PRESCRIBING INFORMATION

Ephedrine Sulfate Injection USP

50 mg / mL

Sterile Solution for Subcutaneous, Intravenous or Intramuscular administration

Sympathomimetic

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CLINICAL PHARMACOLOGY

Ephedrine is an adrenergic drug which exerts peripheral effects resembling those of epinephrine and central effects resembling those of the amphetamines. Ephedrine produces a more sustained action but is less potent than epinephrine. It stimulates both α and β receptors and its peripheral actions are due partly to norepinephrine release and partly to direct effects on receptors. Ephedrine stimulates the heart, elevating the systolic and usually the diastolic blood pressure. Its vasopressor effect results largely from increased cardiac output and to a lesser extent from peripheral vasoconstriction. Ephedrine produces relaxation of bronchial muscle which is more sustained but less pronounced than that produced by epinephrine. It also stimulates the central nervous system to a greater extent than epinephrine but its central action is less potent than that of the amphetamines. The central effects of ephedrine are overshadowed to a large extent by its peripheral actions. It produces sympathomimetic effects when administered orally, parenterally or topically.

INDICATIONS

Ephedrine is used as a bronchodilator in the symptomatic treatment of mild bronchial asthma and reversible bronchospasm which may occur in association with chronic bronchitis, emphysema, and other obstructive pulmonary diseases.

Ephedrine is also used parenterally to produce cardiac stimulation and vasoconstriction as an adjunct to correct hemodynamic imbalances, in the treatment of shock which persists after adequate fluid volume replacement. (See **PRECAUTIONS AND CONTRAINDICATIONS.)** Individual hemodynamic abnormalities must be identified and monitored so that therapy can be adjusted as necessary. If severe peripheral vasoconstriction exists, ephedrine may be ineffective and may have a deleterious effect by causing further reductions in plasma volume and blood flow to vital organs.

The value of pressor therapy in shock, especially when due to septicemia, burns, trauma, or drug overdosage, is questionable either because the effectiveness has not been proven or because vasoconstriction caused by the drug may adversely affect the patient. However, ephedrine may be indicated if the patient fails to respond to administration of fluids, a change in position, or other measures directed to the specific cause of shock such as specific antidotes and/or removal of the drug in cases of drug overdosage. Pressor therapy in overdosage of barbiturates or other sedatives is especially controversial; some clinicians have stated that the incidence of mortality may actually be increased when a pressor is given.

Ephedrine has been used to treat hypotension occurring during spinal anesthesia. Although the drug has also been used to prevent hypotension resulting from spinal anesthesia, routine prophylactic use of pressor agents in such cases has been questioned because hypotension does not always occur during spinal anesthesia and treatment can readily be instituted if necessary. It

has been suggested that pressor drugs be administered prophylactically only when a substantial decrease in blood pressure is expected. Ephedrine may be used to treat hypotension occurring during general anesthesia; however, the possibility of cardiac arrhythmias should be considered. The use of vasopressors to correct hypotension resulting from anesthesia in obstetrical patients is controversial. Hypotension can usually be minimized by adequate hydration and changing the position of the patient so that the uterus does not compress the inferior *vena cava.* If a vasopressor is required, however, ephedrine may be the drug of choice.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Use of ephedrine as a pressor 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, the drug 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 hypovolemic patients. Additional volume replacement may also be required during or after administration of the drug, especially if hypotension recurs. Monitoring of central venous pressure or left ventricular filling pressure may be helpful in detecting and treating hypovolemia. In addition, monitoring of central venous or pulmonary arterial diastolic pressure is necessary to avoid overloading the cardiovascular system and precipitating congestive heart failure. Hypoxia, hypercapnia, and acidosis, which may also reduce the effectiveness and/or increase the incidence of adverse effects of ephedrine, must be identified and corrected prior to or concurrently with administration of the drug. Ephedrine may decrease circulating plasma volume which may result in perpetuation of the shock state or the recurrence of hypotension when the drug is discontinued.

Ephedrine may cause hypertension which may result in intracranial hemorrhage. Adverse reactions to ephedrine may be particularly likely to occur in hypertensive or hyperthyroid patients, and the drug must be administered with caution, if at all, to such patients. The drug should be administered with caution to geriatric males (especially those with an enlarged prostate), diabetics, and patients with cardiovascular disease (including coronary insufficiency, angina pectoris, cardiac arrhythmias, and organic cardiac disease) and/or those with a history of sensitivity to ephedrine or other sympathomimetic drugs.

Ephedrine is contraindicated in patients with angle-closure glaucoma or psychoneurosis.

Pregnancy

Animal reproduction studies have not been performed with ephedrine. It is also not known whether ephedrine can cause fetal harm when administered to pregnant women. Ephedrine should be used during pregnancy only when clearly needed. Parenteral administration of ephedrine to maintain blood pressure during spinal anesthesia for delivery can cause acceleration of fetal heart rate and should not be used in obstetric patients when maternal systolic/diastolic blood pressure exceeds 130/80 mm Hg.

Adverse Effects

The central nervous stimulating effects of ephedrine may result in nervousness, anxiety, apprehension, fear, tension, agitation, excitation, restlessness, weakness, irritability, talkativeness, or insomnia. Dizziness, lightheadedness, and vertigo may occur, especially with large doses. Tremor or tremulousness, and hyperactive reflexes have also been reported. CNS disturbances may be prevented or overcome by administration of a sedative or tranquilizer. Large parenteral doses of ephedrine may cause confusion, delirium, hallucinations, or euphoria.

Ephedrine may also cause throbbing headache, respiratory difficulty, fever or a feeling of warmth, pallor, dryness of the nose and throat, precordial pain, sweating, mild epigastric distress, anorexia, nausea, or vomiting.

Ephedrine may deplete norepinephrine stores in sympathetic nerve endings and tachyphylaxis to the cardiac and pressor effects of the drug may develop. Administration of norepinephrine to replace tissue stores may be useful in restoring the pressor effects of ephedrine. In addition, after several doses of ephedrine are administered, hypotension more severe than that originally being treated may result from direct cardiac depression and vasodilation.

Prolonged administration of pressor agents has caused edema, hemorrhage, focal myocarditis, subpericardial hemorrhage, necrosis of the intestine, and hepatic and renal necrosis. These effects have generally occurred in patients with severe shock, and::it is not clear if the drug or the shock state itself was the cause.

Ephedrine increases the work of the heart and probably myocardial oxygen consumption. In patients with coronary insufficiency and/or ischemic heart disease, the drug can induce anginal pain.

Ephedrine increases the irritability of the heart muscle and may alter the rhythmic function of the ventricles. Palpitation and tachycardia may result. Extrasystoles and potentially fatal arrhythmias including ventricular fibrillation may occur, especially in patients with organic heart disease or those receiving other drugs that sensitize the heart to arrhythmias including cardiac glycosides, cyclopropane, or halogenated hydrocarbon anesthetics.

Acute urinary retention or difficulty in urination may occur in patients receiving ephedrine, especially with prolonged use of the drug in geriatric men with prostatic hypertrophy. Some patients may require catheterization. After parenteral use, ephedrine may initially constrict renal blood vessels and decrease urine formation.

DRUG INTERACTIONS

Sympathomimetic Agents

Ephedrine should not be administered concomitantly with other sympathomimetic agents because of the possibility of additive effects and increased toxicity.

α- and β-Adrenergic Blocking Agents

Administration of an α-adrenergic blocking drug reduces the vasopressor response to ephedrine. Phentolamine, by blocking the a-adrenergic effects of ephedrine, can cause vasodilation. However, because of the cardiac stimulating effects of ephedrine, a pressor response may be achieved if sufficient doses are administered.

As with other sympathomimetic drugs having cardiostimulating effects, administration of a B-adrenergic blocking drug such as propranolol may block the cardiac and bronchodilating effects of ephedrine.

General Anesthetics
Administration of ephedrine to patients who have received cyclopropane or halogenated hydrocarbon general anesthetics which increase cardiac irritability may result in arrhythmias. It has been recommended that if a pressor drug is required when these general anesthetics are used, one with minimal cardiac stimulating effects such as methoxamine or phenylephrine should be given. Arrhythmias, if they occur, may respond to administration of a β-adrenergic blocking drug such as propranolol.

Monoamine Oxidase Inhibitors
By increasing the quantity of norepinephrine in adrenergic nervous tissue, monoamine oxidase (MAO) inhibitors potentiate the pressor effects of indirectly acting sympathomimetic drugs such as ephedrine. Potentiation is approximately the same following IV or oral administration of ephedrine. Ephedrine should be used with caution, and should preferably be avoided, in patients receiving drugs with MAO inhibitor activity including furazolidone.

Other Drugs
Drugs such as reserpine and methyldopa which reduce the quantity of norepinephrine in sympathetic nerve endings may reduce the pressor response to ephedrine. Ephedrine may antagonize the neuron blockade produced by guanethidine, resulting in loss of antihypertensive effectiveness. Patients who are receiving guanethidine must be monitored carefully for loss of antihypertensive effect if ephedrine is, given concomitantly and the dosage of guanethidine increased or another antihypertensive drug added to the treatment regimen if necessary.

Atropine sulfate blocks the reflex bradycardia and enhances the pressor response to ephedrine.

Administration of a theophylline derivative such as aminophylline concomitantly with ephedrine has been reported to produce a greater incidence of adverse effects than when either drug is used alone.

Cardiac glycosides can sensitize the myocardium to the effects of sympathomimetic drugs; ephedrine should be used cautiously in patients receiving cardiac glycosides.

Administration of furosemide or other diuretics may decrease arterial responsiveness to pressor drugs such as ephedrine.

Ephedrine may reduce the onset time of neuromuscular blockade when used for intubation with

rocuronium if administered simultaneously with anesthetic induction. Be aware of this potential interaction.

DOSAGE AND ADMINISTRATION

Administration
Ephedrine sulfate is administered intramuscularly (IM), subcutaneously (SC), or intravenously (IV). The route of administration should be determined by the needs of individual patients; patients who are in shock may require IV administration to ensure absorption of the drug.

Dosage
If ephedrine is administered parenterally to relieve severe, acute bronchospasm, the smallest effective dose (usually 12.5-25 mg) should be given. Further dosage should be determined by patient response.

During therapy with a pressor agent, blood pressure should be elevated to slightly less than the patient's normal blood pressure. In previously normotensive patients, systolic blood pressure should be maintained at 80-100 mm Hg; in previously hypertensive patients, the systolic blood pressure should be maintained at 30-40 mm Hg below their usual blood pressure. In some patients with very severe hypotension, maintenance of even lower blood pressure may be desirable if blood or fluid volume replacement has not been completed. When used as a pressor agent, ephedrine should be administered in the lowest effective dosage for the shortest possible time. The usual adult subcutaneous or IM dose is 25-50 mg (range: 10-50 mg). If necessary, a second IM dose of 50 mg or an IV dose of 25 mg may be administered. For direct IV injection, 10-25 mg of the drug may be administered slowly. If necessary to achieve the desired response, additional IV doses may be given in 5-10 minutes. The parenteral adult dose should not exceed 150 mg in 24 hours. Children may receive 3 mg/kg or 100 mg/m^2 SC or IV daily, divided into 4-6 doses.

Availability
Each mL contains ephedrine sulfate 50 mg, glacial acetic acid and sodium hydroxide to adjust pH. Vials of 1 mL, boxes of 10.
Store between 15°C and 30°C. Protect from light. Do not freeze. Do not use product if solution shows haziness, particulate matter, discolouration, or leakage.