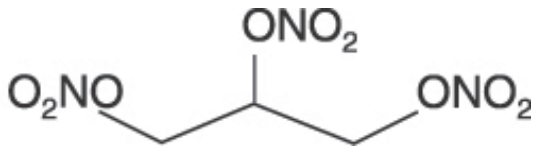
Nitroglycerin in 5% Dextrose Injection

For intravenous use only

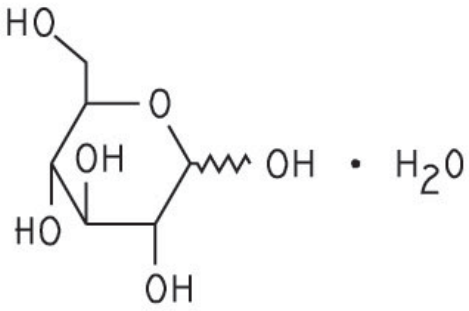
Description

Nitroglycerin is 1,2,3-propanetriol trinitrate, an organic nitrate whose structural formula is



whose empiric formula is $C_3H_5N_3O_9$, and whose molecular weight is 227.09. The organic nitrates are vasodilators, active on both arteries and veins.

Dextrose (Dextrose Hydrous, USP) is D-glucose monohydrate, a hexose sugar whose structural formula is



whose empiric formula is $C_6H_{12}O_6 \cdot H_2O$, and whose molecular weight is 198.17.

Nitroglycerin in 5% Dextrose Injection is a sterile, nonpyrogenic solution of nitroglycerin and dextrose in water for injection. The solution is clear and practically colorless. Each 100 mL contains 10 mg, 20 mg, or 40 mg nitroglycerin (added as Diluted Nitroglycerin, USP with propylene glycol); 5 g Dextrose Hydrous, USP; 0.84 mL Alcohol, USP (added as a dissolution aid); and 105 mg Citric Acid Hydrous, USP (added as a buffer). The pH of the solution is adjusted with sodium hydroxide and, if necessary, hydrochloric acid.

Although dry nitroglycerin is explosive, nitroglycerin in 5% dextrose is not.

Composition, osmolarity and pH are given in Table 1.

Table 1	Composition		*Osmolarity (mOsmol/L) (calc)	pH
	Nitroglycerin (mcg/mL)	Dextrose Hydrous, USP (g/L)		
25 mg Nitroglycerin in 5% Dextrose Injection	100	50	428	4.0 (3.0 to 5.0)
50 mg Nitroglycerin in 5% Dextrose Injection	200	50	440	4.0 (3.0 to 5.0)
100 mg Nitroglycerin in 5% Dextrose Injection	400	50	465	4.0 (3.0 to 5.0)

* Normal physiologic osmolarity range is approximately 280 to 310 mOsmol/L. Administration of substantially hypertonic solutions (≥600 mOsmol/L) may cause vein damage.

Clinical Pharmacology

The principal pharmacological action of nitroglycerin 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. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their anti-anginal efficacy been restored.

Pharmacokinetics: The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow; known sites of extrahepatic metabolism include red blood cells and vascular walls.

The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1,2-and 1,3- dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin, but they are longer-lived in the serum, and their net contribution to the overall effect of chronic nitroglycerin regimens is not known. The dinitrates are further metabolized to (non-vasoactive) mononitrates and, ultimately, to glycerol and carbon dioxide.

To avoid development of tolerance to nitroglycerin, drug-free intervals of 10-12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was *less* than that exhibited by the parallel group receiving placebo.

Clinical Trials: Blinded, placebo-controlled trials of intravenous nitroglycerin have not been reported, but multiple investigators have reported open-label studies, and there are scattered reports of studies in which intravenous nitroglycerin was tested in blinded fashion against sodium nitroprusside.

In each of these studies, therapeutic doses of intravenous nitroglycerin were found to reduce systolic and diastolic arterial blood pressure. The heart rate was usually increased, presumably as a reflexive response to the fall in blood pressure. Coronary perfusion pressure was usually, but not always, maintained.

Intravenous nitroglycerin reduced central venous pressure (CVP), right atrial pressure (RAP), pulmonary arterial pressure (PAP), pulmonary-capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR). When these parameters were elevated, reducing them toward normal usually caused a rise in cardiac output. Conversely, intravenous nitroglycerin usually *reduced* cardiac output when it was given to patients whose CVP, RAP, PAP, PCWP, PVR, and SVR were all normal.

Most clinical trials of intravenous nitroglycerin have been brief; they have typically followed hemodynamic parameters during a single surgical procedure. In one careful study, one of the few that lasted more than a few hours, continuous intravenous nitroglycerin had lost almost all of its hemodynamic effect after 48 hours. In the same study, patients who received nitroglycerin infusions for only 12 hours out of each 24 demonstrated no similar attenuation of effect. These results are consistent with those seen in multiple large, double-blind, placebo-controlled trials of other formulations of nitroglycerin and other nitrates.

Indications and Usage

Nitroglycerin in 5% Dextrose Injection is indicated for treatment of peri-operative hypertension; for control of congestive heart failure in the setting of acute myocardial infarction; for treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and ß-blockers; and for induction of intraoperative hypotension.

Contraindications

Nitroglycerin in 5% Dextrose Injection is contraindicated in patients who are allergic to it.

In patients with pericardial tamponade, restrictive cardiomyopathy, or constrictive pericarditis, cardiac output is dependent upon venous return. Intravenous nitroglycerin is contraindicated in patients with these conditions.

Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

Do not use Nitroglycerin in 5% Dextrose Injection in patients who are taking certain drugs for erectile dysfunction (phosphodiesterase inhibitors) such as sildenafil, tadalafil, or vardenafil. Concomitant use can cause severe hypotension, syncope, or myocardial ischemia.

Do not use nitroglycerin in 5% dextrose in patients who are taking the soluble guanylate cyclase stimulator riociguat. Concomitant use can cause hypotension.

Warnings

Nitroglycerin readily migrates into many plastics, including the polyvinyl chloride (PVC) plastics commonly used for intravenous administration sets. Nitroglycerin absorption by PVC tubing is increased when the tubing is long, the flow rates are low, and the nitroglycerin concentration of the solution is high. The delivered fraction of the solution's original nitroglycerin content has been 20-60% in published studies using PVC tubing; the fraction varies with time during a single infusion, and no simple correction factor can be used. PVC tubing has been used in most published studies of intravenous nitroglycerin, but the reported doses have been calculated by simply multiplying the flow rate of the solution by the solution's original concentration of nitroglycerin. **The actual doses delivered have been less, sometimes much less, than those reported.**

Relatively non-absorptive intravenous administration sets are available. **If intravenous nitroglycerin is administered through non-absorptive tubing, doses based upon published reports will generally be too high.**

Some in-line intravenous filters also absorb nitroglycerin; these filters should be avoided.

Solutions containing dextrose without electrolytes should not be administered through the same administration set as blood, as this may result in pseudoagglutination or hemolysis.

The intravenous administration of solutions may cause fluid overloading resulting in dilution of serum electrolyte concentrations, overhydration and congested states of pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the injections. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration of the injections.

Precautions

General: Severe hypotension and shock may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

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 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 these trials, anginal 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 in 5% Dextrose Injection increase the potential precision of dosing, but these concentrations increase the total fluid volume that must be

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