Intravenous Infusions

This course will cover different types of common intravenous medication infusions including insulin, heparin, vasopressors, vasodilators, and anti-arrhythmics. Each drug type will be described and specific medications will be discussed. All dosages described are for adult patients. Medication administration safety issues will also be addressed.

Objectives:
After taking this course, the participant should be able to…

1. Identify the action of commonly used medication infusions.
2. Identify the indication for commonly used medication infusions.
3. Identify the considerations for administration of commonly used medication infusions.
4. Identify some of the common adverse effects of commonly used medication infusion.
5. Identify some safety considerations related to medication infusions.

Insulin

What is insulin?

Insulin is a medication used to lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin is the primary hormone required for proper glucose use in normal metabolic processes.

Insulin comes in many different types and can be given subcutaneously or intravenously. All types of insulin are measured in units. This course will focus on IV insulin infusions of Regular Insulin. Regular insulin is a short-acting insulin with an onset of action between 0.5 and one hour. Its peak action ranges from approximately two to five hours with an average duration lasting between eight and 12 hours. Regular insulin is the only type of insulin that can be given intravenously.

Why is insulin used?

Intravenous insulin is used in clinical settings to manage elevated glucose levels in the blood, or hyperglycemia. Hyperglycemia associated with critical illness (also called stress hyperglycemia or stress diabetes) is a consequence of many factors, including increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis. Insulin resistance may also be a contributing factor, since it has been demonstrated in more than 80% of critically ill patients.

Some indications for IV insulin therapy include:
1. DKA (Diabetic Ketoacidosis)
2. Surgery (before, during & after)
3. IV nutrition (TPN/CPN) or tube feedings
4. Patient with severe infection
5. After a heart attack or open heart surgery
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Hyperglycemia was previously considered an adaptive response essential for survival and was not routinely controlled in intensive care units. However, more recent evidence indicating that uncontrolled hyperglycemia is associated with poor outcomes has prompted efforts to routinely correct and prevent hyperglycemia in critically ill patients. While most clinicians agree that such glycemic control is a desirable intervention, the optimal blood glucose range remains controversial. Recent studies have shown that a blood glucose range of 140-180 mg/dL may be optimal yielding better patient outcomes and fewer complications of hypoglycemic episodes.

Considerations during administration & Side effects

During IV insulin therapy, blood glucose levels should be measured frequently, usually every hour. Many facilities have protocols for titrating the insulin infusion based on the hourly blood glucose level. A sample dosing chart is shown below. Insulin is measured in units (u) and dosed in units per hour (u/hr.) A typical infusion range is one to 20 units per hour.

<table>
<thead>
<tr>
<th>Blood glucose level</th>
<th>Insulin u/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 110</td>
<td>0</td>
</tr>
<tr>
<td>111-130</td>
<td>2</td>
</tr>
<tr>
<td>131-150</td>
<td>4</td>
</tr>
<tr>
<td>151-170</td>
<td>6</td>
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<tr>
<td>171-190</td>
<td>8</td>
</tr>
<tr>
<td>191-210</td>
<td>10</td>
</tr>
<tr>
<td>211-230</td>
<td>12</td>
</tr>
<tr>
<td>231-250</td>
<td>14</td>
</tr>
<tr>
<td>251-270</td>
<td>16</td>
</tr>
</tbody>
</table>

Frequent blood glucose checks are important to ensure the efficacy of the medication and to avoid episodes of hypoglycemia, or having the blood glucose levels get too low (i.e. below 50 mg/dL.) Hypoglycemia is the most common side effect that may occur during insulin therapy. Symptoms of hypoglycemia include confusion, nausea, hunger, tiredness, perspiration, headache, heart palpitations, numbness around the mouth, tingling in the fingers, tremors, muscle weakness, blurred vision, cold temperature, excessive yawning, irritability, and loss of consciousness. If left untreated, hypoglycemia can lead to death.

Mild episodes of hypoglycemia can be treated with oral glucose or carbohydrates. Adjustments in drug dosage, or nutritional intake may be needed. More severe episodes with coma, seizure, or neurological impairment may be treated with IM/subcutaneous glucagon or concentrated IV glucose. Sustained monitoring and treatment may be necessary because hypoglycemia may recur after apparent clinical recovery.
A true allergy to insulin is rare, but drug interactions with insulin are not uncommon. If possible, insulin should be infused through a dedicated IV site, (this can be a peripheral site) together with only maintenance fluids. If this is not possible, regular insulin is compatible with a few other drugs including Amiodarone, Esmolol, Heparin, Lidocaine, Milrinone, Nitroglycerin, Nitroprusside, and Procainamide. Always check compatibility before running medications together and ensure that the insulin will not be bolused if another medication is being titrated as this may cause hypoglycemia.

Heparin

What is Heparin?

Heparin is an anticoagulant that prevents the formation of blood clots. It works by blocking reactions in the body that lead to blood clots. It is used to decrease the clotting ability of the blood and help prevent harmful clots from forming in the blood vessels. This medicine is sometimes called a blood thinner, although it does not actually thin the blood; it decreases the clotting ability of the blood. Heparin will not dissolve blood clots that have already formed, but it may prevent the clots from becoming larger and causing more serious problems.

Why is Heparin used?

Heparin is used to prevent or treat certain blood vessel, heart, and lung conditions. Heparin is also used to prevent blood clotting during open-heart surgery, bypass surgery, kidney dialysis, and blood transfusions. It is used in low doses to prevent the formation of blood clots in certain patients, especially those who must have certain types of surgery or who must remain in bed for a long time. Heparin may also be used to diagnose and treat a serious blood condition called disseminated intravascular coagulation (DIC.) Heparin is also used to stop the growth of clots that have already formed in the blood vessels, but it cannot be used to decrease the size of clots that have already formed.

Considerations during administration

Heparin can be administered via subcutaneous injection or intravenous (IV) infusion. This course will focus on the IV infusion of heparin. Heparin is measured in units (u) and dosed in units per hour (u/hr.) The dosage rate is calculated and adjusted based on the patients’ coagulation lab test results. Intravenous heparin has an immediate onset and a duration of two to six hours. The laboratory test used to measure patients’ coagulation is the activated partial thromboplastin time (aPTT). During continuous heparin infusion therapy, the aPTT should be measured every four to six hours and the heparin infusion rate should be adjusted accordingly. Dosage is considered adequate when the aPTT is 1.5 to 2 times normal (usually 55-90 seconds.)

Heparin is commonly supplied in 250mL bags containing 25,000 units of heparin (100u/mL) and typical infusion rates range from 500 u/hr (5 ml/hr) to 2000 u/hr (20 u/hr.) Always note the concentration and double check the infusion rate however because overdoses of heparin can have catastrophic consequences. Different organizations may have slightly different guidelines regarding dosing, or multiple dosing tables for varied indications. An example dosing schedule is shown below.
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<table>
<thead>
<tr>
<th>Heparin Dosage for DVT Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aPTT (seconds)</strong></td>
</tr>
<tr>
<td>&lt; 45</td>
</tr>
<tr>
<td>45 to 54</td>
</tr>
<tr>
<td>55 to 85</td>
</tr>
<tr>
<td>86 to 110</td>
</tr>
<tr>
<td>&gt; 110</td>
</tr>
</tbody>
</table>

Ideally, heparin would be infused through a dedicated IV site (this can be a peripheral site) alone or with only maintenance fluids, but if this is not possible, heparin is compatible with some other drugs including Dopamine, Epinephrine, Insulin, Isoproterenol, Lidocaine, Milrinone, Nitroglycerin, Nitroprusside, Norepinephrine, Phenylephrine, and Procainamide. Always check compatibility before running medications together and ensure that the heparin will not be bolused if another medication is being titrated as this may cause a change in the aPTT.

### Side effects & complications

The primary side effect of a heparin infusion is hemorrhage. Hemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure or any other unexplained symptom should lead to serious consideration of a hemorrhagic event. An overly prolonged coagulation test or bleeding can usually be controlled by withdrawing the drug. Signs and symptoms will vary according to the location and extent of bleeding and may be present as paralysis, headache, chest, abdomen, joint or other pain, shortness of breath, difficulty breathing or swallowing, unexplained swelling or unexplained shock. Nosebleeds, hematuria or tarry stools may be the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding GI or urinary tract bleeding may indicate an underlying occult lesion. Certain hemorrhagic complications may be difficult to detect.

Another side effect may be thrombocytopenia. Thrombocytopenia has occurred in patients receiving heparin with a reported incidence of up to 30%. The development of thrombocytopenia does not necessarily imply a causal relationship. Often patients have other potential causes for thrombocytopenia; they can be ill, receiving several medications or in a postoperative phase. Exclude these potential causes for thrombocytopenia before implicating heparin. The severity of thrombocytopenia appears to be related to heparin dosage, with low-dose therapy resulting in fewer complications.

Other side effects of heparin may include hypersensitivity reactions, local irritation, hyperkalemia or vasospastic reactions. Vasospastic reactions may develop 6 to 10 days after starting therapy and last four to six hours. The affected limb is painful, ischemic and cyanotic. An artery to this limb may have been recently catheterized. After repeated injections, the reaction may gradually increase to generalized vasospasm with cyanosis, tachypnea, feeling of oppression and headache. Chest pain, elevated blood pressure, arthralgias or headache have also been reported in the absence of definite peripheral vasospasm.

As previously stated, an overly prolonged aPTT or mild bleeding can usually be controlled by stopping the heparin infusion. In more extreme cases of heparin overdose, protamine sulfate is used. Each 1mg of protamine neutralizes approximately 100 heparin units.
Vasopressors & Inotropes

This section of the course will focus on vasopressors and inotropic medications. Vasopressors are medications that increase the patients’ blood pressure through constricting the blood vessels. These medications can be tremendously useful and effective. Inotropic drugs are medications that increase the strength of the cardiac muscle contractions that pump blood from the heart. Both of these types of drugs are used to manage patients in shock, to address dangerous drops in blood pressure, and to manage patients in the operating room. The following section will cover Dobutamine, Dopamine, Isoproterenol, Norepinephrine, and Phenylephrine.

Dobutamine

What is Dobutamine?

Dobutamine is an inotropic drug whose primary activity results from stimulation of the beta receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. Systemic vascular resistance (SVR) is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed. The onset of action of dobutamine is within one to two minutes; however, as much as 10 minutes may be required to obtain the peak effect of a particular infusion rate.

Why is Dobutamine used?

Dobutamine is used when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

Considerations during administration

Dobutamine is measured in micrograms (mcg) and is dosed based on weight, thus infusion rates are given as mcg/kg/min. Infusion of dobutamine should be started at a low rate (0.5 to 1.0 mcg/kg/min) and titrated at intervals of a few minutes, guided by the patient's response, including systemic blood pressure, urine flow, frequency of ectopic activity, heart rate and (whenever possible) measurements of cardiac output (CO), central venous pressure (CVP), and/or pulmonary capillary wedge pressure (PCWP). In reported trials, the optimal infusion rates have varied from patient to patient, usually 2 to 20 mcg/kg/min but sometimes slightly outside of this range. On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Administration of dobutamine via a central line is preferred, but it can be given peripherally if central access is not available. Dobutamine is compatible with amiodarone, dopamine, epinephrine, esmolol, isoproterenol, lidocaine, milrinone, nitroglycerin, phenylephrine and procainamide.

Side effects & Complications
Side effects of dobutamine include a marked increase in heart rate and blood pressure, especially systolic pressure. A 10 to 20 mm Hg increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/min have been noted in most patients. Approximately 10% of adult patients in clinical studies have had rate increases of 30 beats/min or more, and about 7.5% have had a 50 mm Hg or greater increase in systolic pressure. Usually, reduction of dosage promptly reverses these effects. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with dobutamine. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response. Approximately 5% of patients have had increased premature ventricular beats (PVC’s) during infusions. These effects are dose related.

Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to baseline values. In rare cases, however, intervention may be required and reversibility may not be immediate. Other side effects may include anginal pains, mild decrease in serum potassium concentration, nausea, headache, non-specific chest pain, shortness of breath and palpitations. Isolated cases of thrombocytopenia have been reported and phlebitis has occasionally been reported with local inflammatory changes described following inadvertent infiltration.

Dopamine

What is Dopamine?

Dopamine is a drug used in critically ill patients that produces positive chronotropic and inotropic effects on the myocardium, resulting in increased heart rate and cardiac contractility. Dopamine is used for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure. Patients most likely to respond adequately to Dopamine are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Research has indicated that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and Dopamine, the better the prognosis.

Why is Dopamine used?

Dopamine is used for several indications including hypotension, low cardiac output, poor perfusion of vital organs, and shock.

Hypotension

Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of dopamine, which have little effect on systemic vascular resistance (SVR). At high therapeutic doses, the alpha-adrenergic activity of dopamine becomes more prominent and, thus, may correct hypotension because of diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, dopamine should be administered as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

Low cardiac output
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Increased cardiac output is related to the direct inotropic effect of dopamine on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased SVR. Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g., femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances, the renal fraction of the total cardiac output has been found to increase. The increase in cardiac output produced by dopamine is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Poor perfusion of vital organs
Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, during dopamine infusion, observe the patient for signs of reversal of mental confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Research has shown that when dopamine is administered before urine flow has diminished to levels approximating 0.3 mL/min, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of dopamine has resulted in an increase in urine flow, which, in some cases, reached normal levels. Dopamine may also increase urine flow in patients whose output is within normal limits and, thus, may be of value in reducing the degree of preexisting fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Coadministration of dopamine and diuretic agents may produce an additive or potentiating effect.

Shock
Dopamine can be used in the treatment of shock states to increase blood pressure and tissue perfusion. Shock is a state of inadequate tissue perfusion. It can be caused by, or cause, a decreased supply of, or an increased demand for, oxygen and nutrients. The imbalance between supply and demand interferes with normal cellular function. Widespread cellular dysfunction can result in death. Inadequate tissue perfusion can occur even if cardiac output, peripheral resistance, and other factors that determine blood pressure (e.g., blood volume) are normal or elevated. Therefore, hypotension need not be present for the patient to be in shock.

Shock produces various physiologic responses. Some, such as lactic acidosis, occur as a direct result of tissue hypoperfusion. Others, such as catecholamine release, also serve to compensate for the absolute or relative reduction in tissue perfusion. The systemic responses to shock can be beneficial in the early stages and classically consist of an increase in circulating catecholamines, vasodilation, and increased vascular permeability. These early responses produce a “hyperdynamic” state, which may be referred to as “warm” shock, so named because blood flow to the skin and extremities is still maintained. If left uncorrected, however, these responses become counterproductive and contribute to the relentless progression of the shock state. Profound vascular decompensation occurs, which is associated with a further loss of blood flow to the vital organs, skin, and extremities. Thus, more advanced shock is “cold” shock.

Considerations during administration
Dopamine is a potent drug used for critically ill patients. When appropriate, increase blood volume with whole blood or plasma until central venous pressure (CVP) is 10 to 15 cm H₂O or pulmonary wedge pressure is 14-18 mm Hg prior to starting a dopamine infusion. Dopamine is measured in micrograms (mcg) and is dosed according
to patient weight in micrograms per kilogram per minute (mcg/kg/min.) Each patient must be individually titrated to
the desired hemodynamic and/or renal response. In titrating to the desired increase in systolic blood pressure, the
optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the
hemodynamic condition is stabilized.

Dopamine infusions are commonly started at doses of 2-5 mcg/kg/minute in patients who are likely to respond to
modest increments of heart force and renal perfusion. In more seriously ill patients, infusions may be started at
doses of 5 mcg/kg/minute and increased gradually, using 5 to 10 mcg/kg/minute increments, up to 20 to 50
mcg/kg/minute as needed. If doses of Dopamine in excess of 50 mcg/kg/minute are required, it is suggested that
urine output be checked frequently. Should the urine flow begin to decrease in the absence of hypotension,
reduction of Dopamine dosage should be considered. Research has shown that more than 50% of the patients
were satisfactorily maintained on doses of Dopamine less than 20 mcg/kg/minute. In patients who do not respond
to these doses with adequate arterial pressures or urine flow, additional increments of Dopamine may be
employed in an effort to produce an appropriate arterial pressure and central perfusion.

Administration of dopamine at rates greater than 50 mcg/kg/minute have safely been used in advanced circulatory
decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be
preferred over increasing the flow rate of a less concentrated dilution. And when discontinuing the infusion, it may
be necessary to gradually decrease the dose of dopamine while expanding blood volume with IV fluids, since
sudden cessation may result in marked hypotension.

Administration of dopamine via a central line is preferred, but it can be given peripherally if central access is not
available. Dopamine is compatible with amiodarone, diltiazem, dobutamine, epinephrine, esmolol, heparin,
isoproterenol, lidocaine, milrinone, nicardipine, nitroglycerin, nitroprusside, phenylephrine, and procainamide.

**Side effects & complications**

Many of the complications of dopamine are cardiac in nature including ventricular arrhythmias (at higher doses),
ectopic beats, tachycardia, angina, palpitations, cardiac conduction abnormalities, widened QRS complexes,
decreased pulse pressure, and hypotension. Other side effects or complications may include fluid overload,
hypokalemia, dyspnea, nausea, vomiting, anxiety or headache. These complications are more likely to occur at
higher doses and will usually subside after the infusion rate is decreased.
Isoproterenol (Isuprel)

What is Isoproterenol?

Isoproterenol is a potent nonselective beta-adrenergic agonist with very low affinity for alpha-adrenergic receptors. IV infusion of isoproterenol lowers peripheral vascular resistance (PVR), primarily in skeletal muscle but also in renal and mesenteric vascular beds. Isoproterenol usually causes diastolic pressure to fall. Renal blood flow is decreased in normotensive patients but is increased markedly in patients with shock. Systolic blood pressure may remain unchanged or rise although mean arterial pressure typically falls. Cardiac output is increased because of the positive inotropic and chronotropic effects of the drug in the face of diminished peripheral vascular resistance (PVR).

Isoproterenol relaxes almost all varieties of smooth muscle when the tone is high, but this action is most pronounced on bronchial and gastrointestinal smooth muscle. It prevents or relieves bronchoconstriction, but tolerance to this effect develops with overuse of the drug.

Why is Isoproterenol used?

Isoproterenol is administered for mild or transient episodes of heart block that do not require electric shock or pacemaker therapy. It is also used for serious episodes of heart block and Adams-Stokes attacks (except when caused by ventricular tachycardia or fibrillation). Isoproterenol may be used in cardiac arrest until electric shock or pacemaker therapy, the treatments of choice, are available. Isoproterenol can also be used for bronchospasm occurring during anesthesia.

Finally, Isoproterenol can be administered for treatment of hypovolemic and septic shock, low cardiac output (hypoperfusion) states, CHF, or cardiogenic shock. It is used as an adjunct to fluid and electrolyte replacement therapy and the use of other drugs and procedures in the treatment of these conditions.

Considerations during administration

Isoproterenol is measured in micrograms (mcg) and dosed in micrograms per minute (mcg/min.) Isoproterenol infusions should generally be started at the lowest recommended dose and the rate of administration gradually increased if necessary while carefully monitoring the patient. Typical infusion rates are 0.5mcg/min to 5mcg/min. Rates over 30 mcg/min have been used in advanced stages of shock. The rate of infusion should be adjusted on the basis of heart rate, central venous pressure (CVP), systemic blood pressure, and urine flow. If the heart rate exceeds 110 beats per minute, it may be advisable to decrease or temporarily discontinue the infusion. Doses sufficient to increase the heart rate to more than 130 beats per minute may increase the likelihood of inducing ventricular arrhythmias. Such increases in heart rate will also tend to increase cardiac work and oxygen requirements which may adversely affect the failing heart or the heart with a significant degree of arteriosclerosis.

In addition to the routine monitoring of systemic blood pressure, heart rate, urine flow, and the ECG, the response to therapy should also be monitored by frequent determination of the central venous pressure (CVP) and arterial blood gases (ABG's). Patients in shock should be closely observed during isoproterenol infusions. Determinations of cardiac output and circulation time may also be helpful. Appropriate measures should be taken to ensure adequate ventilation. Careful attention should be paid to acid-base balance and to the correction of electrolyte disturbances. In cases of shock associated with bacteremia, suitable antimicrobial therapy is, of course, imperative.
Suggested minimal precautions while infusing isoproterenol continuously include careful monitoring of blood pressure and pulse, ECG monitoring of heart rate, arrhythmias, and evidence of myocardial ischemia, and where ECG evidence suggests myocardial ischemia, daily determination of cardiac enzymes including the more specific CPK-MB isoenzyme, monitoring arterial pH and blood gases carefully and maintaining PaO2 above 60 torr by administration of supplemental oxygen.

Administration of isoproterenol via a central line is preferred, but it can be given peripherally if central access is not available. Isoproterenol is compatible with amiodarone, dobutamine, dopamine, esmolol, heparin, lidocaine, milrinone, nitroglycerin, nitroprusside, phenylephrine, and procainamide.

**Side effects & complications**

Side effects and complications of Isoproterenol include tachycardia, palpitations, angina, Adams-Stokes attacks, pulmonary edema, hypertension, hypotension, ventricular arrhythmias, and tachyarrhythmias. Isoproterenol may also cause nervousness, headache, dizziness, sweating, weakness, flushing of the skin, or dyspnea. Use of isoproterenol is contraindicated in patients with tachyarrhythmias; tachycardia or heart block caused by digitalis intoxication; ventricular arrhythmias which require inotropic therapy; and angina pectoris.

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**Norepinephrine (Levophed)**

**What is Norepinephrine?**

Norepinephrine functions as a peripheral vasoconstrictor and as an inotropic stimulator of the heart and dilator of coronary arteries. Both of these actions result in an increase in systemic blood pressure and coronary artery blood flow.

In hypotension that persists after correction of blood volume deficits, norepinephrine helps raise the blood pressure to an optimal level and establish a more adequate circulation. In myocardial infarction norepinephrine has been shown to greatly increase the patient survival rate. Norepinephrine not only corrects systemic shock (through cardiotonic and peripheral vasoconstrictor action), but also markedly dilates the coronary arteries, thereby increasing coronary blood flow, reducing the area of ischemia and promoting myocardial oxygenation. There is increased venous return and the heart tends to resume a more normal rate and rhythm. On the coronary arteries norepinephrine causes about two and one half times the degree of vasodilatation that epinephrine produces and therefore has a greater effect in increasing coronary flow.

**Why is Norepinephrine used?**

Norepinephrine is used for blood pressure control in certain acute hypotensive states (e.g. spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions.) Because of the selective peripheral vasoconstrictive action of norepinephrine, pooled or stagnant blood in the dilated capillaries is driven into the central circulation, thus maintaining vital functions (e.g. brain, heart, kidneys, etc.) Norepinephrine is also useful as an adjunct in the treatment of cardiac arrest and profound hypotension.

**Considerations during administration**
Blood volume depletion should always be corrected as fully as possible before any vasopressor is administered. When, as an emergency measure, intraaortic pressures must be maintained to prevent cerebral or coronary artery ischemia, norepinephrine can be administered before and concurrently with blood volume replacement.

Use caution to avoid hypertension during administration, because of the potency of norepinephrine and because of varying response to pressor substances, the possibility always exists that dangerously high blood pressure may be produced with overdoses of this pressor agent. It is desirable, therefore, to record the blood pressure every two minutes from the time administration is started until the desired blood pressure is obtained, then every five minutes if administration is to be continued. The rate of flow must be monitored constantly, and a patient should never be left unattended while receiving norepinephrine. Headache may be a symptom of hypertension due to overdosage.

Norepinephrine is measured in micrograms (mcg) and dosed in micrograms per minute (mcg/min.) For blood pressure control in acute hypotensive states the initial dosage is 8 to 12 mcg/min. The rate of infusion should be titrated to establish and maintain a low normal blood pressure (usually 80 to 100 mm Hg systolic) sufficient to maintain the circulation to vital organs. In previously hypertensive patients, raise the blood pressure no more than 40 mm Hg below the preexisting systolic pressure.

Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, titrate the dosage of norepinephrine according to the response of the patient. Occasionally much larger or even enormous daily doses may be necessary if the patient remains hypotensive, but suspect occult blood volume depletion and correct when present. Central venous pressure (CVP) monitoring is usually helpful in detecting and treating this situation. Upon discontinuation of therapy, reduce infusions gradually avoiding abrupt withdrawal.

Administration of Norepinephrine via a central line is preferred, but it can be given peripherally if central access is not available. Norepinephrine is compatible with heparin and nitroprusside.

**Side effects & complications**

Side effects of norepinephrine include bradycardia (often as a reflex result of a rise in blood pressure), anxiety, headache, respiratory difficulty or Ischemic injury due to potent vasoconstrictor action and tissue hypoxia.

Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate fluid and electrolyte replacement therapy. If plasma volumes are not corrected, hypotension may recur when the Norepinephrine infusion is discontinued, or blood pressure may be maintained at the risk of severe peripheral and visceral vasoconstriction (e.g., decreased renal perfusion) with diminution in blood flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischemic injury. Gangrene of extremities is rare.

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of Norepinephrine into the tissues, as local necrosis might ensue due to the vasoconstrictive action of the drug. Blanching along the course of the infused vein, sometimes without obvious extravasation, has been attributed to vasoconstriction with increased permeability of the vein wall, permitting some leakage. This also may progress on rare occasions to superficial slough, particularly during infusion into leg veins in elderly patients or in those suffering from obliterative vascular disease. Hence, if blanching occurs, consideration should be given to the advisability of changing the infusion site at intervals to allow the effects of local vasoconstriction to subside. To treat extravasation, consider injecting phentolamine 5 to 10mg (diluted in 10 to 15 mL normal saline) into the site of extravasation.
Phenylephrine (Neo-Synephrine)

What is Phenylephrine?

Phenylephrine is a powerful vasoconstrictor with properties very similar to those of norepinephrine but almost completely lacking the chronotropic and inotropic actions on the heart. Cardiac irregularities are seen only very rarely even with large doses of this drug.

Phenylephrine is a powerful postsynaptic, alpha-receptor stimulant with little effect on the beta receptors of the heart. In therapeutic doses, it produces little if any stimulation of either the spinal cord or cerebrum. A singular advantage of this drug is the fact that repeated injections produce comparable effects.

Phenylephrine produces vasoconstriction that lasts longer than that of epinephrine and ephedrine. Responses are more sustained than those to epinephrine, lasting 20 minutes after IV administration. Its action on the heart contrasts sharply with that of epinephrine and ephedrine, in that it slows the heart rate and increases the stroke output, producing no disturbance in the rhythm of the pulse.

The predominant actions of phenylephrine are on the cardiovascular system. Intravenous administration causes a rise in systolic and diastolic pressures. Accompanying the pressor response to phenylephrine is a marked reflex bradycardia that can be blocked by atropine; after atropine, large doses of the drug increase the heart rate only slightly. Typically with Phenylephrine infusion, cardiac output is slightly decreased, and peripheral resistance is considerably increased. Circulation time is slightly prolonged, and venous pressure is slightly increased; venous constriction is not marked. Most vascular beds are constricted; renal splanchnic, cutaneous, and limb blood flows are reduced, but coronary blood flow is increased. Pulmonary vessels are constricted, and pulmonary arterial pressure is raised.

Why is Phenylephrine used?

Phenylephrine is used for the maintenance of an adequate level of blood pressure during spinal and inhalation anesthesia and for the treatment of vascular failure in shock, shock-like states and drug-induced hypotension or hypersensitivity. It is also employed to overcome paroxysmal supraventricular tachycardia, to prolong spinal anesthesia, and as a vasoconstrictor in regional analgesia.

Considerations during administration

Phenylephrine is measured in micrograms (mcg) and dosed in micrograms per minute (mcg/min). To raise the blood pressure rapidly, infusions are usually started at about 100 mcg to 180 mcg/min. When the blood pressure is stabilized (at a low normal level for the individual), a maintenance rate of 40 to 60 mcg/min usually suffices.

Hypertension should be avoided. The blood pressure should be checked frequently during administration. Headache or bradycardia may indicate hypertension. Arrhythmias are rare.

Administration of Phenylephrine via a central line is preferred, but it can be given peripherally if central access is not available. Phenylephrine is compatible with Amiodarone, Diltiazem, Dobutamine, Dopamine, Epinephrine, Esmolol, Heparin, Isoproterenol, Lidocaine, Milrinone, Nitroglycerin, Nitroprusside, and Procainamide.
**Side effects & complications**

Side effects of Phenylephrine include headache, reflex bradycardia, excitability, restlessness and rarely arrhythmias. The infusion site should be monitored closely, especially with peripheral sites as tissue necrosis may develop if extravasation occurs. To treat extravasation, consider injecting phentolamine as previously described.

**Vasodilators**

This section of the course will focus on vasodilators. Vasodilators relax the smooth muscle in blood vessels, which causes the vessels to dilate. Dilation of arterial vessels leads to a reduction in systemic vascular resistance, which leads to a fall in arterial blood pressure. Dilation of venous vessels decreases venous blood pressure. The following section will cover esmolol, milrinone, nicardipine, nitroglycerin and nitroprusside.

Vasodilators are used to treat hypertension, heart failure and angina; however, some vasodilators are better suited than others for these indications. Vasodilators that act primarily on resistance vessels (arterial dilators) are used for hypertension and heart failure, but not for angina because of reflex cardiac stimulation. Venous dilators are very effective for angina, and sometimes used for heart failure, but are not used as primary therapy for hypertension. Most vasodilator drugs are mixed (or balanced) vasodilators in that they dilate both arteries and veins; however, there are some very useful drugs that are highly selective for arterial or venous vasculature. Some vasodilators, because of their mechanism of action, also have other important actions that can in some cases enhance their therapeutic utility as vasodilators or provide some additional therapeutic benefit. For example, some calcium channel blockers not only dilate blood vessels, but also depress cardiac mechanical and electrical function, which can enhance their antihypertensive actions and confer additional therapeutic benefit such as blocking arrhythmias.

**Esmolol**

**What is Esmolol?**

Esmolol is a beta 1 selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane-stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately nine minutes. Esmolol inhibits the beta$_2$ receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit beta 2 receptors located chiefly in the bronchial and vascular musculature.

**Why is Esmolol used?**

Esmolol is used for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short-term control of ventricular rate with a short-acting agent is desirable. Esmolol is also indicated in noncompensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention. Esmolol is not intended for use in chronic settings where transfer to another agent is anticipated.
Esmolol can also be used for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated. However, the use of esmolol to prevent such events is not recommended.

**Considerations during administration**

Esmolol is measured in micrograms (mcg) and dosed based on the patient's weight in micrograms per kilogram per minute (mcg/kg/min). Dosage needs to be titrated, using ventricular rate as the guide for treatment of supraventricular tachycardia. Responses to Esmolol usually (over 95% of the time) occur within the range of 50 to 200 mcg/kg/min. The average effective dosage is approximately 100 mcg/kg/min, although dosages as low as 25 mcg/kg/min have been adequate in some patients. Dosage of Esmolol in supraventricular tachycardia (SVT) must be individualized by titration in which each step consists of a loading dosage followed by a maintenance dosage. This specific dosage regimen has not been studied intraoperatively and, because of the time required for titration, may not be optimal for intraoperative use. The maximum recommended dose of Esmolol is 200 mcg/kg/min though higher dosages (250 to 300 mcg/kg/min) may be required for adequate control of blood pressure than those required for the treatment of atrial fibrillation, flutter and sinus tachycardia.

A loading dose of Esmolol may be required in cases of SVT where 500 mcg/kg is infused over a minute duration followed by a maintenance infusion of 50 mcg/kg/min for the next four minutes is recommended. This should give a rough guide with respect to the responsiveness of ventricular rate. After the four minutes of initial maintenance infusion (total treatment duration, 5 minutes), depending upon the desired ventricular response, the maintenance infusion may be continued at 50 mcg/kg/min or increased step-wise (e.g., 100 mcg/kg/min, 150 mcg/kg/min, to a maximum of 200 mcg/kg/min) with each step being maintained for four or more minutes.

The use of infusions of Esmolol for up to 24 hours has been well documented; but should not be continued longer than 48 hours. After achieving an adequate control of the heart rate and a stable clinical status in patients with supraventricular tachycardia, transition to alternative antiarrhythmic agents, such as propranolol, digoxin, or verapamil, may be accomplished. The infusion rate of the esmolol should be sequentially reduced as the first two doses of alternative agent are given (usually six hours apart.)

Administration of Esmolol via a central line is preferred, but it can be given peripherally if central access is not available. Esmolol is compatible with amiodarone, diltiazem, dobutamine, dopamine, epinephrine, insulin, isoproterenol, lidocaine, nicardipine, nitroglycerin, nitroprusside, phenylephrine, and procainamide.

**Side effects & complications**

Side effects of Esmolol include hypotension, dizziness, somnolence, confusion, headache, agitation, nausea, and infusion site reactions including inflammation and induration.

**Milrinone (Primacor)**

**What is Milrinone?**

Milrinone is a positive inotrope and vasodilator, with little chronotropic activity different in structure and mode of action from either the digitalis glycosides or catecholamines. In addition to increasing myocardial contractility, milrinone improves diastolic function as evidenced by improvements in left ventricular diastolic relaxation. Milrinone is a phosphodiesterase inhibitor that has direct positive inotropic and vasodilatory actions. Milrinone increases cardiac contractility which results in an increase in cardiac output. Milrinone also relaxes both arterial
and venous smooth muscle, thereby reducing both preload and afterload. In addition, Milrinone slightly increases atrioventricular (AV) conduction velocity.

**Why is Milrinone used?**

Milrinone is used for the short-term (less than 5 days) IV treatment of patients with acute decompensated heart failure.

**Considerations during administration**

Milrinone is measured in micrograms (mcg) and dosed based on the patient’s weight in micrograms per kilogram per minute (mcg/kg/min.) Milrinone should be administered with a loading dose followed by a continuous infusion or maintenance dose. The infusion rate should be titrated according to hemodynamic and clinical response but should not exceed 1.13 mg/kg/day. Heart rate and blood pressure in patients receiving IV milrinone should be closely monitored. In controlled clinical studies of milrinone infusions, most patients showed an improvement in hemodynamic status as evidenced by increases in cardiac output and reductions in pulmonary capillary wedge pressure. Reductions in the infusion rate may be necessary in patients with renal impairment.

When initiating a Milrinone infusion, a loading dose of 50 mcg/kg is usually administered intravenously (IV) slowly over 10 minutes. After the loading dose is infused, the continuous infusion should be started and titrated to effect according to hemodynamic and clinical response. A guideline for maintenance infusion rates is shown below:

<table>
<thead>
<tr>
<th>Infusion Rate</th>
<th>(24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0.375 mcg/kg/min</td>
</tr>
<tr>
<td>Standard</td>
<td>0.50 mcg/kg/min</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.75 mcg/kg/min</td>
</tr>
</tbody>
</table>

Administration of Milrinone via a central line is preferred, but it can be given peripherally if central access is not available. Milrinone is compatible with amiodarone, diltiazem, dobutamine, dopamine, epinephrine, heparin, insulin, isoproterenol, nicardipine, nitroglycerin, nitroprusside and phenylephrine.

**Side effects & complications**

Side effects of milrinone infusions include ventricular arrhythmias, hypotension, headache, liver function test abnormalities and rash at the injection site.

**Nicardipine**

**What is Nicardipine?**

Nicardipine is a drug that inhibits the trans-membrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. Nicardipine produces significant decreases in systemic vascular resistance (SVR.)

**Why is Nicardipine used?**

Nicardipine is used for the short-term treatment of hypertension when oral therapy is not feasible or not desirable.
Considerations during administration

Nicardipine is measured in milligrams (mg) and dosed in milligrams per hour (mg/hr.) Nicardipine infusions should be titrated to achieve the desired blood pressure reduction. Dosages should be individualized depending on the blood pressure to be obtained and the response of the patient.

Nicardipine therapy is typically initiated at 5 mg/hr. If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 2.5 mg/hr every 5 minutes (for rapid titration) to 15 minutes (for gradual titration) up to a maximum of 15 mg/hr, until desired blood pressure reduction is achieved.

Blood pressure and heart rate should be monitored continually during nicardipine infusions and care should be taken to avoid too rapid or excessive blood pressure drop during treatment. If there is concern of impending hypotension or tachycardia, the infusion should be discontinued. Then, when blood pressure has stabilized, the nicardipine infusion may be restarted at low doses such as (3-5 mg/hr and adjusted to maintain desired blood pressure.

Nicardipine can be administered via a central line or through a large peripheral vein, though the infusion site should be changed every 12 hours if administered via peripheral vein. Nicardipine is compatible with diltiazem, dobutamine, dopamine, epinephrine, esmolol, lidocaine, milrinone, nitroglycerin and nitroprusside.

Side effects & complications

Side effects of nicardipine include headache, hypotension, nausea, vomiting, and tachycardia. Other, less common side effects of nicardipine include fever, neck pain, deep vein thrombosis (DVT), thrombocytopenia, peripheral edema, confusion and respiratory distress.

Nitroglycerin

What is Nitroglycerin?

Nitroglycerin is a drug whose primary action is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs.

Nitroglycerin has a dose-dependent vasodilator effect in arteries and veins and is active in the systemic and pulmonary circulations. When the drug is given by continuous infusion, venous dilator effects are prominent at low dose rates (< 40 mcg/min) and arterial dilator effects predominate at high dose rates (> 200 mcg/min). As low-dose infusions are titrated upward, the earliest response is a decrease in cardiac filling pressures (i.e. central venous pressure and wedge pressure) with little or no change in cardiac output. As the dose rate is increased further, the cardiac output begins to rise as a result of progressive arterial vasodilation. Further increases in the dose rate will eventually produce a drop in blood pressure. The hemodynamic responses to intravenous nitroglycerin have a rapid onset and short duration, which permits rapid dose titration.

Why is Nitroglycerin used?
Nitroglycerin infusion is indicated for the treatment of peri-operative hypertension; for control of congestive heart failure in the setting of acute myocardial infarction; for treatment of angina pectoris (chest pain) in patients who have not responded to sublingual nitroglycerin and beta-blockers; and for induction of intraoperative hypotension.

**Considerations during administration**

Nitroglycerin binds to soft plastics such as polyvinylchloride (PVC), which is a common constituent in plastic bags and infusion tubing. As much as 80% of the drug can be lost by sorption. Glass and hard plastics do not adsorb nitroglycerin, so the problem of adsorption can be eliminated by using glass bottles and stiff polyethylene tubing. Drug manufacturers often provide specialized infusion sets to deliver nitroglycerin.

Nitroglycerin is measured in micrograms (mcg) and dosed in micrograms per minute (mcg/min.) Nitroglycerin infusions should begin at a rate of 5 mcg/min. The dose rate is then increased in 5-mcg/min increments every three to five minutes until the desired effect is achieved. If no response occurs at 20mcg/min, increments of 10 even 20 mcg/min can be used. Once a partial blood pressure response is observed, reduce the dose and lengthen the interval between increments. Although effective dose rates vary, the dose requirement should not exceed 400 mcg/min in most patients. High dose requirements (e.g. > 350 mcg/min) are often the result of drug loss via adsorption, or nitrate tolerance. Some patients with normal or low left ventricular filling pressure or PCWP (i.e. angina patients without other complications) may be hypersensitive to the effects of nitroglycerin and may respond fully to doses as small as 5 mcg/min.

Administration of Nitroglycerin via a central line is preferred, but it can be given peripherally if central access is not available. Nitroglycerin is compatible with amiodarone, diltiazem, dobutamine, dopamine, epinephrine, esmolol, heparin, insulin, isoproterenol, lidocaine, milrinone, nicardipine, nitroprusside, phenylephrine and procainamide.

**Side effects & complications**

Side effects and adverse effects of nitroglycerin are generally dose related and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of the nitroglycerin infusion. Syncope, light-headedness, crescendo angina and rebound hypertension have been reported but are uncommon. The most common side effect of nitroglycerin is headache, which can be severe.

**Nitroprusside (Nitropress)**

**What is Nitroprusside?**

Nitroprusside is a vasodilator agent that shares many features with nitroglycerin. The principal pharmacological action of nitroprusside is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins. Other smooth muscle (e.g. uterus, duodenum) is not affected. Nitroprusside is more active on veins than on arteries, but this selectivity is much less marked than that of nitroglycerin. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs.

In association with the decrease in blood pressure, nitroprusside administered intravenously to hypertensive and normotensive patients produces slight increases in heart rate and a variable effect on cardiac output. In
hypertensive patients, moderate doses induce renal vasodilatation roughly proportional to the decrease in systemic blood pressure, so there is no appreciable change in renal blood flow or glomerular filtration rate.

The hypotensive effect of nitroprusside is seen within a minute or two after the start of an adequate infusion, and it dissipates almost as rapidly after an infusion is discontinued.

**Why is Nitroprusside used?**

Nitroprusside is indicated for the immediate reduction of blood pressure of patients in hypertensive crises. Concomitant longer-acting antihypertensive medication should be administered so that the duration of treatment with nitroprusside can be minimized.

Nitroprusside is also indicated for producing controlled hypotension in order to reduce bleeding during surgery and for the treatment of acute congestive heart failure.

**Considerations during administration**

Nitroprusside is measured in micrograms (mcg) and dosed based on the weight of the patient in micrograms per kilogram per minute (mcg/kg/min.) While the average effective rate in adults and children is about 3 mcg/kg/min, some patients will become dangerously hypotensive when they receive nitroprusside at this rate. Infusion of nitroprusside should therefore be started at a very low rate (0.3 mcg/kg/min), with upward titration every few minutes until the desired effect is achieved or the maximum recommended infusion rate (10 mcg/kg/min) has been reached.

Because nitroprusside's hypotensive effect is very rapid in onset and in dissipation, small variations in infusion rate can lead to wide, undesirable variations in blood pressure. Sodium nitroprusside should not be infused through ordinary I.V. apparatus, regulated only by gravity and mechanical clamps. Only an infusion pump, preferably a volumetric pump, should be used.

Because nitroprusside can induce essentially unlimited blood-pressure reduction, the blood pressure of a patient receiving this drug must be continuously monitored, using either a continually reinflated sphygmomanometer or (preferably) an intra-arterial pressure sensor. Special caution should be used in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.

When nitroprusside is used in the treatment of acute congestive heart failure, titration of the infusion rate must be guided by the results of invasive hemodynamic monitoring with simultaneous monitoring of urine output. Nitroprusside can be titrated by increasing the infusion rate until measured cardiac output is no longer increasing, systemic blood pressure cannot be further reduced without compromising the perfusion of vital organs, or the maximum recommended infusion rate has been reached, whichever comes earliest. Specific hemodynamic goals must be tailored to the clinical situation, but improvements in cardiac output and left ventricular filling pressure must not be purchased at the price of undue hypotension and consequent hypo-perfusion.

Administration of Nitroprusside via a central line is preferred, but it can be given peripherally if central access is not available. Nitroprusside is compatible with diltiazem, dopamine, epinephrine, esmolol, heparin, insulin, isoproterenol, lidocaine, milrinone, nicardipine, norepinephrine, phenylephrine, and procainamide.

**Side effects & complications**
The most common adverse effects of nitroprusside are hypotension and cyanide toxicity.

Small transient excesses in the infusion rate of nitroprusside can result in excessive hypotension, sometimes to levels so low as to compromise the perfusion of vital organs. These hemodynamic changes may lead to a variety of associated symptoms. Nitroprusside-induced hypotension will be self-limited within one to 10 minutes after discontinuation of the nitroprusside infusion; during these few minutes, it may be helpful to put the patient into a head-down (Trandelenburg) position to maximize venous return. If hypotension persists more than a few minutes after discontinuation of the infusion of nitroprusside is not the cause, and the true cause must be sought.

Except when used briefly or at low (< 2 mcg/kg/min) infusion rates, nitroprusside gives rise to important quantities of cyanide ion, which can reach toxic, potentially lethal levels. The usual dose rate of nitroprusside is 0.5-10 mcg/kg/min, but infusion at the maximum dose rate should never last more than 10 minutes. If blood pressure has not been adequately controlled after 10 minutes of infusion at the maximum rate, administration of sodium nitroprusside should be terminated immediately. Although acid-base balance and venous oxygen concentration should be monitored and may indicate cyanide toxicity, these laboratory tests provide imperfect guidance.

Other side effects of nitroprusside include bradycardia, methemoglobinemia, ECG changes, tachycardia, decreased platelet aggregation, flushing, venous streaking, irritation at the infusion site, rash, hypothyroidism, ileus, and increased intracranial pressure.

**Anti-Arrhythmics**

Anti-arrhythmic drugs are used to treat abnormal heart rhythms. The ultimate goal of antiarrhythmic drug therapy is to restore normal rhythm and conduction. When it is not possible to revert to normal sinus rhythm, drugs may be used to prevent more serious and possibly lethal arrhythmias from occurring. Antiarrhythmic drugs are used to decrease or increase conduction velocity, alter the excitability of cardiac cells by changing the duration of the effective refractory period, or suppress abnormal automaticity. There are four classes of antiarrhythmic drugs known as Vaughan Williams classes:

- Class I – Sodium channel blockers
- Class II – Beta blockers
- Class III – Potassium channel blockers
- Class IV – Calcium channel blockers

The following section will cover amiodarone, diltiazem, epinephrine, lidocaine, and procainamide.

**Amiodarone**

**What is Amiodarone?**

Amiodarone is Amiodarone is generally considered a class III antiarrhythmic, but it possesses electrophysiologic characteristics of all four classes. Like class I drugs, amiodarone blocks sodium channels at rapid pacing frequencies, and like class II drugs, it exerts a noncompetitive antisympathetic action. One of its main effects, with prolonged administration, is to lengthen the cardiac action potential, a class III effect. The negative chronotropic effect of amiodarone in nodal tissues is similar to the effect of class IV drugs. In addition to blocking sodium channels, amiodarone blocks myocardial potassium channels, which contributes to slowing of conduction and prolongation of refractoriness. The antisympathetic action and the block of calcium and potassium channels are
intravenous infusions

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responsible for the negative dromotropic effects on the sinus node and for the slowing of conduction and prolongation of refractoriness in the atrioventricular (AV) node. Its vasodilatory action can decrease cardiac workload and consequently myocardial oxygen consumption.

Why is Amiodarone used?

Amiodarone is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy. Intravenous amiodarone also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication. During or after treatment with intravenous amiodarone, patients may be transferred to oral amiodarone therapy.

Intravenous amiodarone should be used for acute treatment until the patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48 to 96 hours, but intravenous amiodarone may be safely administered for longer periods if necessary.

Considerations during administration

Amiodarone is measured in milligrams (mg) and dosed in milligrams per minute (mg/min.) Amiodarone shows considerable inter-individual variation in response. Thus, although a starting dose adequate to suppress life-threatening arrhythmias is needed, close monitoring with adjustment of dose as needed is essential. The recommended starting dose of intravenous amiodarone is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen:

| First: Loading infusion - administered quickly | 150mg over 10 minutes (15mg/min) |
| Followed by: Slower infusion                 | 360mg over next 6 hours (1mg/min) |
| Next: Maintenance infusion                   | 540mg over remaining 18 hours (0.5mg/min) |

After the first 24 hours, the maintenance infusion rate of 0.5 mg/min (720 mg/24 hours) should be continued utilizing a concentration of 1 to 6 mg/mL (amiodarone injection concentrations greater than 2 mg/mL should be administered via a central venous catheter). In the event of breakthrough episodes of VF or hemodynamically unstable VT, 150 mg supplemental infusions of amiodarone injection mixed in 100 mL of D5W may be administered. Such infusions should be administered over 10 minutes to minimize the potential for hypotension. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

The first 24-hour dose may be individualized for each patient; however, in controlled clinical trials, mean daily doses above 2100 mg were associated with an increased risk of hypotension. The initial infusion rate should not exceed 30 mg/min.

Based on the experience from clinical studies of amiodarone injection, a maintenance infusion of up to 0.5 mg/min can be cautiously continued for two to three weeks regardless of the patient’s age, renal function, or left ventricular function. There has been limited experience in patients receiving amiodarone injection for longer than three weeks.

Amiodarone injection should, whenever possible, be administered through a central venous catheter dedicated to that purpose. An in-line filter should be used during administration. Amiodarone injection infusions exceeding two hours must be administered in glass or polyolefin bottles containing D5W due to its adsorbsion to polyvinyl chloride (PVC) tubing.
Patients whose arrhythmias have been suppressed by intravenous amiodarone may be switched to oral amiodarone. The optimal dose for changing from intravenous to oral administration of amiodarone will depend on the dose of intravenous amiodarone already administered, as well as the bioavailability of oral amiodarone. When changing to oral amiodarone therapy, clinical monitoring is recommended, particularly for elderly patients.

Infused amiodarone is compatible with diltiazem, dobutamine, dopamine, epinephrine, esmolol, insulin, isoproterenol, lidocaine, milrinone, nitroglycerin, phenylephrine and procainamide.

**Side effects & complications**

Hypotension is the most common adverse effect seen with intravenous amiodarone. Clinically significant hypotension during infusions is seen most often in the first several hours of treatment and is not dose related, but appears to be related to the rate of infusion. Hypotension should be treated initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion.

Other side effects of amiodarone infusion include fever, atrial fibrillation, prolonged QT interval, diarrhea, abnormal kidney function, thrombocytopenia, Stevens-Johnson syndrome, neutropenia, bradycardia, liver enzyme elevation, congestive heart failure (CHF), hypotension, ventricular tachycardia, bronchospasm, confusion and nausea.

**Diltiazem (Cardizem)**

**What is Diltiazem?**

Diltiazem is a class IV antiarrhythmic drug and inhibits the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic benefits of diltiazem in supraventricular tachycardias (SVT) are related to its ability to slow AV nodal conduction such that it may selectively reduce the heart rate during tachycardias involving the AV node with little or no effect on normal AV nodal conduction at normal heart rates. Diltiazem slows the ventricular rate in patients with a rapid ventricular response during atrial fibrillation or atrial flutter. Like other calcium channel antagonists, because of its effect on vascular smooth muscle, diltiazem decreases total peripheral resistance resulting in a decrease in both systolic and diastolic blood pressure.

**Why is Diltiazem used?**

Diltiazem is used for temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.

Diltiazem is also used in the rapid conversion of paroxysmal supraventricular tachycardias (PSVTs) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of diltiazem.

The administration of diltiazem should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.


Considerations during administration

Diltiazem is measured in milligrams (mg) and dosed according to patient weight in milligrams per kilogram (mg/kg.) The initial dosage of 0.25 mg/kg is administered as a bolus over two minutes (20 mg is a reasonable dose for the average patient.) if a response is inadequate after 15 minutes, a second dose of 0.35 mg/kg is administered over two minutes (25 mg is a reasonable dose for the average patient.) Subsequent IV bolus doses should be individualized.

For continued reduction of heart rate (up to 24 hours) immediately following the bolus dose, a maintenance dosage infusion may be started. The initial infusion rate is typically 10 mg/hr. Some patients may maintain response to an initial infusion rate of 5 mg/hr. The infusion rate may be increased in 5mg/hr increments up to 15 mg/hr as needed. Infusion duration exceeding 24 hours and infusion rates exceeding 15 mg/hr are not recommended.

Transition to other antiarrhythmic agents following administration of diltiazem is generally safe.

Diltiazem can be given via a peripheral IV site, however, the site should be assessed frequently for irritation or extravasation. Diltiazem is compatible with amiodarone, dobutamine, dopamine, epinephrine, esmolol, isoproterenol, lidocaine, milrinone, nicardipine, nitroglycerin, nitroprusside, and phenylephrine.

Side effects & complications

The most common side effect of diltiazem is hypotension which is commonly reversed with administration of saline or placing the patient in the Trandelenburg position. Other side effects of diltiazem include first degree AV block, second degree AV block, bradycardia, chest pain, syncope, ventricular arrhythmias, dizziness, sweating, pruritus, nausea, vomiting, headache, and dry mouth.

Epinephrine (Adrenalin)

What is Epinephrine?

Epinephrine is a sympathomimetic drug. It activates an adrenergic receptive mechanism on effector cells and imitates all actions of the sympathetic nervous system except those on the arteries of the face and sweat glands. Epinephrine acts on both alpha and beta receptors and is the most potent alpha receptor activator.

When given by rapid IV infusion, it produces a rapid rise in blood pressure, mainly systolic, by a direct stimulation of the cardiac muscle which increases the strength of ventricular contraction, increasing the heart rate, and constriction of the arterioles in the skin, mucosa, and splanchnic areas of circulation.

When given by slow IV infusion, epinephrine usually produces only a moderate rise in systolic and a fall in diastolic pressure. Although some increases in pulse pressure occurs, there is usually no great elevation in mean blood pressure. Total peripheral resistance decreases by action of epinephrine on beta receptors of the skeletal muscle vasculature and blood flow is thereby enhanced. Usually, this vasodilator effect of the drug on the circulation predominates so that the modest rise in systolic blood pressure that follows slow infusion or absorption is mainly the result of direct cardiac stimulation and increase in cardiac output. Epinephrine relaxes the smooth muscles of
the bronchi and iris and is a physiologic antagonist of histamine. The drug also produces an increase in blood sugar and glycogenesis in the liver.

**Why is Epinephrine used?**

Epinephrine infusions are primarily used as a second-line drug to treat symptomatic bradycardia and symptomatic hypotension when other medications have failed to do so.

**Considerations during administration**

Epinephrine is measured in micrograms (mcg) and dosed in micrograms per minute (mcg/min.) The initial dosage of an epinephrine infusion is 1 mcg/min titrated to the desired hemodynamic response, which is typically achieved at a dose of 2 to 10 mcg/min.

Administration of Epinephrine via a central line is preferred, but it can be given peripherally if central access is not available. If administered peripherally, however, the site should be assessed frequently as extravasation of epinephrine can cause tissue necrosis.

An Epinephrine infusion is compatible with amiodarone, diltiazem, dobutamine, dopamine, esmolol, heparin, isoproterenol, lidocaine, milrinone, nicardipine, nitroglycerin, nitroprusside, phenylephrine, and procainamide.

**Side effects & complications**

Side effects of epinephrine include angina pain in patients with angina pectoris or coronary artery disease, cardiac arrhythmias, excessive rise in blood pressure (which can cause cerebral hemorrhage), transient palpitations, dizziness, restlessness, anxiety, tremor, weakness, pallor, sweating, nausea, vomiting and respiratory difficulty.

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**Lidocaine**

**What is Lidocaine?**

Lidocaine causes antiarrhythmic effects by raising the electrical stimulation threshold of the ventricle during diastole. In usual therapeutic doses, lidocaine infusions produce no change in myocardial contractility, systemic arterial pressure, or in absolute refractory period. The onset of action of IV lidocaine varies from about 45 to 90 seconds. Duration of action of IV lidocaine is 10 to 20 minutes.

**Why is Lidocaine used?**

Lidocaine is used to treat ventricular tachycardia occurring during cardiac manipulation, such as surgery or catheterization, or which may occur during acute myocardial infarction, digitalis toxicity, or other cardiac diseases.

**Considerations during administration**

Continuous ECG and blood pressure monitoring, with meticulous regulation of infusion rate, in order to avoid potential overdosage and toxicity is essential for the proper administration of a lidocaine IV infusion. Signs of excessive depression of cardiac conductivity, such as prolongation of PR interval and QRS complex, and the
appearance of aggravation of arrhythmias, should be followed by prompt cessation of the IV infusion. It is mandatory to have emergency resuscitative equipment and drugs immediately available to manage possible adverse reactions involving the cardiovascular, respiratory, or central nervous systems while a lidocaine IV infusion is being administered.

Lidocaine should be used with caution in patients with bradycardia, severe digitalis intoxication, or first or second degree heart block in the absence of a pacemaker. In unconscious patients, circulatory collapse should be watched for, since CNS effects may not be apparent as an initial manifestation of toxicity.

I.V. administration of lidocaine is sometimes accompanied by a hypotensive response, and, in overdosage, this may be precipitous. For this reason the IV dose should not exceed 100 mg in a single injection, and no more than 200 to 300 mg in a one hour period. When high doses are used and the patient's myocardial function is impaired, combination with other drugs which reduce the excitability of cardiac muscle requires caution.

Administration of lidocaine via a central line is preferred, but it can be given peripherally if central access is not available. Lidocaine IV infusions are compatible with amiodarone, diltiazem, dobutamine, dopamine, epinephrine, esmolol, heparin, insulin, isoproterenol, nicardipine, nitroglycerin, nitroprusside, phenylephrine and procainamide.

**Side effects & complications**

The adverse reactions from infused lidocaine are, in general, dose related, and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse reactions are generally systemic in nature. Common adverse effects include allergic reactions, bradycardia, hypotension, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and extravasation.

**Procainamide**

**What is Procainamide?**

Procainamide increases the effective refractory period of the atria, and to a lesser extent the bundle of His-Purkinje system and ventricles of the heart. It reduces impulse conduction velocity in the atria, His-Purkinje fibers, and ventricular muscle, but has variable effects on the atrioventricular (AV) node, a direct slowing action and a weaker vagolytic effect which may speed AV conduction slightly. Myocardial excitability is reduced in the atria, Purkinje fibers, papillary muscles, and ventricles by an increase in the threshold for excitation, combined with inhibition of ectopic pacemaker activity by retardation of the slow phase of diastolic depolarization, thus decreasing automaticity especially in ectopic sites. Contractility of the undamaged heart is usually not affected by therapeutic concentrations, although slight reduction of cardiac output may occur, and may be significant in the presence of myocardial damage. Therapeutic levels of procainamide may exert vagolytic effects and produce slight acceleration of heart rate, while high or toxic concentrations may prolong AV conduction time or induce AV block, or even cause abnormal automaticity and spontaneous firing, by unknown mechanisms.

The electrocardiogram may reflect these effects by showing slight sinus tachycardia (due to the anticholinergic action) and widened QRS complexes and, less regularly, prolonged Q-T and P-R intervals (due to longer systole and slower conduction), as well as some decrease in QRS and T wave amplitude. These direct effects of
procainamide on electrical activity, conduction, responsiveness, excitability and automaticity are characteristic of a class I antiarrhythmic agent.

**Why is Procainamide used?**

Procainamide is used for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgment of the physician, are life-threatening. Because of the proarrhythmic effects of procainamide, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

**Considerations during administration**

Procainamide is measured in milligrams (mg) and dosed in milligrams per minute (mg/min). IV administration of procainamide injection should be done cautiously to avoid a possible hypotensive response. If the blood pressure falls 15 mm Hg or more, procainamide administration should be temporarily discontinued. Continuous electrocardiographic (ECG) monitoring is advisable as well, both for observation of the progress and response of the arrhythmia under treatment, and for early detection of any tendency to excessive widening of the QRS complex, prolongation of the PR interval, or any signs of heart block. Intravenous therapy with procainamide should be limited to use in hospitals in which monitoring and intensive supportive care are available, or to emergency situations in which equivalent observation and treatment can be provided. Initial arrhythmia control, under blood pressure and ECG monitoring, may usually be accomplished safely within a half-hour.

When starting a procainamide infusion, a loading infusion containing procainamide 20 mg/mL (1 g diluted to 50 mL with dextrose 5% injection) may be administered at a constant rate of 1 mL/min for 25 to 30 minutes to deliver 500 to 600 mg of procainamide. Some effects may be seen after infusion of the first 100 or 200 mg; it is unusual to require more than 600 mg to achieve satisfactory antiarrhythmic effects.

To maintain therapeutic levels, a more dilute IV infusion at a concentration of 2 mg/mL is convenient (1 g procainamide injection in 500 mL of dextrose 5% injection), and may be administered at 1 mL/min to 3 mL/min. If daily total fluid intake must be limited, a 4 mg/mL concentration (1 g of procainamide injection in 250 mL of dextrose 5% injection) administered at 0.5 mL/min to 1.5 mL/min will deliver an equivalent 2 mg to 6 mg/min. The amount needed in a given patient to maintain the therapeutic level should be assessed principally from the clinical response, and will depend upon the patient's weight and age, renal elimination, hepatic acetylation rate, and cardiac status, but should be adjusted for each patient based upon close observation. A maintenance infusion rate of 50 mcg/kg/min to a person with a healthy renal procainamide elimination half time of three hours may be expected to produce a plasma level of approximately 6.5 mcg/mL.

IV therapy should be terminated if persistent conduction disturbances or hypotension develop. As soon as the patient's basic cardiac rhythm appears to be stabilized, oral antiarrhythmic maintenance therapy is preferable, if indicated and possible. A period of about three to four hours (one half time for renal elimination, ordinarily) should elapse after the last IV dose before administering the first dose of oral procainamide.

Administration of procainamide via a central line is preferred, but it can be given peripherally if central access is not available. Procainamide IV infusions are compatible with amiodarone, dobutamine, dopamine, epinephrine, esmolol, heparin, insulin, isoproterenol, lidocaine, nitroglycerin, nitroprusside and phenylephrine.

**Side effects & complications**
Adverse effects of procainamide infusions include hypotension and serious disturbances of cardio-rhythm such as ventricular asystole or fibrillation. Because procainamide is a peripheral vasodilator in concentrations higher than the usual therapeutic range, transient high plasma levels which may occur especially during intravenous administration may produce temporary but at times severe lowering of blood pressure. Other side effects include dizziness, giddiness, weakness, mental depression, psychosis with hallucinations, pruritus, flushing, anorexia, nausea, vomiting, abdominal pain, bitter taste, and diarrhea.

Procainamide should not be administered to patients with complete heart block because of its effects in suppressing nodal or ventricular pacemakers and the hazard of asystole. It may be difficult to recognize complete heart block in patients with ventricular tachycardia, but if significant slowing of ventricular rate occurs during procainamide treatment without evidence of AV conduction appearing, the procainamide infusion should be stopped. In cases of second degree AV block or various types of hemiblock, procainamide should be avoided or discontinued because of the possibility of increased severity of block, unless the ventricular rate is controlled by an electrical pacemaker.

Medication Safety Issues

Medication administration is a large component of a nurse's professional role. Medication administration is also one of the most potentially dangerous tasks a nurse can perform. Medication errors, defined as, “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer” are costly from human, economic, and societal perspectives. Studies show that medication errors affect three to five percent of hospitalized patients in the US. Patients may suffer discomfort, complications, prolonged hospitalization, disability, or death. Researchers estimate that medication errors cause over 7000 deaths in the US each year; though not all medication errors cause patient harm and not all errors are recognized or reported.

Medication errors are a significant problem in the US and worldwide. The economic cost of medication errors has been estimated at $5000 per error or an annual impact of $2.8 million for an average 700-bed teaching hospital. Patient length of stay is prolonged by approximately two days when errors occur. This financial significance is magnified if litigation occurs. Financial judgments are awarded in 13% of cases related to serious errors and average approximately $3.1 million per award.

From the human perspective, healthcare professionals and patients are affected by medication errors. The healthcare professional responsible for an error, especially errors that cause patient harm, frequently suffer severe emotional distress. Nurses frequently associate errors with harm to the patient and failure of their moral and ethical responsibility to “do no harm.”

Though all medication errors are potentially serious, studies have shown that patients who are critically ill are more likely to have life-threatening consequences to adverse drug events than any other patient population. Also, intravenous route errors have the greatest potential for harm.

In 2008, the Institute for Safe Medication Practices (ISMP), a nonprofit research group that advocates for patient safety, developed a list of medications that are known to contribute to a significant number of medication errors and are associated with a risk for poor outcome with improperly administered. These drugs, referred to as high-alert medications, require special safeguards to reduce the risk of injury to patients. The ISMP warns that 20 drugs are responsible for 80% of medication error fatalities. Most of the medications described in this course are included on this list of medications.
Intravenous Infusions

The Joanna Briggs Institute is an International not-for-profit Research and Development Organization specializing in Evidence-Based resources for healthcare professionals in nursing, midwifery, medicine, and allied health. With over 54 Centers and groups, servicing over 90 countries, The Joanna Briggs Institute is a recognized global leader in Evidence-Based Healthcare. In 2009, the Joanna Briggs Institute published best-practice recommendations related to the preparation and administration of intravenous medications.

These recommendations included that:

- Medications should always be prepared in the pharmaceutical setting if possible.
- Administration sets not containing blood, lipids, or blood products can remain in place for up to 96 hours without increasing the incidence of infection.
- Methods to avoid contamination should be followed, such as accessing the port with only sterile devices, wiping the port with an appropriate antiseptic solution and capping stock ports when not in use.
- Ensure all components of an IV system are compatible to minimize possible leaks and breaks in the system.
- When utilizing piggyback systems, use care to ensure the rubber membrane of an injection port is not exposed to air or comes in direct contact with non-sterile tape to reduce infection risk.

Following these best practice recommendations and taking extra care when administering the high-alert medications will reduce the risk of medication errors and increase the safety of patients.
References


