedrine.

Clonidine
Pretreatment with clonidine may increase the pressor effect of ephedrine.

Urinary Alkalinizers, such as acetazolamide, dichlorphenamide, sodium bicarbonate and sodium citrate
These drugs may increase the half life and decrease the elimination of ephedrine leading to enhanced therapeutic or toxic effects of ephedrine.

Theophylline
Concurrent use of ephedrine and theophylline may result in an increased incidence of adverse effects than when either drug is used alone. Adverse effects include those in the central nervous and the gastrointestinal systems.

Corticosteroids
Ephedrine has been shown to increase the clearance of dexamethasone.

Antiepileptics

Increased plasma concentration of Phenytoin and possibly of phenobarbitone and primidone.

Adverse effects

Very common: ≥1/10; **Common:** ≥1/100 to <1/10; **Uncommon:** ≥1/1,000 to <1/100; **Rare:** ≥1/10,000 to <1/1,000; **Very rare:** <1/10,000; **Not known:** cannot be estimated from the available data

Blood and lymphatic system disorders:
Not known: primary hemostasis modifications

Immune system disorders:
Not known: hypersensitivity

Psychiatric disorders:
Common: confusion, anxiety, depression
Not known: psychotic states, fear

Nervous system disorders:
Common: nervousness, irritability, restlessness, weakness, insomnia, headache, sweating
Not known: tremor, hypersalivation, fever, mood or mental changes, Large doses may cause dizziness, lightheadedness, vertigo, delirium, euphoria. Long term therapy in large doses may lead to psychosis characterized by paranoia, hallucinations, bizarre mentation

Eye disorders:
Not known: episodes of angle-closure glaucoma

Cardiac disorders:
Common: palpitations, hypertension, tachycardia
Rare: cardiac arrhythmias, cardiac arrest
Not known: angina pain, reflex bradycardia, cardiac arrest, hypotension, extrasystole and precordial pain

Vascular disorders:
Not known: cerebral haemorrhage

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea
Not known: pulmonary oedema, dryness of nose, mouth and throat

Gastrointestinal disorders:
Common: nausea, vomiting
Not known: Mild epigastric distress

Musculoskeletal and connective tissue disorders:
Not known: muscular weakness,

Renal and urinary disorders:
Not known: difficulty in micturition. In the case of patients with prostatic hypertrophy the retention of urine may become acute.

Investigations:
Not known: hypokalaemia, changes in blood glucose levels, Pallor

Dosage and administration

Ephedrine Hydrochloride SXP Injection is not approved for use in children (see PRECAUTIONS).

Ephedrine Hydrochloride SXP Injection must be diluted prior to administration.

Ephedrine Hydrochloride Injection is administered by the intravenous route. The injection should be given slowly. Care should be taken to avoid extravasation, since this may result in tissue necrosis and sloughing. Ephedrine hydrochloride should be administered in the lowest effective dose. The parenteral adult dose should not exceed 150 mg in 24 hours.

A lack of efficacy after 30 mg should lead to reconsideration of the choice of the therapeutic agent.

Product is for single use in one patient only. Discard any residue.

As a pressor:

Adult dose:

Dilute 1mL of Ephedrine Hydrochloride SXP to 10 mL with 0.9% Sodium chloride to produce a 3 mg/mL solution. This medicine should be administered immediately after

dilution

Up to 30 mg in increments of 3 to 7.5 mg (maximum of 10mg). After the development of hypotension, by slow intravenous administration.

Patients with renal or hepatic impairment

There are no specific dosage recommendations for patients with renal or hepatic impairment.

Compatibilities

Ephedrine hydrochloride is reported to be compatible with 0.9% sodium chloride, lactated Ringer's injection, and 10% glucose in water.

Incompatibilities

Ephedrine hydrochloride is reported to be physically incompatible with the phenobarbitone sodium, pentobarbitone sodium, quinalbarbitone sodium and thiopentone sodium, and with hydrocortisone sodium succinate in some infusion solutions.

Overdosage

Due to the rapid onset, but short duration of the drug, it is rarely necessary to actively manage adverse effects, as they tend to be of short duration and self limiting.

Clinical features

Symptoms associated with overdosage of ephedrine include headache, severe nausea or vomiting, chills or fever, dizziness or lightheadedness, anxiety, nervousness, restlessness, mood changes, convulsions, severe weakness, blurred vision or enlarged pupils, ongoing fast heartbeat, severe or ongoing chest pain, severe hypertension or hypotension, and severe breathing difficulties.

Paranoid psychosis, delusions and hallucinations may also follow ephedrine overdosage.

Treatment

Treatment of overdose involves the following measures:

- reduce dosage or discontinue administration of ephedrine
- general supportive therapy, including monitoring and maintaining vital signs, blood gases, electrolytes and ECG.

The following additional measures may need to be considered:

- Beta blockers (e.g. propranolol) to control tachycardia and arrhythmia
- phentolamine or nitroprusside to reduce severe hypertension
- diazepam to control convulsions. General anaesthesia and neuromuscular blocking agents may need to be considered to treat refractory seizures
- dexamethasone to treat pyrexia

For information on the management of an overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Presentation and storage conditions

Solution for injection, 30 mg/mL ephedrine hydrochloride: Type I clear glass ampoule containing 1 mL of solution. Pack of 5 ampoules.

Store below 25°C.

Name and address of the sponsor

Southern Cross Pharma Pty Ltd
56 Illabunda Drive
Malua Bay
NSW 2536

Poison schedule of the medicine

PRESCRIPTION ONLY MEDICINES - S4

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)
Date Month Year