NITROGLYCERIN ALCOHOL FREE 1 MG/ML FOR I.V. INFUSION

NOT FOR DIRECT INTRAVENOUS INJECTION

Toxicity may occur with extremely high doses, or in unusually sensitive patients. Nitroglycerin must be diluted in Dextrose (5%) injection, or Sodium chloride (0.9%) injection, prior to its infusion (see dosage and administration section). The administration set used for infusion will affect the amount of Nitroglycerin delivered to the patient. (See warnings and dosage and administration section).

**Composition:** Nitroglycerin 1 mg/ml
   Dextrose 5.0%

**Clinical Pharmacology:**
Relaxation of vascular smooth muscle is the principal pharmacologic action of nitroglycerin. Although venous effects predominate, nitroglycerin produces in a dose-related manner, dilatation of both arterial and venous beds. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, reducing left ventricular end-diastolic pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload). Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin, and a more favourable supply-demand ratio can be achieved.

Therapeutic doses of i.v. nitroglycerin reduce systolic, diastolic and mean arterial blood pressure.

Effective coronary perfusion pressure is usually maintained but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased or unchanged. Patients with elevated left ventricular filling pressure and systemic vascular resistance values, in conjunction with a depressed cardiac index, are likely to experience an improvement in cardiac index. On the other hand, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced by i.v. nitroglycerin.

Nitroglycerin is widely distributed in the body with an apparent volume distribution of approximately 200 liters in adult male subjects and is rapidly metabolized to dinitrates and mononitrates, with a short half-life estimated at 1-4 minutes. This results in a low plasma concentration after i.v. infusion.

At plasma concentrations of between 50 and 500 mcg/ml the binding of nitroglycerin to plasma proteins is approximately 60% while that of 1,2 dinitroglycerin and 1,3 dinitroglycerin is 60% and 30% respectively. The activity and half-life of the dinitroglycerin metabolites are not well characterized. The mononitrate is not active.

**Indications and usage:**
Nitroglycerin is indicated for:

1. Control of hypertension during cardiac surgery.
2. Unresponsive congestive heart failure associated with acute myocardial infarction.
3. Treatment of angina pectoris in hospitalized patients who have not responded to organic nitrates and/or beta blockers.
Contraindications:
Nitroglycerin should not be administered to individuals with:
1. A known hypersensitivity to nitroglycerin or known idiosyncrasy to nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of nitroglycerin in such states could produce severe hypotension or shock.
3. Increased intracranial pressure.
4. Constrictive pericarditis and pericardial tamponade.
5. Restrictive cardiomyopathy.

Warnings:
1. Nitroglycerin readily migrates into many plastics. To avoid adsorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of nitroglycerin for i.v. infusion should be made in specific nitroglycerin kits, or in glass parenteral solution bottles.
2. Some filters adsorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion can be adsorbed by the polyvinyl chloride (PVC) tubing of the i.v. administration sets currently in general use. The higher rates of adsorption occur when flow rates are low, nitroglycerin concentrations are high, and the tubing is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting: consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of infusion solution) to the actual delivery rate.

Precautions:
Nitroglycerin should be used with caution in patients with severe liver or renal disease.
Severe hypotension and shock may occur with even small doses of Nitroglycerin IV. This drug should, therefore, be used with caution in patients who may be volume-depleted; who, for whatever reason, are already hypotensive; or who, because of inadequate circulation to the brain or to other vital organs would be unusually compromised by undue hypotension.
Excessive hypotension especially for prolonged periods of time must be avoided because of possible deleterious effects on the brain, heart, liver and kidneys from poor perfusion, and the attendant risk of ischemia, thrombosis and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of nitroglycerin. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.
Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence. Some clinical trials in angina patients have provided nitroglycerin for about 12 continuous hours of every 24-hour day. During the nitrate-free intervals in some of the trials, angina attacks have been more easily provoked than before treatment, and patients have demonstrated hemodynamic rebound and decreased exercise tolerance.
The importance of these observations to the routine, clinical use of intravenous nitroglycerin is not known.
Lower concentrations of nitroglycerin increase the potential precision of dosing, but these concentrations increase the total fluid volume that must be delivered to the patient. Total fluid load may be a dominant consideration in patients with compromised function of the heart, liver, and/or kidneys.
Nitroglycerin infusions should be administered only via a pump that can maintain a constant infusion rate.
Intracoronary injection of nitroglycerin infusions has not been studied.

Use in pregnancy or lactation only when potential benefits outweigh the possible risks.

Pediatric use:
Safety and effectiveness in pediatric patients have not been established.

Drug interactions:
The vasodilating effects of nitroglycerin may be additive with those of other vasodilators.
Administration of nitroglycerin infusions through the same infusion set as blood can result in pseudoagglutination and hemolysis. More generally, nitroglycerin in 5% dextrose or sodium chloride 0.9% should not be mixed with any other medication of any kind.
Intravenous nitroglycerin interferes, at least in some patients, with the anticoagulant effect of heparin. In patients receiving intravenous nitroglycerin, concomitant heparin therapy should be guided by frequent measurement of the activated partial thromboplastin time.

Adverse reactions:
Adverse reactions to IV nitroglycerin are generally dose related, and almost all of these reactions are the result of nitroglycerin’s activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients, it may be severe enough to warrant discontinuation of therapy.
Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.
Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis for fixed eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.
Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients; for further discussion of its diagnosis and treatment, see OVERDOSAGE.
Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

Overdosage:
HEMODYNAMIC EFFECTS
The ill effects of nitroglycerin IV overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and
hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of the following: persistent throbbing headache, confusion, and moderate fever; vertigo; palpitation; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death. Laboratory determinations of serum levels of Nitroglycerin IV and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of Nitroglycerin IV overdose. No data are available to suggest physiological maneuvers leg, maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of Nitroglycerin IV is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good. In patients with renal disease or congestive heart failure, therapy resulting in central volume expression is not without hazard. Treatment of Nitroglycerin IV overdose in these patients may be subtle and difficult invasive monitoring may be required.

METHEMOGLOBINEMIA
Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant (>\=10\%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses: of nitroglycerin. In one study in which 36 patients received 2 to 4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/h, the average methemoglobin level measured was 0.2\%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial p02. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.
When methemoglobinemia is diagnosed, the treatment of choice is methylene blue 1 to 2 mg/kg intravenously.

**Dosage and Administration:**
Not for direct intravenous injection. Nitroglycerin is a concentrated, potent drug which must be diluted in Dextrose (5%) injection, or Sodium Chloride (0.9%) injection, prior to its infusion. Nitroglycerin I.V. should not be admixed with other drugs.

**Dilution:** It is important to consider the fluid requirements of the patient as well as the expected duration of infusion in selecting the appropriate dilution of nitroglycerin. After preparation, the solution is stable for 24 hours at room temperature.

**Dosage:**
Important Notice: Dosage is affected by the type of container used as well as the type of infusion set used (See warning). Although the usual starting adult dose range reported in clinical studies was 25 mcg/min or more, those studies used PVC TUBING. The use of nonabsorbing tubing will result in the need to use reduced doses. The recommended dosage when using the nonabsorbing I.V. infusion set should initially be 5 mcg/ min delivered through an infusion pump capable of exact and constant delivery of the drug. Subsequent titration must be adjusted to the clinical situation, with more caution as partial response is seen. Initial titration should be in 5 mcg/min. increments, with increases every 3-5 minutes until some response is noted. If no response is seen at 20 mcg/min, increments of 10, and later 20 mcg/min, can be used. Once a partial blood pressure response is observed, the dose increase should be reduced and the interval between increments should be lengthened. Patients with normal or low left ventricular filling pressure or pulmonary capillary wedge pressure (eg. 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. These patients require especially careful titration and monitoring. There is no fixed optimum dose of nitroglycerin. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate) must be performed, to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

Detailed information about this drug has been circulated to the medical profession and is based on:
Facts & Comparisons; PDR 1998

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