SYMPATHOMIMETIC AGENTS¾Cardiovascular Use (Parenteral-Systemic)

Introduction

This monograph includes information on the following:1) Dobutamine; 2) Dopamine ; 3) Ephedrine ; 4) Epinephrine ; 5) Isoproterenol; 6) Mephentermine b; 7) Metaraminol b; 8) Methoxamine ; 9) **Norepinephrine** ; 10) Phenylephrine .

INN:

Norepinephrine¾Levarterenol
BAN:

Norepinephrine¾Noradrenaline
VA CLASSIFICATION (Primary/Secondary)
Dobutamine¾AU100/CV900
Dopamine¾AU100/
Ephedrine¾AU100/
Epinephrine¾AU100/
Isoproterenol¾AU100/
Mephentermine¾AU100/
Metaraminol¾AU100/
Methoxamine¾AU100/
Norepinephrine¾AU100/
Phenylephrine¾AU100/; CV300
Commonly used brand name(s):Adrenalin4; Aramine7; Dobutrex1; Intropin2; Isuprel5; Levophed9; Neo-Synephrine10; Revimine2; Vasoxyl8; Wyamine6.

Category

Antiarrhythmic¾Isoproterenol; Phenylephrine.

Cardiac stimulant¾Dobutamine; Dopamine; Epinephrine.

Vasopressor¾Dopamine; Ephedrine; Epinephrine; Mephentermine; Metaraminol; Methoxamine; Norepinephrine; Phenylephrine.

Indications

Accepted

Bradycardia (treatment)¾Isoproterenol is indicated for the temporary control of hemodynamically significant bradycardia, such as bradycardia associated with a denervated transplanted heart or third degree heart block due to conduction system disease. 20, 60, 71 Electrical pacing is the preferred treatment for maintenance of an adequate ventricular rate and isoproterenol is used only for temporary

support when electrical pacing is unavailable. 60 Isoproterenol may also be used in long QT-related arrhythmias where underlying bradycardia is common. 71

Hypotension, acute (prophylaxis and treatment) or

Shock (treatment)¾The sympathomimetic agents (except isoproterenol) are indicated for the correction of hypotension, unresponsive to adequate fluid volume replacement, as part of shock syndrome caused by myocardial infarction, trauma, bacteremia 77 , open-heart surgery, renal failure, chronic cardiac decompensation, drug overdose 65, 76 , or other major systemic illness 70.

2, 3, 6, 8, 41

The specific choice of drug must be determined by clinical assessment. 20 This assessment may include hemodynamic status, mental status, urine output, and other measures of tissue perfusion. 20 In refractory cases, the use of multiple drug therapy may be necessary for blood pressure support. 20

In septic shock, low-dose dopamine may be used in conjunction with norepinephrine to maintain renal blood flow. 21, 25, 31, 32, 33

In hypovolemic shock, the sympathomimetic agents should be used only as adjuncts to energetic fluid volume replacement to provide temporary support for maintaining coronary and cerebral artery perfusion until volume replacement therapy is completed. 6, 20 These medications must not be used as the sole therapy in hypovolemic patients. 6, 20

In acute hypotension associated with myocardial infarction, sympathomimetic agent-induced increases in myocardial oxygen demand and the work of the heart may outweigh the beneficial effect of the medication. Also, cardiac arrhythmias induced by the sympathomimetic agents may be more likely to occur in patients with myocardial infarction. 20

Although norepinephrine is indicated in the treatment of acute hypotension occurring during spinal anesthesia, vasopressors that have a longer duration of action (e.g., metaraminol or phenylephrine) are also useful 67.

Ephedrine is indicated for the correction of hypotension secondary to spinal or other types of nontypical conduction anesthesia. 4, 28 It is also used in hypotensive states following sympathectomy, or following overdose with ganglionic blocking agents, antiadrenergic agents, or other medications that lower blood pressure in the treatment of hypertension. 4

Metaraminol is indicated for the prevention and treatment of acute hypotension occurring with spinal anesthesia and in the adjunctive treatment of hypotension resulting from hemorrhage, reactions to medications, surgical complications, and shock associated with brain damage due to trauma or tumor. 5 However, metaraminol is not indicated as the sole treatment for hypotension secondary to decreased plasma volume.
Mephentermine is indicated in the treatment of hypotension secondary to ganglionic blockade and hypotension occurring with spinal anesthesia. 15

Methoxamine is indicated for supporting, restoring, or maintaining blood pressure during general anesthesia with agents that sensitize the myocardium to arrhythmias, such as halothane. 7

Dobutamine is not recommended for the adjunctive treatment of hypovolemic shock. 20

Cardiac output, low (treatment) or

Congestive heart failure (treatment)¾Dobutamine is indicated to improve cardiac function during cardiac decompensation in congestive heart failure or depressed contractility from cardiac or major vascular surgery. 20, 53

If a vasopressor is also needed, norepinephrine or dopamine is useful for short-term management. 20 However, stimulation of alpha-1 adrenergic receptors produces vasoconstriction, which is undesirable in most patients with severe heart failure. 20, 24 In certain circumstances, a vasodilating agent such as nitroprusside or nitroglycerin may be used as an adjunct to dobutamine to decrease afterload and pulmonary pressures. 20, 24

Cardiac arrest (treatment)¾Epinephrine is indicated during resuscitation of cardiac standstill or cardiac arrest. 1, 60 Epinephrine is used as an adjunct to restore cardiac rhythm in the treatment of cardiac arrest due to various causes. 1 It also has beneficial hemodynamic effects in the setting of cardiopulmonary resuscitation (CPR), improving myocardial and cerebral blood flow. Epinephrine injection may be used for resuscitation in cardiac arrest following anesthetic accidents; 1 however, it should be used with great caution in patients receiving halogenated hydrocarbon anesthetics, especially halothane, because these anesthetics sensitize the myocardium and cardiac arrhythmias may be induced.
In acute attacks of ventricular standstill, physical measures should be used prior to administration of epinephrine. However, if external cardiac compression and attempts to restore circulation by electrical defibrillation or use of a pacemaker fail, intravenous injection of epinephrine into a major vein may be effective.

Shock, anaphylactic (treatment)¾Epinephrine injection is indicated in the emergency treatment of anaphylactic shock. 20

Tachycardia, supraventricular, paroxysmal (treatment)¾Phenylephrine is indicated in the termination of some episodes of paroxysmal supraventricular tachycardia (PSVT). 7

Unaccepted

Isoproterenol is no longer routinely recommended as an inotropic agent. It has been replaced in most clincial settings by newer agents that are less prone to induce ischemia, arrhythmias, or a hypotensive response. 20, 60, 72

Mephentermine is not recommended in the treatment of hypotension induced by chlorpromazine because it may potentiate, rather than correct, the hypotension secondary to the adrenolytic effects of chlorpromazine. 20

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾Dobutamine: 337.85 12

Dopamine hydrochloride: 189.64 12

Ephedrine sulfate: 428.54 12

Epinephrine: 183.21 12

Isoproterenol hydrochloride: 247.72 12

Mephentermine sulfate: 424.60 12

Metaraminol bitartrate: 317.29 12

Methoxamine hydrochloride: 247.72 12

Norepinephrine bitartrate: 337.28 12

Phenylephrine hydrochloride: 203.67 12

Other characteristics¾pH¾
Dobutamine¾9.4
Dopamine Hydrochloride Injection, USP¾2.5 to 5 2

Mechanism of action/Effect:

Dobutamine¾

A direct-acting inotropic agent. Dobutamine acts primarily on beta-1 adrenergic receptors, with little effect on beta-2 or alpha receptors. 47, 53 Dobutamine directly stimulates beta-1 receptors of the heart to increase myocardial contractility and stroke volume, resulting in increased cardiac output. 47, 53 Coronary blood flow and myocardial oxygen consumption are usually increased because of increased myocardial contractility. Dobutamine has little effect on systemic vascular resistance, 23, 24 and systolic blood pressure and pulse pressure may remain unchanged or be increased because of increased cardiac output. However, in septic patients with decreased systemic vascular resistance, dobutamine may lower blood pressure without increasing cardiac output. 70 Dobutamine reduces elevated ventricular filling pressure (preload reduction) and facilitates atrioventricular (AV) node conduction. At appropriate doses, an increase in heart rate does not usually occur, but excessive doses have a chronotropic effect. 53 Renal blood flow and urine output may be improved as a result of increased cardiac output rather than as a dopaminergic effect. 53

Dopamine¾

Dopamine stimulates postsynaptic beta-1 receptors in the myocardium, mediating its positive inotropic and chronotropic effects. 2, 3, 9, 24 Dopamine causes vascular relaxation and promotes sodium excretion through its stimulation of postsynaptic dopamine-1 receptors on vascular smooth muscle and on the kidney. 9 In addition, dopamine stimulates both alpha-1 and alpha-2 receptors, which mediate smooth muscle vasoconstriction. 9 These pharmacologic effects are dose-related, requiring various infusion rates of dopamine to activate different receptors. 2, 3, 10

In low doses (0.5 to 3 17, 20 mcg per kg of body weight [mcg/kg] per minute), dopamine acts predominantly on dopaminergic receptors to cause vasodilation in the renal, mesenteric, coronary, and intracerebral vascular beds. 2, 3, 47 Renal vasodilation results in increased renal blood flow, glomerular filtration rate, urine flow (usually), and sodium excretion. 2, 3, 11

In low to moderate doses (2 to 10 mcg/kg per minute), beta-1 receptors are stimulated, resulting in a positive inotropic effect on the myocardium and an increase in cardiac output. 2, 3, 9, 11, 23 Systolic blood pressure and pulse pressure may be increased with either no change or a slight increase in diastolic blood pressure. 2, 3 Total peripheral resistance is usually unchanged. 2, 3 Coronary blood flow and myocardial oxygen consumption are usually increased. 2, 3

In higher doses (10 mcg/kg per minute or above), alpha-adrenergic receptor stimulation predominates, resulting in increased peripheral vascular resistance and renal vasoconstriction (this vasoconstriction may decrease previously increased renal blood flow and urine output). 2, 3, 9 Both systolic and diastolic blood pressures are increased as a result of increased cardiac output and increased peripheral resistance. 2, 3

Ephedrine¾

Ephedrine stimulates both alpha and beta adrenergic receptors and enhances the release of endogenous norepinephrine from sympathetic neurons, resulting in increased systolic and diastolic blood pressure and increased cardiac output. 4, 26 Ephedrine also stimulates the central nervous system (CNS), although to a lesser extent than does amphetamine. 4, 26

Epinephrine¾

Epinephrine predominantly stimulates alpha and beta-1 adrenergic receptors, and has moderate activity at beta-2 adrenergic receptors. 27 At very low doses, (less than 0.01 mcg/kg per minute), epinephrine may decrease blood pressure through dilatation of skeletal muscle vasculature. 27, 47 At doses of 0.04 to 0.1 mcg/kg per minute, stimulation of beta-receptors predominates, increasing heart rate, cardiac output, and stroke volume and decreasing peripheral vascular resistance. 22, 27 At doses exceeding 0.2 mcg/kg per minute, stimulation of alpha adrenergic receptors produces vasoconstriction and increased total peripheral resistance. 22, 27 Doses exceeding 0.3 mcg/kg per minute decrease renal blood flow, gastrointestinal motility, pyloric tone, and splanchnic vascular bed perfusion. 27, 47

Epinephrine also increases conduction velocity in the myocardium and increases ectopic pacemaker activity. 23 Myocardial oxygen demand is also increased. 23

Isoproterenol¾

Isoproterenol is a pure beta receptor agonist. 17, 59, 60 It is a potent inotrope and chronotrope, increasing cardiac output despite a reduction in mean blood pressure due to peripheral vasodilation. 60

Mephentermine¾

Mephentermine is an alpha adrenergic receptor agonist, but also acts indirectly by releasing endogenous norepinephrine. 15, 26 Cardiac output and systolic and diastolic pressures are usually increased. 15, 26 A change in heart rate is variable, depending on the degree of vagal tone. 15, 26 Sometimes the net vascular effect may be vasodilation. 15 Large doses may depress the myocardium or produce central nervous system (CNS) effects. 15

Metaraminol¾

Metaraminol acts directly on peripheral alpha adrenergic receptors, as well as, indirectly through release of endogenous norepinephrine. 26 Metaraminol produces a positive inotropic effect on the heart and peripheral vasoconstriction. 5

Methoxamine¾

Methoxamine is a relatively selective alpha-1 adrenergic receptor agonist, producing an increase in peripheral vascular resistance. 7, 26 At high doses beta adrenergic receptors may be stimulated, resulting in increased blood pressure. 26 A reflex sinus bradycardia may occur. 26

Norepinephrine¾

Norepinephrine stimulates alpha and beta-1 adrenergic receptors in a dose-related fashion. 23, 27 At lower doses (less than 2 mcg per minute), stimulation of beta-1 receptors results in a positive inotropic and chronotropic effect. 23, 27, 47 At higher doses (greater than 4 mcg per minute), the alpha adrenergic effect predominates, resulting in elevated total peripheral resistance. 27 Chronotropy diminishes as a result of baroreceptor-mediated vagal stimulation. 27

Norepinephrine may produce vasoconstriction in the mesenteric vascular bed, which can induce splanchnic ischemia and facilitate bacterial translocation from the gut. 23, 27 Norepinephrine also increases renal vascular resistance. However, renal perfusion may actually increase in hypotensive patients through norepinephrine's effect of increasing blood pressure. 23, 27

Phenylephrine¾

Phenylephrine is primarily an alpha-1 adrenergic agonist, which causes marked vasoconstriction. 26

The following table represents relative receptor agonist activity of the sympathomimetic agents 20¾

	RECEPTOR TYPE				
	Alpha-1	Alpha-2	Beta-1	Beta-2	Dopamine
Norepinephrine	+++	+++	++	None	None
Epinephrine				None	
low dose			++	+++	
moderate dose	+		+++	+++	
high dose	+++	+++	+++	+++	
Dobutamine	+	None	+++	+	None
Dopamine		None		None	
low dose				+++	
moderate dose			+++		
high dose	+++				
Isoproterenol	None	None	+++	+++	None
Ephedrine (indirect effects via norepinephrine release)	+++	+++	++	None	None
Mephentermine	+++	None	None	None	None
Metaraminol (indirect effects via norepinephrine release)	+++	+++	++	None	None
Methoxamine	+++	None	None	None	None

Phenylephrine	+++	None	None	None	None

Distribution:

Dopamine¾
Adults: Widely distributed in the body; 2 does not extensively cross the blood-brain barrier. 2 About 25% of a dose is taken up into specialized neurosecretory vesicles where hydroxylation occurs, forming norepinephrine. 2

Neonates: Apparent volume of distribution¾1.8 L per kg. 29

Biotransformation:

Dobutamine¾Hepatic, to inactive compounds.
Dopamine¾Metabolized in the liver, kidney, and plasma by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) to inactive metabolites. 2, 34

Ephedrine¾Small amounts in the liver. 4

Epinephrine¾Metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). 47

Isoproterenol¾Metabolism in liver, lungs, and other tissues. 30

Mephentermine¾Hepatic, by N-demethylation and then p-hydroxylation. 15

Metaraminol¾Hepatic. 30

Methoxamine¾Hepatic. 30

Norepinephrine¾Metabolized in the liver, kidney, and plasma by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) to inactive metabolites. 30

Phenylephrine¾Hepatic and gastrointestinal. 30

Half-life:

Dobutamine¾
About 2 minutes. 30, 53

Dopamine¾
Adults:
Plasma¾About 2 minutes. 2, 34

Elimination¾About 9 minutes. 34

Neonates:

Elimination¾6.9 minutes (range 5 to 11 minutes). 29

Epinephrine¾
1 minute. 30

Ephedrine¾
3 to 6 hours. 4, 26

Mephentermine¾
17 to 18 hours. 15

Norepinephrine¾
1 minute. 30

Onset of action:

Dobutamine¾
1 to 2 minutes; 30, 53 however, up to l0 minutes may be required when infusion rate is slow. 53

Dopamine¾
Within 5 minutes. 2

Epinephrine¾
Rapid. 30

Isoproterenol¾
Less than 5 minutes. 30

Mephentermine¾
Intravenous: Very rapid. 15, 30

Intramuscular: 5 to 15 minutes. 15, 26

Metaraminol¾
Intravenous: 1 to 2 minutes. 5, 30

Intramuscular: About 10 minutes. 5

Methoxamine¾
0.5 to 2 minutes. 7

Norepinephrine¾
Rapid. 30

Phenylephrine¾
Very rapid. 30

Duration of action:

Dobutamine¾
Less than 5 minutes. 30

Dopamine¾
Less than 10 minutes. 2

Ephedrine¾
1 hour. 4

Epinephrine¾
1 to 2 minutes. 30

Isoproterenol¾
10 minutes. 30

Mephentermine¾
Intravenous: 15 to 30 minutes. 15, 30

Intramuscular: 1 to 4 hours. 15

Metaraminol¾
20 to 60 minutes. 5, 30

Methoxamine¾
5 to 15 minutes. 7, 30

Norepinephrine¾
1 to 2 minutes. 30

Phenylephrine¾
5 to 20 minutes. 8, 30

Elimination:

Dobutamine¾Renal; as metabolites. 53

Dopamine¾Renal; 80% of a dose excreted within 24 hours, primarily as metabolites. 2 A very small fraction of a dose is excreted unchanged. 2

Ephedrine¾Renal; mostly as unchanged drug. 4, 26

Mephentermine¾Renal. 15

Methoxamine¾Renal. 30

Norepinephrine¾Renal; primarily as metabolites. 30

Precautions to Consider

Cross-sensitivity and/or related problems

Dobutamine, dopamine, epinephrine, isoproterenol, metaraminol, methoxamine, norepinephrine, and phenylephrine preparations contain sulfites.

Carcinogenicity/Mutagenicity

Long-term studies have not been done. 2, 5, 6, 7, 8, 59

Pregnancy/Reproduction

Fertility¾Dobutamine: Studies in rats and rabbits have revealed no evidence of fertility impairment. 53

Dopamine: Long-term studies have not been done. 2

Isoproterenol: Studies have not been done. 59

Mephentermine: Long-term studies have not been done. 15

Metaraminol: Long-term studies have not been done. 5

Methoxamine: Long-term studies have not been done. 7

Norepinephrine: Studies have not been done. 6

Phenylephrine: Long-term studies have not been done. 8

Pregnancy¾Dobutamine¾
Adequate and well-controlled studies in humans have not been done.
Reproduction studies in rats and rabbits found no evidence of teratogenicity or harm to the fetus. 53

Dopamine¾
Adequate and well-controlled studies in humans have not been done. 2

Studies in animals have not revealed evidence of teratogenic effects. 2 However, administration of dopamine to pregnant rats resulted in a decreased survival rate of the newborn and a potential for the development of cataracts in survivors. 2

FDA Pregnancy Category C. 2

Ephedrine¾
Adequate and well-controlled studies have not be done in humans. 4

Studies have not been done in animals. 4

FDA Pregnancy Category C. 4

Epinephrine¾

Adequate and well-controlled studies in humans have not been done. 1

Studies in rats given epinephrine at doses 25 times the human dose have revealed teratogenic effects. 1

FDA Pregnancy Category C. 1

Isoproterenol¾

Adequate and well-controlled studies have not been done in humans. 59

Studies have not been done in animals. 59

FDA Pregnancy Category C. 59

Mephentermine¾

It is not known whether mephenterine crosses the placenta. 15 However, mephentermine may increase uterine contractions in pregnant women, especially during the third trimester. 15

Studies have not been done in animals. 15

FDA Pregnancy Category C. 15

Metaraminol¾

Adequate and well-controlled studies have not been done in humans. 5

Metaraminol given to pregnant ewes at a dose of 0.025 mg per kg of body weight (mg/kg) decreased uterine blood flow. 37

FDA Pregnancy Category C. 5

Methoxamine¾

Adequate and well-controlled studies in humans have not been done. 7 However, a fetal death has been reported when the mother received methoxamine concomitantly with other medications. 7 A direct causal relationship has not been established. 7

Methoxamine administered to pregnant ewes and monkeys at doses comparable to those used in humans decreased uterine blood flow and heart rate, and adversely affected fetal acid-base status, as evidenced by hypoxia, hypercarbia, and metabolic acidosis. 7 In pregnant ewes, an inverse relationship between pressor response to methoxamine and uteroplacental blood flow was shown at doses ranging from 0.025 to 0.2 mg/kg. 7, 37 A study in baboons given methoxamine at a dose of 1.3 mg/kg over 57 minutes revealed a decrease in uterine blood flow and a possible association with fetal asphyxia. 7, 38

FDA Pregnancy Category C. 7

Norepinephrine¾

Adequate and well-controlled studies have not been done in humans. 6

Studies have not been done in animals. 6

FDA Pregnancy Category C. 6

Phenylephrine¾
Adequate and well-controlled studies have not been done in humans.
Studies have not been done in animals. 8

FDA Pregnancy Category C. 8

Labor and delivery¾If vasopressor medications are used to correct hypotension or added to the local anesthetic solution during labor and delivery, some oxytocic medications (e.g., vasopressin, ergotamine, ergonovine, methylergonovine) may cause severe persistent hypertension, 3, 7, 8 and rupture of a cerebral blood vessel may occur during the postpartum period. 8

Ephedrine: Ephedrine, when used to maintain blood pressure during low or other spinal anesthesia for delivery, may accelerate fetal heart rate. 4 Use is not recommended when maternal blood pressure exceeds 130/80 mm Hg. 4

Epinephrine: Use during labor is not recommended because epinephrine may delay the second stage of labor. 1

Mephentermine: Mephentermine may cause a decrease in uterine blood flow, which may result in fetal hypoxia. 15 Transient fetal hypertension has also been reported in animals. 15

Breast-feeding

It is not known whether these medications are distributed into breast milk.

Pediatrics

Dobutamine¾Dobutamine has been studied in a limited number of pediatric patients up to 18 years of age. 54, 55, 56, 57 There do not appear to be pediatric-specific problems that would limit the usefulness of dobutamine in pediatric patients.
Dopamine¾Dopamine has been studied in a limited number of pediatric patients up to 18 years of age. 19, 34, 35, 36 Close hemodynamic monitoring is recommended since there is a lack of controlled studies investigating age-dependent dosages and the maximum dosage at which therapeutic response occurs without causing toxicity. 34 In addition, cardiac arrhythmias and gangrene due to extravasation have been reported in pediatric patients. 34

Epinephrine¾Epinephrine has been used in pediatric patients during cardiac arrest and there do not appear to be pediatrics-specific problems that would limit its usefulness in this setting. However, caution is recommended to avoid errors in concentration selection and dosing, since two different dilutions of epinephrine are necessary for the dosing regimen. 51, 52

Geriatrics

Isoproterenol¾Data seem to indicate that elderly patients may exhibit a decreased chronotropic and peripheral vascular response to isoproterenol. 73, 74

Norepinephrine¾The pressor response to norepinephrine does not appear to be altered with aging. 73, 75

Phenylephrine¾The baroreceptor reflex response to phenylephrine appears to decrease with age. 73

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Alpha-adrenergic blocking agents, such as:
Doxazosin
Labetalol
Phenoxybenzamine
Phentolamine
Prazosin
Terazosin
Tolazoline, or

Other medications with alpha-adrenergic blocking action, such as:
Haloperidol
Loxapine
Phenothiazines
Thioxanthenes

(concurrent use may antagonize the peripheral vasoconstriction of sympathomimetic agents; however, phentolamine may be used for therapeutic benefit 3)

>> Anesthetics, hydrocarbon inhalation, such as:
Chloroform
Enflurane
>> Halothane
Isoflurane
Methoxyflurane

(concurrent use of these medications with the sympathomimetic agents may increase the risk of severe atrial 72 and ventricular arrhythmias because these anesthetics greatly sensitize the myocardium; sympathomimetic agents should be used with caution and in substantially reduced doses in patients receiving these anesthetics 2, 3, 5, 6)
(enflurane, isoflurane, or methoxyflurane may also sensitize the myocardium to the effects of sympathomimetics; caution is recommended during concurrent use)

>> Antidepressants, tricyclic or

>> Maprotiline

(concurrent use may potentiate the cardiovascular and pressor effects of sympathomimetic agents, possibly resulting in arrhythmias, tachycardia, or severe hypertension or hyperpyrexia 3, 5)

Antihypertensives or

Diuretics used as antihypertensives

(antihypertensive effects may be reduced when these medications are used concurrently; the patient should be carefully monitored to confirm that the desired effect is being obtained)

Beta-adrenergic blocking agents, ophthalmic or

>> Beta-adrenergic blocking agents, systemic

(concurrent use with sympathomimetic agents may result in mutual inhibition of therapeutic effects; beta-blockade may antagonize the beta-1 adrenergic cardiac effects of sympathomimetic agents 3)

>> Cocaine, mucosal-local

(concurrent use with sympathomimetic agents may increase the cardiovascular effects of either or both medications and the risk of adverse effects 20)

>> Digitalis glycosides

(concurrent use with sympathomimetic agents possessing beta-1 adrenergic agonist activity may increase the risk of cardiac arrhythmias; 1, 4, 5 in addition, concurrent use may produce additive inotropic effects; 39, 40 although these medications may be used with digitalis glycosides for therapeutic advantage, caution and close electrocardiographic monitoring are recommended during concurrent use)

Diuretics

(concurrent use may increase the diuretic effect of the diuretic medications or dopamine as a result of dopamine's direct action on dopaminergic receptors to produce vasodilation of renal vasculature and increase renal blood flow; dopamine also has a direct natriuretic effect 3)

>> Doxapram

(concurrent use may increase the pressor effects of either the sympathomimetic agents or doxapram)

Ergonovine or

>> Ergotamine or

Methylergonovine or

Methysergide or

Oxytocin

(concurrent use of ergonovine, methylergonovine, or methysergide with a sympathomimetic agent may result in enhanced vasoconstriction; dosage adjustments may be necessary 3, 6, 7)
(concurrent use of ergotamine with these medications may produce peripheral vascular ischemia and gangrene and is not recommended 3, 6)
(concurrent use of ergonovine, ergotamine, methylergonovine, or oxytocin may potentiate the pressor effect of these medications with possible severe hypertension and rupture of cerebral blood vessels)

Guanadrel or

Guanethidine

(in addition to possibly decreasing the hypotensive effect of guanadrel or guanethidine, 4, 44 concurrent use may potentiate the pressor response to the sympathomimetic agents; these actions are a result of inhibition of sympathomimetic uptake by adrenergic neurons and may lead to hypertension and cardiac arrhythmias)

Levodopa

(concurrent use with dopamine may increase the possibility of cardiac arrhythmias; dosage reduction of the sympathomimetic is recommended)

Mecamylamine or

Methyldopa 4

(in addition to possibly decreasing the hypotensive effects of these medications, concurrent use may enhance the pressor response to sympathomimetic agents)

Methylphenidate

(concurrent use may potentiate the pressor effect of sympathomimetic agents)

>> Monoamine oxidase (MAO) inhibitors, including furazolidone, procarbazine, and selegiline 1, 3, 4, 5

(concurrent use may prolong and intensify cardiac stimulation and vasopressor effects because of the release of catecholamines, which accumulate in intraneuronal storage sites during MAO inhibitor therapy; this may result in headache, cardiac arrhythmias, vomiting, or sudden and severe hypertensive and/or hyperpyretic crises; for patients who have been receiving MAO inhibitors 2 to 3 weeks prior to administration of sympathomimetic agents, the initial dosage should be reduced to no more than one-tenth of the usual dose)

Nitrates 20

(concurrent use with sympathomimetic agents may reduce the antianginal effects of these medications; also, nitrates may counteract the pressor effect of sympathomimetic agents, possibly resulting in hypotension; however, nitrates and sympathomimetic agents may be used concurrently for therapeutic advantage)

Phenoxybenzamine

(in addition to phenoxybenzamine antagonizing the peripheral vasoconstriction of the sympathomimetic agents, concurrent use of phenoxybenzamine may produce an exaggerated hypotensive response and tachycardia)

Phenytoin, and possibly other hydantoins

(concurrent use with dopamine may result in sudden hypotension and bradycardia; this reaction is considered to be dose-rate dependent; if anticonvulsant therapy is necessary during administration of dopamine, an alternative to phenytoin should be considered; caution is also advised with concurrent use of other hydantoins 3, 45)

Rauwolfia alkaloids 4

(in addition to possibly decreasing the hypotensive effects of rauwolfia alkaloids, concurrent use may theoretically prolong the action of direct-acting sympathomimetics, such as dopamine, by preventing uptake into storage granules; a "denervation supersensitivity" response is also possible; although concurrent use is not known to produce severe adverse effects, a significant increase in blood pressure has been documented when phenylephrine ophthalmic drops were administered to patients taking reserpine, and caution and close observation are recommended)

Sympathomimetics, other

(concurrent use may increase the cardiovascular effects and the potential for side effects)

Thyroid hormones

(concurrent use may increase the effects of either these medications or the sympathomimetic agents; thyroid hormones enhance risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease; dosage adjustment is recommended, although the problem is reduced in euthyroid patients 20)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis)

(obstruction may increase as myocardial contractility improves with sympathomimetic agents possessing beta-1 adrenergic agonist activity 20, 53)

>> Pheochromocytoma

(severe hypertension may occur 3)

>> Tachyarrhythmias 3 or

Ventricular fibrillation 3

(exacerbation of arrhythmia may occur; however, epinephrine may be used as an adjunct in the treatment of ventricular fibrillation 65)

Risk-benefit should be considered when the following medical problems exist

Acidosis, metabolic 47 or

Hypercapnia or

Hypoxia

(may reduce effectiveness and/or increase incidence of side/adverse effects of the sympathomimetic agents; should be corrected prior to or concurrently with administration of sympathomimetic agents 3, 47)

Atrial fibrillation

(rapid ventricular response may occur since dobutamine facilitates atrioventricular conduction; in patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with dobutamine)

Glaucoma, narrow angle 1, 4

(condition may be exacerbated with sympathomimetic agents possessing alpha-1 adrenergic agonist activity 20)

Hypertension, pulmonary

(condition may be exacerbated due to pulmonary vasoconstriction)

>> Hypovolemia 20, 53

(prior to initiation of sympathomimetic therapy, hypovolemia should be corrected with appropriate volume expanders; volume should be maintained throughout treatment)

Mechanical obstruction, severe, such as severe valvular aortic stenosis 53

(these agents may be ineffective)

>> Myocardial infarction

(excessive doses of sympathomimetic agents possessing beta-1 adrenergic agonist activity may intensify ischemia by increasing myocardial oxygen demands 20, 53)

Occlusive vascular disease, history of, including:
Arterial embolism
Atherosclerosis
Buerger's disease
Cold injury, e.g., frostbite
Diabetic endarteritis
Raynaud's disease

(possible risk of necrosis and gangrene with sympathomimetic agents possessing alpha-1 adrenergic agonist activity; patients should be closely monitored for decreased circulation to extremities; if decreased circulation occurs, rate of infusion should be reduced or the infusion discontinued 3)

Sensitivity to other sympathomimetics

>> Tachyarrhythmias or ventricular arrhythmias

(condition may be exacerbated 2, 3)

For dopamine and dextrose injection only

Diabetes mellitus, subclinical or overt

(condition may be exacerbated)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
>> Blood pressure, preferably intra-arterial and

>> Electrocardiogram (ECG) 3, 20 and

>> Urine flow 3, 20

(continuous monitoring is recommended during therapy with sympathomimetic agents)

>> Cardiac output and

>> Central venous pressure and

>> Pulmonary artery pressure and

>> Pulmonary capillary wedge pressure 3

(recommended during therapy with sympathomimetic agents; however, therapy with low-dose dopamine may not require such intensive monitoring 3, 20, 53)

For dobutamine and epinephrine, in addition to the above

Potassium, serum 53

(monitoring may be considered due to risk of hypokalemia)

Side/Adverse Effects

Note: Peripheral vasoconstriction, possibly leading to necrosis or gangrene, may occur with prolonged use of sympathomimetic agents with alpha-1 adrenergic agonist activity in high doses or low doses in the presence of peripheral vascular disease. 3

Allergic reaction may occur in preparations containing sulfites.
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Angina 3, 47; bradycardia 3; dyspnea 3; hypertension 3, 47; hypotension 3; palpitations 3; tachycardia 47; ventricular arrhythmias 3, 47¾especially with high doses

Note: Angina, dyspnea, palpitations, tachycardia, and ventricular arrhythmias are associated with agents possessing beta-adrenergic agonist activity. They may also occur with agents possessing alpha-adrenergic agonist activity if marked degrees of hypertension are induced. 72

Incidence rare¾for dobutamine and epinephrine 67, 69Hypokalemia
Incidence rare¾for dopaminePolyuria

Note: Polyuria has been reported in patients receiving dopamine at nonrenal doses. 42, 43

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Headache; nausea or vomiting
Incidence less frequent

Nervousness or restlessness

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Hypertension, severe
Treatment of overdose

For excessive hypertensive effect¾The rate of administration should be reduced or the medication temporarily discontinued until blood pressure is decreased. 2, 3 Additional measures are usually not necessary because the duration of action of these agents is short. However, if reduction in the rate of administration or discontinuation of therapy fails to lower the blood pressure, a short-acting alpha-adrenergic blocking agent may be administered. 2, 3

General Dosing Information

Patients receiving sympathomimetic agent therapy should be closely monitored. See Patient monitoring .
Sympathomimetic agent therapy is not a substitute for replacement of blood, plasma, fluids, and/or electrolytes. 2, 3

Prior to initiation of therapy, hypovolemia should be fully corrected, if possible, with either whole blood or a plasma volume expander as indicated. 2, 3

An infusion pump or other suitable metering device should be used to control the rate of infusion in order to avoid unintentional administration of bolus doses.
Dosage must be adjusted to meet the individual requirements of each patient, on the basis of clinical response. Some patients may need higher than usually recommended doses for a time. 70

Infusions of sympathomimetic agents should be given into a large vein, 6 or preferably, directly into the central circulation 67, 70.

Caution is recommended to avoid extravasation, which may cause tissue necrosis and sloughing of surrounding tissues. 2, 3, 6

When discontinuing therapy, the dosage should be reduced gradually, since sudden cessation of therapy may result in severe hypotension. 2, 3, 6, 60 Intravascular fluid should be repleted if necessary to avoid hypotension. 60

For treatment of adverse effects

For extravasation ischemia¾To prevent necrosis and sloughing of tissue in areas where extravasation has occurred, the site should be infiltrated promptly with 10 to 15 mL of 0.9% sodium chloride injection containing 5 to 10 mg of phentolamine. 2, 3, 6 A syringe with a fine hypodermic needle should be used and the solution infiltrated liberally throughout the affected area. 2, 3, 6 If the area is infiltrated within

12 hours, the sympathetic blockade with phentolamine produces immediate and noticeable local hyperemic changes. 2, 3, 6 This treatment should be proportionally reduced for pediatric patients. 67

DOBUTAMINE

Summary of Differences

Indications¾
Indicated for congestive heart failure and low cardiac output.

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Primarily beta-1 adrenergic agonist; mild alpha-1 and beta-2 agonist.

Precautions to consider¾
Patient monitoring¾Serum potassium.

Side/adverse effects¾
Hypokalemia.

Additional Dosing Information

The concentration of solution administered depends on the dosage and fluid requirements of the patient, but should not exceed 5 mg of dobutamine per mL. 53

Parenteral Dosage Forms

Note: The dosing and strengths of the dosage forms available are expressed in terms of dobutamine base (not the hydrochloride salt).

DOBUTAMINE HYDROCHLORIDE INJECTION

Usual adult dose

Cardiac stimulant¾
Intravenous infusion, administered at a rate of 2.5 to 10 mcg (0.0025 to 0.01 mg) (base) per kg of body weight per minute. 53

Rates of infusion for concentrations of 250, 500, and 1000 mcg per mL:

Drug delivery rate (mcg/kg/min)	250 mcg/mL a (mL/kg/min)	Infusion delivery rate 500 mcg/mL b (mL/kg/min)	1000 mcg/mL c (mL/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075

10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

a 250 mg per L of diluent.

b 500 mg per L or 250 mg/500 mL of diluent.

c 1000 mg per L or 250 mg/250 mL of diluent.

Usual pediatric dose

Cardiac stimulant¾
Intravenous infusion, 5 to 20 mcg per kg of body weight per minute. 63, 64

Size(s) usually available:

U.S.¾12.5 mg (base) per mL (Rx)[Dobutrex (sodium bisulfite 0.24 mg per mL)]

Canada¾12.5 mg (base) per mL (Rx)[Dobutrex (sodium bisulfite 0.245 mg per mL)]

Packaging and storage:

Prior to dilution, store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form:

The solution must be further diluted to at least 50 mL prior to administration in 5% dextrose injection, 5% dextrose and 0.45% sodium chloride injection, 5% dextrose and 0.9% sodium chloride injection, 10% dextrose injection, lactated Ringer"s injection, 5% dextrose in lactated Ringer"s injection, 0.9% sodium chloride injection, or sodium lactate injection. 53

Stability:

Solutions diluted for intravenous infusion should be used within 24 hours. 53

Freezing may cause crystallization and should be avoided. 53

Pink discoloration of dobutamine solution indicates slight oxidation of the medication, but there is no significant loss of potency if administered within the recommended time periods. 53

Incompatibilities:

Dobutamine is incompatible with alkaline solutions and should not be mixed with solutions such as 5% sodium bicarbonate injection.

Dobutamine injection should not be used in conjunction with other agents or diluents containing both sodium bisulfite and ethanol 53.

It is recommended that dobutamine injection not be mixed in the same solution with other medications. 53

Mixture or administration of dobutamine through the same intravenous line as heparin, hydrocortisone sodium succinate, cefazolin, cefamandole, neutral cephalothin, penicillin, or sodium ethacrynate is not recommended.

DOPAMINE

Summary of Differences

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Dose-related alpha, beta, and dopamine receptor agonist.
Biotransformation¾Metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

Precautions to consider¾
Drug interactions¾Levodopa, phenytoin.
Pediatrics¾Cardiac arrhythmias and gangrene reported.

Side/adverse effects¾
Polyuria reported at nonrenal doses.

Additional Dosing Information

Dopamine hydrochloride injection must be diluted prior to administration. 2, 3

When dopamine hydrochloride and dextrose injection is used, the less concentrated 800 mcg (0.8 mg) per mL solution may be preferred when fluid expansion is not a problem. 62 The more concentrated 1.6 or 3.2 mg per mL solutions may be preferred in patients who are fluid restricted or when a slower rate of infusion is desired. 62

Parenteral Dosage Forms

DOPAMINE HYDROCHLORIDE INJECTION USP

Usual adult dose

Vasopressor or
Cardiac stimulant¾
Dopaminergic (renal) effects: Intravenous infusion, 0.5 to 3 mcg per kg of body weight per minute. 2, 3, 20, 47

Beta-1 adrenergic effects: Intravenous infusion, 2 to 10 mcg per kg of body weight per minute. 2, 3, 9, 11, 23

Alpha adrenergic effects: Intravenous infusion, 10 mcg per kg of body weight per minute. The dose may be increased gradually as clinically indicated. 2, 3, 9

Usual pediatric dose

Vasopressor or
Cardiac stimulant¾
Intravenous infusion, 5 to 20 mcg per kg of body weight per minute. 19, 34

Note: Renal doses of dopamine (0.5 to 3 mcg per kg of body weight per minute) appear to be effective in increasing renal blood flow in pediatric patients, even in premature infants. 34

Close hemodynamic monitoring is recommended since only limited studies have been conducted in pediatric patients and there is a lack of data evaluating age-dependent doses. 34, 68

Strength(s) usually available

U.S.¾40 mg per mL (Rx)[Intropin (sodium metabisulfite 1%)] [Generic]

80 mg per mL (Rx)[Intropin (sodium metabisulfite 1%)] [Generic]

160 mg per mL (Rx)[Intropin (sodium metabisulfite 1%)] [Generic]

Canada¾40 mg per mL (Rx)[Intropin (sodium bisulfite 1%)] [Revimine (sodium metabisulfite 1%)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Preparation of dosage form:

Diluents used for preparation of intravenous infusion solutions of dopamine include 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, 5% dextrose in 0.45% sodium chloride solution, 5% dextrose in lactated Ringer"s solution, sodium lactate injection (1/6 molar), and lactated Ringer"s injection. 2, 3

Sodium bicarbonate or other alkaline intravenous solutions should not be used as diluents because dopamine is inactivated in alkaline solutions. 2, 3

To prepare an intravenous infusion of dopamine hydrochloride, 400 to 800 mg of dopamine should be added to 250 mL of an appropriate diluent solution. The resultant solution contains 1600 or 3200 mcg of dopamine per mL. 60

Stability:

Injection should be diluted immediately prior to administration. 2, 3

After dilution in appropriate intravenous solution for infusion, dopamine is stable for at least 24 hours. 2, 3

Dopamine injection should not be used if it is darker than slightly yellow or discolored. 2, 3

Incompatibilities:

Dopamine is inactivated in alkaline solution (solution becomes pink to violet); therefore, it should not be added to 5% sodium bicarbonate or other alkaline diluent solution. Dopamine is also sensitive to oxidizing agents and iron salts. 2, 3

DOPAMINE HYDROCHLORIDE AND DEXTROSE INJECTION USP

Usual adult dose

See Dopamine Hydrochloride Injection USP.

Usual pediatric dose

See Dopamine Hydrochloride Injection USP.

Strength(s) usually available

U.S.¾800 mcg (0.8 mg) of dopamine hydrochloride per mL and 5% dextrose (Rx) [Generic]

1.6 mg of dopamine hydrochloride per mL and 5% dextrose (Rx) [Generic]

3.2 mg of dopamine hydrochloride per mL and 5% dextrose (Rx) [Generic]

Canada¾800 mcg (0.8 mg) of dopamine hydrochloride per mL and 5% dextrose (Rx) [Generic]

1.6 mg of dopamine hydrochloride per mL and 5% dextrose (Rx) [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Stability:

Solution should not be administered unless it is clear.
Discard unused portion.

Incompatibilities:

Dopamine is inactivated in alkaline solution (solution becomes pink to violet); therefore, it should not be added to 5% sodium bicarbonate or other alkaline diluent solution. 62 Dopamine is also sensitive to oxidizing agents and iron salts. 62

Dextrose solutions without electrolytes should not be administered simultaneously with blood through the same infusion set because of possible pseudoagglutination of red cells.
Additive medications should not be delivered via dopamine in dextrose injection because of possible incompatibilities.

EPHEDRINE

Summary of Differences

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Alpha and beta-1 adrenergic agonist; indirect effects via norepinephrine release.

Additional Dosing Information

When ephedrine is administered intravenously, the injection should be given slowly.

Parenteral Dosage Forms

EPHEDRINE SULFATE INJECTION USP

Usual adult dose

Vasopressor¾
Intramuscular or subcutaneous, 25 to 50 mg. 4 Dose may be repeated based on blood pressure response. 4

Note: The intravenous route of administration may be used if an immediate effect is needed. 4

Usual pediatric dose

Vasopressor¾
Intravenous or subcutaneous, 750 mcg per kg of body weight or 25 mg per square meter of body surface area four times a day as needed according to patient response. 4

Strength(s) usually available

U.S.¾25 mg per mL (Rx) [Generic]

50 mg per mL (Rx) [Generic]

Canada¾50 mg per mL (Rx) [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light.

Stability:

Should not use if solution is not clear.
Unused portion should be discarded.

EPINEPHRINE

Summary of Differences

Indications¾
Indicated for anaphylactic shock and cardiac arrest.

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Has alpha and beta adrenergic receptor action.
Biotransformation¾Metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

Precautions to consider¾
Patient monitoring¾Serum potassium.

Side/adverse effects¾
Hypokalemia.

Additional Dosing Information

The 1:1000 (1 mg/mL) concentration of epinephrine injection must be diluted before administering intravenously. 1

Intra-arterial administration of epinephrine injection is not recommended since marked vasoconstriction may result in gangrene.

Parenteral Dosage Forms

EPINEPHRINE HYDROCHLORIDE INJECTION

Usual adult dose

Vasopressor¾
Intravenous infusion, 1 mcg per minute. The dose may be titrated up to 2 to 10 mcg per minute for desired hemodynamic response. 60

Cardiac arrest¾
Intravenous, 1 mg every three to five minutes during resuscitation. 48, 60

Note: Epinephrine may be given by the endotracheal route. 48, 60 However, the optimal dose for this route of administration is not known. 48, 49, 60 A dose that is at least two to two and a half times the peripheral intravenous dose may be needed. 48, 60

Usual pediatric dose

Cardiac arrest¾
Neonates¾
Intravenous, 10 to 30 mcg (0.01 to 0.03 mg) per kg of body weight every three to five minutes. 51

Note:
Endotracheal administration may be used. However, this may result in low plasma concentrations. 51

Children¾
Intravenous, 10 mcg (0.01 mg) per kg of body weight. 52 Subsequent doses of 100 mcg (0.1 mg) per kg of body weight every three to five minutes may be given if needed. 52 In refractory situations, following at least two standard doses, a higher dose may be used. 66 Subsequent doses of 200 mcg (0.2 mg) per kg of body weight every five minutes may be given. 66, 67

Note:
Two different dilutions of epinephrine are necessary for this dosing regimen. Caution is recommended to avoid errors in concentration selection and dosing. 52

Endotracheal administration may be used. However, absorption and resulting plasma concentrations may be unpredictable. 52

Strength(s) usually available

U.S.¾0.1 mg (100 mcg) per mL (1:10,000) (Rx/OTC) [Generic]

1 mg per mL (1:1000) (Rx)[Adrenalin (benzyl alcohol) (chlorobutanol 0.5%) (sodium bisulfite < 0.1% in ampuls and < 0.15% in vials)] [Generic]

Canada¾1 mg per mL (1:1000) (Rx) [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

Preparation of dosage form:

Epinephrine 1:1000 should be diluted.

Stability:

Epinephrine is readily destroyed by alkalies and oxidizing agents (for example, oxygen, chlorine, bromine, iodine, permanganates, chromates, nitrites, and salts of easily reducible metals, especially

iron). Do not use if solution is pinkish or brownish in color or contains a precipitate. Discard unused portion.

ISOPROTERENOL

Summary of Differences

Indications¾
Indicated for bradycardia only.

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Pure beta-adrenergic agonist.

Parenteral Dosage Forms

ISOPROTERENOL HYDROCHLORIDE INJECTION USP

Usual adult dose

Bradycardia¾
Intravenous infusion, initially, 2 mcg per minute, the dosage being gradually titrated according to heart rate up to 10 mcg per minute if needed. 60

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾20 mcg (0.02 mg) per mL (Rx) [Generic]

200 mcg (0.2 mg) per mL (Rx)[Isuprel (sodium chloride) (sodium lactate) (sodium metabisulfite) (lactic acid)] [Generic]

Canada¾200 mcg (0.2 mg) per mL (Rx)[Isuprel (sodium lactate) (sodium metabisulfite)] [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

Preparation of dosage form:

For preparation of solutions for injection, see manufacturer''s package insert.

Stability:

When exposed to air, alkalies, or metals, isoproterenol may turn pinkish to brownish in color because of oxidation. Do not use if solution is pinkish to brownish in color or contains a precipitate.

MEPHENTERMINE

Summary of Differences

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Alpha-adrenergic agonist.

Additional Dosing Information

Mephentermine can be administered intramuscularly. 15

Parenteral Dosage Forms

MEPHENTERMINE SULFATE INJECTION

Usual adult dose

Vasopressor¾
Hypotension, secondary to spinal anesthesia (prophylaxis)¾
Intramuscular, 30 to 45 mg, administered ten to twenty minutes prior to anesthesia, operation, or termination of operative procedure. 15

Hypotension, secondary to spinal anesthesia (treatment)¾
Intravenous, 30 to 45 mg given as a single dose. 15 Doses of 30 mg may be repeated as needed to maintain the desired level of blood pressure. 15

Intravenous infusion (continuous), administered as a 0.1% (1 mg per mL) solution in 5% dextrose in water, the rate of administration and duration of therapy being adjusted according to patient response. 15

In obstetrical patients¾Intravenous, 15 mg initially, the dose being repeated if needed. 15

Usual pediatric dose

Safety and efficacy have not been established. 15

Strength(s) usually available

U.S.¾15 mg per mL (Rx)[Wyamine (methylparaben 1.8 mg) (propylparaben 0.2 mg) (sodium acetate)]

30 mg per mL (Rx)[Wyamine (methylparaben 1.8 mg) (propylparaben 0.2 mg) (sodium acetate)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Preparation of dosage form:

To prepare a 0.1% (1 mg per mL) solution of mephentermine for continuous intravenous infusion, 600 mg of mephentermine should be added to 500 mL of 5% dextrose in water. 15

Stability:

Do not use if solution is discolored or contains a precipitate. 15

METARAMINOL

Summary of Differences

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Alpha and beta-1 receptor agonist; indirect effects via norepinephrine release.

Additional Dosing Information

Metaraminol may be given intramuscularly, subcutaneously, or intravenously. 5

The site for intramuscular or subcutaneous injection should be carefully selected, 5 since use of areas with poor circulation may produce poor patient response and increase the possibility of tissue necrosis, sloughing of tissue, or abscess formation.
Patient"s response to initial dose should be observed for at least 10 minutes before increasing dose since the maximum effect is not immediately evident. 5

Parenteral Dosage Forms

Note: The dosing and strengths of the dosage forms available are expressed in terms of metaraminol base (not the bitartrate salt).

METARAMINOL BITARTRATE INJECTION USP

Usual adult dose

Hypotension (prophylaxis)¾
Intramuscular or subcutaneous, 2 to 10 mg (base). 5

Hypotension (treatment)¾
Intravenous infusion, 15 to 100 mg (base) in 500 mL of 0.9% sodium chloride injection or 5% dextrose injection, administered at a rate adjusted to maintain the desired blood pressure. 5

Shock, severe¾

Intravenous, 500 mcg (0.5 mg) to 5 mg (base), followed by an intravenous infusion of metaraminol for control of blood pressure. 5

Usual adult prescribing limits

Intravenous infusion, up to 500 mg (base) in 500 mL of infusion fluid (with caution). 5

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾10 mg (base) per mL (Rx)[Aramine (sodium chloride 4.4 mg per mL) (methylparaben 0.15%) (propylparaben 0.02%) (sodium bisulfite 0.2%)] [Generic]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

Preparation of dosage form:

Metaraminol bitartrate 1% must be diluted prior to use.
The preferred solutions for dilution of metaraminol bitartrate are 0.9% sodium chloride injection and 5% dextrose injection. However, other diluents that may be used include Ringer"s injection and lactated Ringer"s injection. 5

Stability:

After metaraminol and infusion solutions are mixed, they should be used within 24 hours because of the absence of preservatives. 5

Incompatibilities:

Metaraminol bitartrate tends to be physically incompatible with other medications of poor solubility in acidic media, such as sodium salts of barbiturates, penicillins, and phenytoin. 5

METHOXAMINE

Summary of Differences

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Selective alpha-1 adrenergic agonist.

Additional Dosing Information

If methoxamine is administered prophylactically to prevent hypotension during spinal anesthesia, it should be administered by intramuscular injection shortly before or at the time of spinal anesthesia administration. 7 Those patients suffering from hypertension are more likely to experience a greater reduction in blood pressure during spinal anesthesia than patients with blood pressure in a normal range. Higher levels of anesthesia will usually cause a greater drop in blood pressure, which in turn will require an increased dose of methoxamine for control. 7

Although it is sometimes necessary to repeat intramuscular doses of methoxamine, it is very important to allow adequate time (about l5 minutes) for the previous intramuscular dose to elicit its effect before administration of additional doses. 7

Methoxamine is administered by slow, intravenous injection when the systolic blood pressure falls to 60 mm of mercury (Hg) or less, or when an emergency situation occurs. 7

When methoxamine is administered intravenously during emergencies, supplemental doses may be given intramuscularly to provide a prolonged effect. 7

Rapid administration of methoxamine should be avoided because it would produce added stress on the myocardium from markedly increased peripheral resistance during a reduction in stroke volume and cardiac output.

Parenteral Dosage Forms

METHOXAMINE HYDROCHLORIDE INJECTION USP

Usual adult dose

Vasopressor¾
Intramuscular, 10 to 15 mg. 7 In cases of moderate hypotension, 5- to 10-mg doses may be adequate. 7 If used during spinal anesthesia, a 10-mg dose may be adequate at low spinal anesthesia levels; however, a 15- to 20-mg dose may be required at high spinal anesthesia levels. 7

Intravenous, 3 to 5 mg administered slowly. 7

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾20 mg per mL (Rx)[Vasoxyl (citric acid 0.3%) (potassium metabisulfite 0.1%) (sodium citrate 0.3%)]

Canada¾20 mg per mL (Rx)[Vasoxyl (bisulfites)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

NOREPINEPHRINE

Summary of Differences

Pharmacology/pharmacokinetics¾
Mechanism of action/effect¾Alpha and beta-1 adrenergic agonist.
Biotransformation¾Metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

Additional Dosing Information

Prior to administration, norepinephrine injection must be diluted with 5% dextrose in distilled water or 5% dextrose in sodium chloride solution because the dextrose in these fluids protects against significant loss of potency due to oxidation. Administration of norepinephrine in sodium chloride solution alone is not recommended. 6

When norepinephrine is used as an emergency measure, it can be administered before or concurrently with blood volume replacement, but intra-aortic pressure should be maintained to prevent cerebral or coronary artery ischemia. 6

If whole blood or plasma is indicated to increase blood volume, it should be administered separately (e.g., use of a Y-tube and individual flasks if given simultaneously). 6

Norepinephrine is administered only by intravenous infusion. Subcutaneous or intramuscular administration is not recommended because of the potent vasoconstrictor effect of norepinephrine.

Parenteral Dosage Forms

Note: The dosing and strengths of the dosage forms available are expressed in terms of norepinephrine base (not the bitartrate salt).

NOREPINEPHRINE BITARTRATE INJECTION USP

Usual adult dose

Vasopressor¾
Initial: Intravenous infusion, 0.5 to 1 mcg (base) per minute; the dosage being adjusted gradually to achieve desired blood pressure. 60

Maintenance: Intravenous infusion, 2 to 12 mcg (base) per minute. 60

Note: Patients with refractory shock may require dose up to 30 mcg (base) per minute. 60

Usual pediatric dose

Vasopressor¾
Intravenous infusion, 0.1 mcg (base) per kg of body weight per minute; the dosage being adjusted gradually to achieve desired blood pressure, up to 1 mcg per kg of body weight per minute. 63

Strength(s) usually available

U.S.¾1 mg (base) per mL (Rx)[Levophed (sodium chloride) (sodium metabisulfite not more than 2 mg per mL)]

Canada¾1 mg (base) per mL (Rx)[Levophed (sodium bisulfite not more than 2 mg per mL) (sodium chloride)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a light-resistant container. Protect from freezing.

Preparation of dosage form:

Diluents used for preparation of infusion solutions of norepinephrine are 5% dextrose in distilled water or 5% dextrose in sodium chloride solution because the dextrose in these fluids protects against significant loss of potency due to oxidation. Sodium chloride solution alone is not recommended as a diluent. 6

To prepare an intravenous infusion solution of norepinephrine, add 4 mg of norepinephrine (base) to 250 mL of 5% dextrose solution. 60 The resultant solution contains 16 mcg of norepinephrine base per mL. 60

Stability:

Do not use discolored (pink, yellow, or brown) solutions or those containing a precipitate; they should be discarded. 6

Discard unused portion of norepinephrine solution.

Incompatibilities:

Norepinephrine is incompatible with iron salts, alkalies, and oxidizing agents; contact should be avoided. 6

PHENYLEPHRINE

Summary of Differences

Indications¾
Also indicated as an antiarrhythmic.

Pharmacology/pharmacokinetics¾

Mechanism of action/effect¾Alpha-1 adrenergic agonist.

Parenteral Dosage Forms

PHENYLEPHRINE HYDROCHLORIDE INJECTION USP

Usual adult dose

Vasopressor¾
Mild or moderate hypotension¾
Intramuscular or subcutaneous, 2 to 5 mg, repeated not more often than every ten to fifteen minutes. 8

Intravenous, 200 mcg (0.2 mg), repeated not more often than every ten to fifteen minutes. 8

Note:
The initial intramuscular or subcutaneous dose should not exceed 5 mg; the initial intravenous dose should not exceed 500 mcg (0.5 mg). 8

Severe hypotension and shock¾
Intravenous infusion, 10 mg in 500 mL of 5% dextrose injection USP or 0.9% sodium chloride injection USP, administered initially at a rate of about 100 to 180 mcg (0.1 to 0.18 mg) per minute until blood pressure is stabilized; then at a rate of 40 to 60 mcg (0.04 to 0.06 mg) per minute. 8 If necessary, additional doses in increments of 10 mg or more may be added to the infusion solution and the rate of flow adjusted until the desired blood pressure level is obtained. 8

Hypotension during spinal anesthesia¾
Prophylaxis¾Intramuscular or subcutaneous, 2 to 3 mg three to four minutes prior to injection of spinal anesthetic. 8

Hypotensive emergencies¾Intravenous, initially 200 mcg (0.2 mg), the dosage being increased by not more than 200 mcg (0.2 mg) for each subsequent dose, up to a maximum of 500 mcg (0.5 mg) per dose. 8

Antiarrhythmic¾
Intravenous (rapid), initial dose not exceeding 500 mcg (0.5 mg). 8 Additional doses should not exceed the preceding dose by more than 100 to 200 mcg (0.1 to 0.2 mg). 8

Usual pediatric dose

Hypotension during spinal anesthesia¾
Intramuscular or subcutaneous, 500 mcg (0.5 mg) to 1 mg per twenty-five pounds of body weight. 8

Strength(s) usually available

U.S.¾10 mg per mL (Rx)[Neo-Synephrine (sodium chloride 3.5 mg) (sodium citrate 4 mg) (citric acid monohydrate 1 mg) (sodium metabisulfite not more than 2 mg)]

Canada¾10 mg per mL (Rx)[Neo-Synephrine (sodium chloride 3.5 mg) (sodium citrate 4 mg) (citric acid monohydrate 1 mg) (sodium metabisulfite not more than 2 mg)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

Preparation of dosage form:

To prepare a solution of phenylephrine for direct intravenous injection, 10 mg (1 mL) of phenylephrine hydrochloride injection should be diluted with 9 mL of sterile water for injection USP to provide a solution containing 1 mg of phenylephrine per mL. 8