There was no significant difference in the total number of cancers between the gemfibrozil and placebo groups nor in the number of operations for gallstones or for cataract surgery. A higher number of deaths in the gemfibrozil group was mainly due to accident or violence and intracranial haemorrhage.

A follow-up study[2] reported that gastrointestinal symptoms remained more common in patients taking gemfibrozil. Although there was no significant difference between the gemfibrozil and placebo groups cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period. Cancer occurred equally in both groups, but there was increased mortality attributable to cancer in the gemfibrozil group, mainly during the last 1.5 years of follow-up; this difference was no longer apparent after 18 years.[3]

1. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
2. Huttunen JK, *et al.* The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; **235:** 31–9.
3. Tenkanen L, *et al.* Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med* 2006; **166:** 743–8.

Effects on the skin. Psoriasis was exacerbated in a patient within 2 weeks of starting gemfibrozil therapy and recurred when gemfibrozil was subsequently reintroduced.[1]

1. Fisher DA, *et al.* Exacerbation of psoriasis by the hypolipidemic agent, gemfibrozil. *Arch Dermatol* 1988; **124:** 854–5.

Interactions

As for Bezafibrate, p.1232.

Gemfibrozil is an inhibitor of a number of cytochrome P450 isoenzymes, including CYP2C8, CYP2C9, CYP2C19, and CYP1A2 and may increase the plasma concentration of drugs metabolised by these isoenzymes; it also inhibits some UDP-glucuronosyltransferases. Increased plasma concentration of bexarotene (see p.686), pioglitazone (see p.456), and rosiglitazone (see p.459) have been reported with gemfibrozil, and use of gemfibrozil in patients receiving repaglinide is contra-indicated due to the risk of serious hypoglycaemia (see p.458).

Pharmacokinetics

Gemfibrozil is readily absorbed from the gastrointestinal tract; bioavailability is close to 100% and is highest when gemfibrozil is taken 30 minutes before food. Peak concentrations in plasma occur within 1 to 2 hours; the half-life is about 1.5 hours. Plasma protein binding of gemfibrozil is about 98%. About 70% of a dose is excreted in the urine mainly as glucuronide conjugates of gemfibrozil and its metabolites; little is excreted in the faeces.

Uses and Administration

Gemfibrozil, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p.1233).

Gemfibrozil is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. It is also indicated for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164) in hyperlipidaemic men: in the USA this use is restricted to type IIb patients who also have low HDL-cholesterol concentrations and who have not responded to dietary and other measures. The usual oral dose is 1.2 g daily in 2 divided doses given 30 minutes before the morning and evening meals. Alternatively, a single daily dose of 900 mg has been given 30 minutes before the evening meal.

◊ Reviews.

1. Spencer CM, Barradell LB. Gemfibrozil: a reappraisal of its pharmacological properties and place in the management of dyslipidaemia. *Drugs* 1996; **51:** 982–1018.

Administration in renal impairment. Gemfibrozil is contra-indicated in patients with severe renal impairment. However, UK licensed prescribing information allows its use in patients with mild to moderate impairment (glomerular filtration rate 30 to 80 mL/minute per 1.73 m^2); the initial dose should be reduced to 900 mg daily and renal function should be assessed before increasing the dose.

In a study[1] of the pharmacokinetics of gemfibrozil in 17 patients with stable chronic renal failure the mean plasma half-life was 1.8 and 1.9 hours after multiple and single doses respectively, which was comparable with that reported in patients with normal renal function. Gemfibrozil clearance was independent of renal function, but the kinetics of gemfibrozil metabolites were not evaluated.

Beneficial responses[2] were seen in lipid and lipoprotein concentrations in 5 of 6 uraemic patients treated with gemfibrozil 1.2 g daily for six months and in 6 nephrotic patients given gemfibrozil 800 mg daily for 4 months. No significant adverse effects or signs of organ toxicity were seen. Results of a secondary prevention study[3] also suggested that gemfibrozil at a dose of 1.2 g daily was safe and effective in patients with mild to moderate renal impairment.

1. Evans JR, *et al.* The effect of renal function on the pharmacokinetics of gemfibrozil. *J Clin Pharmacol* 1987; **27:** 994–1000.
2. Manninen V, *et al.* Gemfibrozil treatment of dyslipidaemias in renal failure with uraemia or in the nephrotic syndrome. *Res Clin Forums* 1982; **4:** 113–18.
3. Tonelli M, *et al.* for the Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) Investigators. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004; **66:** 1123–30.

Preparations

BP 2008: Gemfibrozil Capsules; Gemfibrozil Tablets;
USP 31: Gemfibrozil Capsules; Gemfibrozil Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Gedun; Hipolixan; Lopid; ***Austral.:*** Ausgem; Gemhexal; Jezil; Lipazil; Lopid; ***Austria:*** Gevilon; ***Braz.:*** Lopid; Lozil; ***Canad.:*** Lopid; ***Chile:*** Grifogemzilo; Lipotril; Lopid; ***Cz.:*** Gevilon†; Innogem†; Ipolipid†; ***Denm.:*** Lopid; ***Fin.:*** Gevilon; Lopid; ***Fr.:*** Lipur; ***Ger.:*** Gemfi; Gevilon; Lipox Gemfi†; ***Gr.:*** Adratan†; Amedran; Antilipid; Cholhepan; Clipostat; Dosamont; Drisofal†; Eklipid; Entianthe†; Fibrolip; Fibrospes; Gebrozil†; Gedizil; Gemfolid; Gemlipid; Gineton; Hobatolex; Lisolip; Lopid; Noxobran†; Parnoxil; Prelisin; Renolip; Solulip; Terostrant; Tiazam; ***Hong Kong:*** Gemzil; Ipolipid; Lipison; Lipistorol; Lipofor; Lopid; Lowin; Marbrozil; Qualipid; Saffid; Synbrozil; ***Hung.:*** Innogem; Minilip; ***India:*** Lopid; Normolip; ***Indon.:*** Detrichol; Fetinor; Fibralip; Hypofil; Inobes; Lapibroz; Lifibron; Lipira; Lipitrop; Lokoles; Lopid; Lowlip; Mersikol; Nufalemzil; Progemzal; Renabrazin; Scantipid; Zilop; ***Irl.:*** Lopid; ***Ital.:*** Fibrocit; Gemlipid; Genlip; Genozil; Lipogen; Lipozid; Lopid; ***Malaysia:*** Brozil; Fibrol†; Ipolipid; Lipistorol†; Lipofor; Lopid†; Mariston†; ***Mex.:*** Apo-Fide; Lopid; Raypid; ***Neth.:*** Lopid; ***NZ:*** Gemizol†; ***Philipp.:*** Lipigem; Lipison; Lipizile; Lipozid; Lopid; Reducel; ***Port.:*** Lipoite; Lopid; ***Rus.:*** Ipolipid (Иполипид); ***S.Afr.:*** Lopid; ***Singapore:*** Brozil; Gemd†; Hidil; Ipolipid; Lipison†; Lipofor; Lopid†; Recozil; ***Spain:*** Bolutol†; Decrelip†; Lopid; Pilder; Trialmin; ***Swed.:*** Lopid; ***Switz.:*** Gevilon; ***Thai.:*** Bisil; Chlorestrol†; Deopid†; Dropid; Gemfibril; GFB; Gozid; Hidil; Lipidys; Lipison; Lipolo; Lipozil; Locholes; Lopid; Manobrozil; Mariston; Norpid; Pharzil; Poli-Fibrozil; Polyxit; Tiba; ***Turk.:*** Lopid; ***UK:*** Lopid; ***USA:*** Lopid; ***Venez.:*** Lipontal; Lopid.

Glyceryl Trinitrate

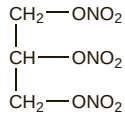
Glicerin-trinitrát; Glicerolio trinitratas; Gliseril Trinitrat; Glonoin; Glyceroli Trinitras; Glyceroli trinitratis; Glycerol-trinitrát; Glycéryle, trinitrate de; Glyceryltrinitrat; Glyseryylitrinitraatti; GTN; Nitroglicerina; Nitrogliserin; Nitroglycerin; Nitroglycerol; NTG; Trinitrin; Trinitroglycerin. Propane-1,2,3-triol trinitrate.

$C_3H_5(NO_3)_3$ = 227.1.

CAS — 55-63-0.

ATC — C01DA02; C05AE01.

ATC Vet — QC01DA02; QC05AE01.



Pharmacopoeias. *Chin., Eur.* (see p.vii), *US*, and *Viet.* include glyceryl trinitrate as diluted solutions.

Ph. Eur. 6.2 (Glyceryl Trinitrate Solution). An ethanolic solution containing 1 to 10% w/w of glyceryl trinitrate. It is a clear, colourless or slightly yellow solution. Miscible with dehydrated alcohol and with acetone.

Pure glyceryl trinitrate is practically insoluble in water; freely soluble in dehydrated alcohol; miscible with acetone.

Protect from light. Diluted solutions (1%) should be stored at 2° to 15°; more concentrated solutions may be stored at 15° to 20°.

USP 31 (Diluted Nitroglycerin). A mixture of glyceryl trinitrate with lactose, glucose, alcohol, propylene glycol, or other suitable inert excipient, usually containing not more than 10% glyceryl trinitrate. When diluted in either alcohol or propylene glycol it is a clear, colourless, or pale yellow liquid. When diluted with lactose, it is a white odourless powder. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Prevent exposure to temperatures above 40°. Protect from light.

Undiluted glyceryl trinitrate is a white to pale yellow, thick, flammable, explosive liquid. Slightly soluble in water; soluble in alcohol, in acetone, in carbon disulfide, in chloroform, in dichloromethane, in ether, in ethyl acetate, in glacial acetic acid, in methyl alcohol, in benzene, in toluene, in nitrobenzene, and in phenol.

Handling. Undiluted glyceryl trinitrate can be exploded by percussion or excessive heat and only exceedingly small amounts should be isolated.

Incompatibility. Studies have found glyceryl trinitrate to be incompatible with phenytoin,[1] alteplase,[2] and levofloxacin.[3]

1. Klamerus KJ, *et al.* Stability of nitroglycerin in intravenous admixtures. *Am J Hosp Pharm* 1984; **41:** 303–5.
2. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.

Stability. ***INTRAVENOUS SOLUTIONS.*** The loss of glyceryl trinitrate from solution by adsorption or absorption into some plastics of intravenous giving sets has been recognised for some years,[1,2] although adsorption does not appear to occur to any great extent with polyolefin[3,4] or polyethylene.[5-7] It is not only infusion containers and plastic tubing that may be involved; some in-line filters can adsorb glyceryl trinitrate.[8,9]

1. Grouthamel WG, *et al.* Loss of nitroglycerin from plastic intravenous bags. *N Engl J Med* 1978; **299:** 262.
2. Roberts MS, *et al.* The availability of nitroglycerin from parenteral solutions. *J Pharm Pharmacol* 1980; **32:** 237–44.
3. Wagenknecht DM, *et al.* Stability of nitroglycerin solutions in polyolefin and glass containers. *Am J Hosp Pharm* 1984; **41:** 1807–11.
4. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.
5. Schaber DE, *et al.* Nitroglycerin adsorption to a combination polyvinyl chloride, polyethylene intravenous administration set. *Drug Intell Clin Pharm* 1985; **19:** 572–5.
6. Tracy TS, *et al.* Nitroglycerin delivery through a polyethylene-lined intravenous administration set. *Am J Hosp Pharm* 1989; **46:** 2031–5.
7. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
8. Baaske DM, *et al.* Nitroglycerin compatibility with intravenous fluid filters, containers, and administration sets. *Am J Hosp Pharm* 1980; **37:** 201–5.
9. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.

TABLETS. Many studies have shown that glyceryl trinitrate tablets are unstable and subject to considerable loss of potency in contact with packaging components such as adhesive labels, cotton and rayon fillers, and plastic bottles and caps. Both the Council of the Royal Pharmaceutical Society of Great Britain and the FDA in the USA have issued packaging and dispensing guidelines. Glyceryl trinitrate tablets should be dispensed only in glass containers sealed with a foil lined cap and containing no cotton wool wadding. In addition, the Council of the Royal Pharmaceutical Society of Great Britain recommends that no more than 100 tablets should be supplied and that the container should be labelled with an indication that any tablets should be discarded after 8 weeks in use.

Adverse Effects

Glyceryl trinitrate may cause flushing of the face, dizziness, tachycardia, and throbbing headache. Large doses cause vomiting, restlessness, blurred vision, hypotension (which can be severe), syncope, and rarely cyanosis, and methaemoglobinaemia; impairment of respiration and bradycardia may ensue. Contact dermatitis has been reported in patients using topical glyceryl trinitrate preparations; local irritation and erythema may also occur. Preparations applied to the oral mucosa frequently produce a localised burning sensation.

Chronic poisoning may occur in industry but tolerance develops when glyceryl trinitrate is regularly handled and nitrate dependence can lead to severe withdrawal symptoms in subjects abruptly removed from chronic exposure. Loss of such tolerance is rapid and may cause poisoning on re-exposure. Tolerance may occur during clinical use and is usually associated with preparations that produce sustained plasma concentrations.

Effects on the heart. Tachycardia, hypotension, and bradycardia are recognised adverse cardiac effects of glyceryl trinitrate. Rarely reported adverse effects include asystole[1] and complete heart block.[2]

1. Ong EA, *et al.* Nitroglycerin-induced asystole. *Arch Intern Med* 1985; **145:** 954.
2. Lancaster L, Fenster PE. Complete heart block after sublingual nitroglycerin. *Chest* 1983; **84:** 111–12.

Effects on taste. A 61-year-old man experienced loss of bitter and salty taste sensations 2 weeks after addition of glyceryl trinitrate patches to his post-myocardial infarction drug regimen.[1] The patient had complete loss of taste after 6 weeks; his taste

sensation returned to normal within 1 week of stopping glyceryl trinitrate patches. Taste sensation was again altered on rechallenge.

1. Ewing RC, *et al.* Ageusia associated with transdermal nitroglycerin. *Clin Pharm* 1989; **8:** 146–7.

Hypersensitivity. Contact dermatitis has been reported in patients using glyceryl trinitrate ointment and patches.[1] Both glyceryl trinitrate and formulation components may be involved in these reactions.

1. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; **10:** 151–9.

Intravenous administration. Some formulations of glyceryl trinitrate for intravenous use may contain substantial quantities of alcohol in the solvent. There have been several reports of alcohol intoxication occurring in patients during high-dose intravenous glyceryl trinitrate infusion.[1-3] In a patient[3] who required glyceryl trinitrate 2 mg/minute, a blood-alcohol concentration of 2.67 mg/mL was reported. PVC tubing had been used for the infusion and it was suggested that adsorption of glyceryl trinitrate onto the tubing may have increased the dose requirement and thus the amount of alcohol given.

Propylene glycol is also used as a solvent in some formulations of glyceryl trinitrate. Infusion of solutions with propylene glycol can lead to hyperosmolarity: see under Propylene Glycol, p.2374, for details.

1. Shook TL, *et al.* Ethanol intoxication complicating intravenous nitroglycerin therapy. *Ann Intern Med* 1984; **101:** 498–9.
2. Daly TJ, *et al.* "Cocktail"-coronary care. *N Engl J Med* 1984; **310:** 1123.
3. Korn SH, Comer JB. Intravenous nitroglycerin and ethanol intoxication. *Ann Intern Med* 1985; **102:** 274.

Treatment of Adverse Effects

Syncope and hypotension should be treated by keeping the patient in a recumbent position with the head lowered; pressor agents may be necessary in extreme hypotension. Oxygen, with assisted respiration, may be needed in severe poisoning and infusion of plasma expanders or suitable electrolyte solutions may be required to maintain the circulation. If methaemoglobinaemia occurs methylthioninium chloride may be given intravenously. In the case of severe poisoning with tablets the stomach may be emptied by lavage. If large amounts have been ingested within 1 hour, activated charcoal may be considered.

Precautions

Glyceryl trinitrate should not be used in patients with severe hypotension, hypovolaemia, marked anaemia, heart failure due to obstruction (including constrictive pericarditis), or raised intracranial pressure due to head trauma or cerebral haemorrhage. Although it has been suggested that glyceryl trinitrate may increase intra-ocular pressure in patients with angle-closure glaucoma and should be avoided in such patients there appears to be no evidence for such a contra-indication.

Glyceryl trinitrate should be used with caution in patients with severe renal or severe hepatic impairment, hypothyroidism, malnutrition, or hypothermia. Metal-containing transdermal patches should be removed before cardioversion or diathermy.

Nitrate tolerance. Although organic nitrates are effective anti-anginal drugs, their use is limited by the development of tolerance and the loss or attenuation of their anti-anginal and anti-ischaemic effects.[1,2] This can occur with all of the organic nitrates, particularly if frequent or continuous dosing is used.[1-3]

The mechanisms of nitrate tolerance are incompletely understood. The vasodilator effect of organic nitrates may depend on their conversion to nitric oxide, a process which requires the presence of a sulfhydryl donor such as cysteine or another thiol. Repeated doses of a nitrate exhaust tissue stores of sulfhydryl groups and this is one mechanism that may account for the development of tolerance.[1,2] The activation of neurohormonal systems, which releases vasoconstrictor hormones that counteract the effects of organic nitrates, has also been proposed as a mechanism.[1,2] An increase in free-radical production during nitrate therapy has also been suggested,[1] and may inhibit bioactivation of the nitrate.[3] Nitrate-induced expansion of plasma volume may also contribute, leading to reversal of the effects of nitrates on ventricular preload.[1,2]

The method most commonly used to avoid the development of tolerance is to provide a nitrate-free interval.[1,2] The optimum duration is not clear, but a nitrate-free period of 10 to 12 hours has been suggested.[1,2] With transdermal glyceryl trinitrate systems, the patch can be removed at night. For oral, buccal, and ointment preparations, the dose given at the end of the day can be omitted. However, rebound myocardial ischaemia may occur during this time,[1] and may require the use of short-acting nitrate preparations.[2] Whether a nitrate-free interval is necessary for all patients is unknown as many patients using continuous nitrates do not experience clinical tolerance. A transdermal patch with a higher release rate during the first part of a 24-hour period has been found not to prevent the development of tolerance.[4]

Various drugs have been reported to reduce the development of nitrate tolerance, including sulfhydryl donors and drugs with antioxidant properties, but none has an established role.[1,3]

1. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. *N Engl J Med* 1998; **338:** 520–31.
2. Rutherford JD. Nitrate tolerance in angina therapy: how to avoid it. *Drugs* 1995; **49:** 196–9.
3. Münzel T, *et al.* Explaining the phenomenon of nitrate tolerance. *Circ Res* 2005; **97:** 618–28.
4. Wiegand A, *et al.* Pharmacodynamic and pharmacokinetic evaluation of a new transdermal delivery system with a time-dependent release of glyceryl trinitrate. *J Clin Pharmacol* 1992; **32:** 77–84.

Transdermal patches. An explosion occurred during defibrillation in a patient with a glyceryl trinitrate transdermal patch on the left side of the chest.[1] There was no visible injury to the patient. Subsequent studies suggested that this was caused by an electrical arc between the defibrillator paddle and the aluminium backing of the patch rather than explosion of the glyceryl trinitrate.

Although removal of transdermal patches before diathermy is usually recommended, a maximum rise in patch temperature of only 2.2° was reported when patches were exposed to power densities up to 800 watts/m^2. It was considered that exposure of transdermal patches to microwave diathermy, for example as part of physiotherapy treatment, was unlikely to cause direct thermal injury to the wearer.[2]

1. Babka JC. Does nitroglycerin explode? *N Engl J Med* 1983; **309:** 379.
2. Moseley H, *et al.* The influence of microwave radiation on transdermal delivery systems. *Br J Dermatol* 1990; **122:** 361–3.

Interactions

The hypotensive effects of glyceryl trinitrate may be enhanced by alcohol, and by vasodilators and other drugs with hypotensive actions. The effectiveness of sublingual and buccal tablet preparations may be reduced by drugs that cause dry mouth since dissolution may be delayed.

Anticoagulants. For the effects of glyceryl trinitrate on *heparin*, see p.1303.

Antimuscarinics. Delayed dissolution of glyceryl trinitrate tablets due to dry mouth has been reported in a patient taking *imipramine*[1] and in a patient treated with *atropine*;[2] this effect should be considered whenever glyceryl trinitrate sublingual tablets are given to patients taking other drugs that can cause dry mouth. Use of the lingual spray[2] rather than a sublingual tablet or addition of 1 mL of saline under the tongue[3] may be used to overcome the problem.

1. Robbins LJ. Dry mouth and delayed dissolution of sublingual nitro-glycerin. *N Engl J Med* 1983; **309:** 985.
2. Kimchi A. Dry mouth and delayed dissolution of nitroglycerin. *N Engl J Med* 1984; **310:** 1122.
3. Rasler FE. Ineffectiveness of sublingual nitroglycerin in patients with dry mucous membranes. *N Engl J Med* 1986; **314:** 181.

Ergot alkaloids. For the effects of glyceryl trinitrate on *dihydroergotamine*, see under Interactions of Ergotamine, p.621.

Phosphodiesterase type-5 inhibitors. The concurrent use of nitrates and phosphodiesterase type-5 inhibitors such as sildenafil is contra-indicated. Significant hypotension may occur due to potentiation of the vasodilator actions of nitrates.[1] Deaths due to a possible interaction have been reported.[2]

1. Webb DJ, *et al.* Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000; **36:** 25–31.
2. Cheitlin MD, *et al.* Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol* 1999; **33:** 273–82. Correction. *ibid.*; **34:** 1850.

Thrombolytics. For the effects of glyceryl trinitrate on *alteplase*, see p.1207.

Pharmacokinetics

Glyceryl trinitrate is rapidly absorbed from the oral mucosa. It is also well absorbed from the gastrointestinal tract and through the skin. Bioavailability is less than 100% when given by any of these routes due to pre-systemic clearance; bioavailability is further reduced after oral use owing to extensive first-pass metabolism in the liver.

Therapeutic effect is apparent within 1 to 3 minutes of use of sublingual tablets, sublingual spray, or buccal tablets; within 30 to 60 minutes of applying an ointment or transdermal patch; and within 1 to 2 minutes after intravenous doses.

Duration of action is about 30 to 60 minutes with sublingual tablets or spray and 3 to 5 hours with modified-release buccal tablets. Transdermal patches are designed to release a stated amount of drug over 24 hours, while therapeutic effects after application of glyceryl trinitrate ointment 2% persist for up to 8 hours. Duration of action after intravenous dosage is about 3 to 5 minutes.

Glyceryl trinitrate is widely distributed with a large apparent volume of distribution. It is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to inorganic nitrite and then to nitric oxide. This reaction requires the presence of cysteine or another thiol. Glyceryl trinitrate also undergoes hydrolysis in plasma and is rapidly metabolised in the liver by glutathione-organic nitrate reductase to dinitrates and mononitrates. The dinitrates are less potent vasodilators than glyceryl trinitrate; the mononitrates may have some vasodilator activity.

◊ References.

1. Bogaert MG. Clinical pharmacokinetics of glyceryl trinitrate following the use of systemic and topical preparations. *Clin Pharmacokinet* 1987; **12:** 1–11.
2. Thadani U, Whitsett T. Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. *Clin Pharmacokinet* 1988; **15:** 32–43.
3. Ridout G, *et al.* Pharmacokinetic considerations in the use of newer transdermal formulations. *Clin Pharmacokinet* 1988; **15:** 114–31.
4. Hashimoto S, Kobayashi A. Clinical pharmacokinetics and pharmacodynamics of glyceryl trinitrate and its metabolites. *Clin Pharmacokinet* 2003; **42:** 205–21.

Uses and Administration

Glyceryl trinitrate is a nitrovasodilator used in the management of angina pectoris (p.1157), heart failure (p.1165), and myocardial infarction (below). Other indications include inducing hypotension and controlling hypertension during surgery.

Glyceryl trinitrate is believed to exert its vasodilator effect through release of nitric oxide, which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. This nucleotide induces relaxation, probably by lowering the free calcium concentration in the cytosol. In its action on vascular muscle, venous dilatation predominates over dilatation of the arterioles. Venous dilatation decreases venous return as a result of venous pooling, and lowers left ventricular diastolic volume and pressure (termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequent effect is a reduction in the primary determinants of myocardial oxygen demand. The effect on preload is not shared by beta blockers or calcium-channel blockers. Glyceryl trinitrate also has a coronary vasodilator effect, which improves regional coronary blood flow to ischaemic areas resulting in improved oxygen supply to the myocardium.

Glyceryl trinitrate may be given by the sublingual, buccal, oral, transdermal, or intravenous route. The dose and choice of formulation depend upon the clinical situation.

In the management of **acute angina** glyceryl trinitrate is given as sublingual tablets, a sublingual aerosol spray, or buccal tablets, which all produce a rapid onset of therapeutic effect and provide rapid relief of anginal pain. These dosage forms may also be used before an activity or stress which might provoke an attack. One sublingual tablet (usual strength 300 to 600 micrograms) is placed under the tongue. The dose may be repeated as required but patients should be advised to seek medical care if pain persists after a total of 3 doses within 15 minutes. If an aerosol spray is used one or two sprays of 400 micrograms each are directed onto or under the tongue, then the mouth is closed; three sprays may be used if necessary. Buccal tablets of glyceryl trinitrate are placed between the upper lip and gum (see below for precautions to be observed during use). The usual dose is 2 mg when required, increased to 3 mg if necessary; a dose of 5 mg may be given in severe angina.

In the long-term management of **stable angina** glyceryl trinitrate is given as modified-release tablets or capsules, transdermal formulations, or buccal tablets, which all provide a long duration of action. Dosage varies according to the specific formulation. In the UK, for example, modified-release oral tablets are available that allow doses of up to 12.8 mg to be given up to three times daily. The transdermal formulations available are ointments and patches. With the ointment a measured amount (½ to 2 inches of glyceryl trinitrate ointment 2%) is applied 3 or 4 times daily, or every 3 to 4 hours if necessary, to the chest, arm, thigh, or back. Transdermal patches applied to the chest, upper arm, or shoulder are more convenient. Patches are generally designed to release glyceryl trinitrate at a constant rate; they are available in a range of sizes, releasing about 0.1 to 0.8 mg/hr (equivalent to about 2.5 to 20 mg in 24 hours, although the patches are generally removed for part of this period to prevent tolerance developing). A maximum daily dose of 20 mg has been suggested. Glyceryl trinitrate ointment and patches should be applied to a fresh area of skin and several days should elapse before re-application to formerly used sites. Buccal tablets are used in doses of 2 to 5 mg three times daily. The tablets are retained in the buccal cavity; the rate of dissolution of the tablet can be increased by touching the tablet with the tongue or drinking hot liquids. It is common practice to remove the tablets at bedtime because of the risk of aspiration. Also patients using buccal tablets should be advised to alternate placement sites and pay close attention to oral hygiene to reduce the risk of dental caries. The tablets are not intended to be chewed; if the buccal tablet is inadvertently swallowed, another may be placed in the buccal cavity.

Tolerance tends to develop in the majority of patients on continuous nitrate therapy and nitrate-free intervals are often employed to avoid this problem (see above under Precautions, Nitrate Tolerance for further details).

In the management of **unstable angina** glyceryl trinitrate may be given by intravenous infusion. Manufacturers' guidelines for dilution of glyceryl trinitrate injection specify glucose 5% or sodium chloride 0.9% as the diluent. During intravenous use of glyceryl trinitrate there should be haemodynamic monitoring of the patient with the dose being adjusted gradually to produce the desired response. The plastic used in the infusion equipment may adsorb glyceryl trinitrate (see Stability, above) and allowance may have to be made for this. The usual initial dose for unstable angina is 5 to 10 micrograms/minute. Most patients respond to doses between 10 and 200 micrograms/minute. The sublingual and buccal routes may also be used; doses of up to 5 mg as buccal tablets may be required to relieve pain in patients with unstable angina.

In the management of acute **heart failure** glyceryl trinitrate is given intravenously in an initial dose of 5 to 25 micrograms/minute. Buccal tablets have been used in doses of 5 mg repeated as needed until symptoms are controlled. In chronic heart failure buccal tablets may be given in doses of 5 to 10 mg three times daily.

Glyceryl trinitrate is also used intravenously in acute **myocardial infarction**, and to induce hypotension or control hypertension during **surgery**. The initial dose is 5 to 25 micrograms/minute, adjusted according to response. The usual range is 10 to 200 micrograms/minute but some surgical patients may require up to 400 micrograms/minute.

Glyceryl trinitrate has also been used as transdermal patches in the prophylactic treatment of **phlebitis and extravasation** secondary to venous cannulation. One 5-mg patch is applied distal to the intravenous site; the patch should be replaced at a different skin site either daily or after 3 to 4 days, depending on the patch. This treatment should continue only as long as the intravenous infusion is maintained.

Glyceryl trinitrate may also be used as a 0.4% ointment for the relief of pain due to chronic **anal fissure** (below). A measured amount equivalent to about 1.5 mg is applied intra-anally every 12 hours for up to 8 weeks.

Anal fissure. Nitrates such as glyceryl trinitrate are used for the treatment of chronic anal fissure (p.1891) because of their ability to relax the anal sphincter. Topical application of glyceryl trinitrate ointment in concentrations of 0.2 to 0.8% has relieved pain and aided healing of anal fissures both in uncontrolled[1-3] and controlled studies,[4,5] although only the effect on pain appears to be significant.[6] One study[5] found that a concentration of 0.6% had no additional benefit over 0.2%. Follow-up[5,7] of some of the patients indicated that after 6 to 38 months most had not had further problems or had had occasional recurrences (relapses of about one-quarter to one-third) which in the majority of cases had responded to further topical treatment. A small placebo-controlled study specifically in children, however, did not find topical glyceryl trinitrate to be of benefit in this patient population.[8]

There is evidence that application of a glyceryl trinitrate patch may be as effective as topical application of a 0.2% ointment.[9]

Encouraging results have also been obtained in an uncontrolled study using a 1% ointment of isosorbide dinitrate.[10]

1. Gorfine SR. Topical nitroglycerin therapy for anal fissures and ulcers. *N Engl J Med* 1995; **333:** 1156–7.
2. Lund JN *et al.* Use of glyceryl trinitrate ointment in the treatment of anal fissure. *Br J Surg* 1996; **83:** 776–7.
3. Watson SJ, *et al.* Topical glyceryl trinitrate in the treatment of chronic anal fissure. *Br J Surg* 1996; **83:** 771–5.
4. Lund JN, Scholefield JH. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure. *Lancet* 1997; **349:** 11–14. Correction. *ibid.*; 656.
5. Carapeti EA, *et al.* Randomised controlled trial shows that glyceryl trinitrate heals anal fissures, higher doses are not more effective, and there is a high recurrence rate. *Gut* 1999; **44:** 727–30.
6. Fenton C, *et al.* 0.4% Nitroglycerin ointment: in the treatment of chronic anal fissure pain. *Drugs* 2006; **66:** 343–9.
7. Lund JN, Scholefield JH. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet* 1998; **352:** 1681.
8. Kenny SE, *et al.* Double blind randomised controlled trial of topical glyceryl trinitrate in anal fissure. *Arch Dis Child* 2001; **85:** 404–7.
9. Zuberi BF, *et al.* A randomized trial of glyceryl trinitrate ointment and nitroglycerin patch in healing of anal fissures. *Int J Colorectal Dis* 2000; **15:** 243–5.
10. Schouten WR, *et al.* Pathophysiological aspects and clinical outcome of intra-anal application of isosorbide dinitrate in patients with chronic anal fissure. *Gut* 1996; **39:** 465–9.

Erectile dysfunction. Erectile dysfunction (p.2179) has been managed by the penile injection of drugs such as papaverine or alprostadil although oral treatment with drugs such as sildenafil is now available. Penile injections are not always acceptable to the patient and a number of studies have investigated topical therapies, mostly glyceryl trinitrate applied either as ointment or as a transdermal patch to the penis.[1-4] Such treatment can produce erections in some subjects, although response rates vary. However, patients must wear a condom to protect their partner against potential adverse effects resulting from the transfer of glyceryl trinitrate. The action of glyceryl trinitrate is believed to be due to smooth muscle relaxation and vasodilatation which are necessary prerequisites for penile erection.

Topical application of a cream containing isosorbide dinitrate, codergocrine mesilate, and aminophylline produced satisfactory erections in 21 of 36 men with erectile dysfunction due to various causes.[5] Eight out of 9 men with erectile dysfunction of psychogenic origin reported a satisfactory response. However, another study[6] was abandoned after the cream produced no effect in 10 consecutive patients. A further study in 14 patients who received a total of 77 applications of the cream reported no benefit over placebo.[7] Topical treatment with a cream containing isosorbide dinitrate, codergocrine mesilate, and testosterone has also been tried for erectile dysfunction; in a study in 42 men with low sexual interest and low or slightly depressed testosterone levels, 28 reported beneficial results.[8]

It should be noted that topical nitrates must not be employed in patients already using sildenafil (see Phosphodiesterase Type-5 Inhibitors, under Interactions, above).

1. Heaton JPW, *et al.* Topical glyceryl trinitrate causes measurable penile arterial dilation in impotent men. *J Urol (Baltimore)* 1990; **143:** 729–31.
2. Meyhoff HH, *et al.* Non-invasive management of impotence with transcutaneous nitroglycerin. *Br J Urol* 1992; **69:** 88–90.
3. Nunez BD, Anderson DC. Nitroglycerin ointment in the treatment of impotence. *J Urol (Baltimore)* 1993; **150:** 1241–3.
4. Anderson DC, Seifert CF. Topical nitrate treatment of impotence. *Ann Pharmacother* 1993; **27:** 1203–5.
5. Gomaa A, *et al.* Topical treatment of erectile dysfunction: randomised double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate. *BMJ* 1996; **312:** 1512–15.
6. Naude JH, Le Roux PJ. Topical treatment of erectile dysfunction did not show results. *BMJ* 1998; **316:** 1318.
7. Le Roux PJ, Naude JH. Topical vasoactive cream in the treatment of erectile failure: a prospective, randomized placebo-controlled trial. *BJU Int* 1999; **83:** 810–11.
8. Gomaa A, *et al.* The effect of topically applied vasoactive agents and testosterone versus testosterone in the treatment of erectile dysfunction in aged men with low sexual interest. *Int J Impot Res* 2001; **13:** 93–9.

Gallstones. Endoscopic removal of gallstones (p.2409) in a small series of 15 patients was facilitated by glyceryl trinitrate 1.2 to 3.6 mg applied as a spray to the tongue. Glyceryl trinitrate 1.2 mg was shown to relax the sphincter of Oddi to about 30% of its normal pressure.[1] The ability of glyceryl trinitrate to relax smooth muscle has also been used to relieve biliary colic (p.5) in 3 patients with gallstones;[2] in one of these patients standard managements for the pain such as oral opioids had been only moderately effective.

1. Staritz M, *et al.* Nitroglycerine dilatation of sphincter of Oddi for endoscopic removal of bileduct stones. *Lancet* 1984; **i:** 956.
2. Hassel B. Treatment of biliary colic with nitroglycerin. *Lancet* 1993; **342:** 1305.

Migraine. Although use of glyceryl trinitrate may precipitate or exacerbate migraine (p.616) inhalation of glyceryl trinitrate at the onset of a migraine aura aborted attacks in a patient at risk of permanent neurological damage from migraine. Standard prophylactic therapy had previously been unsuccessful.[1]

1. Mitchell GK. Nitroglycerine by inhaler as treatment for migraine causing cerebral ischaemia. *Med J Aust* 1999; **171:** 336.

Myocardial infarction. Intravenous nitrates are widely used in acute myocardial infarction (p.1175), although evidence to support their use in patients undergoing reperfusion is limited. An overview of studies carried out before reperfusion (thrombolysis or percutaneous coronary intervention) became routine found that the use of intravenous nitrates (glyceryl trinitrate or sodium nitroprusside) within 24 hours of the onset of pain was associated with a reduction in mortality,[1] but whether they are of benefit in addition to reperfusion is less clear. However, empirical use of intravenous glyceryl trinitrate appears to be safe, and it should therefore be given where clinically indicated for ongoing ischaemic pain. In the GISSI-3 study,[2] glyceryl trinitrate was given by intravenous infusion during the first 24 hours, starting at 5 micrograms/minute and increasing by 5 to 20 micrograms/minute every 5 minutes for the first half hour until systolic blood pressure fell by at least 10% provided it remained above 90 mmHg; after 24 hours it was replaced by a transdermal patch providing 10 mg daily.

Long-term use of nitrates after myocardial infarction may be indicated in patients with myocardial ischaemia or poor left ventricular function, but there is no evidence to support their routine use. In the GISSI-3 study there was no significant benefit from the use of transdermal glyceryl trinitrate when assessed 6 weeks[2] and 6 months[3] post-infarction and in the ISIS-4 study[4] oral isosorbide mononitrate apparently had no effect on 35-day mortality.

1. Yusuf S, *et al.* Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet* 1988; **i:** 1088–92.
2. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
3. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after myocardial infarction: the GISSI-3 trial. *J Am Coll Cardiol* 1996; **27:** 337–44.
4. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.

Obstetrics and gynaecology. The smooth muscle relaxant properties of glyceryl trinitrate have been used in various obstetric or gynaecological situations although most reports are anecdotal or include small numbers of patients. The intravenous injection of glyceryl trinitrate 50 to 100 micrograms repeated to a total dose of 200 micrograms if necessary has produced sufficient uterine relaxation in postpartum women for the manual extraction of retained placentas.[1,2] Use as a sublingual spray has also successfully aided breech extraction in a set of twins.[3]

Glyceryl trinitrate has been given as a sublingual spray to relax the cervix before IUD insertion. In a series of over 100 patients one or two doses of 400 micrograms sublingually were usually adequate.[4]

Beneficial results have been reported in women with possible premature labour (p.2003) after application of glyceryl trinitrate patches to the abdomen.[5,6] In one study[7] this was as effective as ritodrine infusion, but another[8] found transdermal glyceryl trinitrate to be less effective than beta agonists. A study[9] comparing glyceryl trinitrate and magnesium sulfate, both given intravenously, found that glyceryl trinitrate was associated with a higher failure rate and a greater reduction in maternal blood pressure. A systematic review[10] concluded that there was insufficient evidence to support the routine use of glyceryl trinitrate.

Transdermal glyceryl trinitrate has been tried for controlling pain in severe and moderate-to-severe dysmenorrhoea[11,12] (p.6).

Glyceryl trinitrate has been given intravenously in the management of pre-eclampsia (see under Hypertension, p.1171) and is reported to reduce blood pressure without compromising uterine blood flow.[13]

Isosorbide mononitrate given vaginally has been found to produce cervical ripening[14] and although there is some evidence[15] that it is less effective, it may be an alternative to standard treat-

ments such as prostaglandins (see Termination of Pregnancy p.2004). Isosorbide dinitrate has been used similarly after missed abortion.[16]

1. DeSimone CA, *et al.* Intravenous nitro-glycerin aids manual extraction of a retained placenta. *Anesthesiology* 1990; **73:** 787.
2. Lowenwirt IP, *et al.* Safety of intravenous glyceryl trinitrate in management of retained placenta. *Aust N Z J Obstet Gynaecol* 1997; **37:** 20–4.
3. Greenspoon JS, Kovacic A. Breech extraction facilitated by glyceryl trinitrate sublingual spray. *Lancet* 1991; **338:** 124–5.
4. Yadava RP. Sublingual glyceryl trinitrate spray facilitates IUD insertion. *Br J Sex Med* 1990; **17:** 217.
5. Lees C, *et al.* Arrest of preterm labour and prolongation of gestation with glyceryl trinitrate, a nitric oxide donor. *Lancet* 1994; **343:** 1325–6.
6. Smith GN, *et al.* Randomised, double-blind, placebo controlled pilot study assessing nitroglycerin as a tocolytic. *Br J Obstet Gynaecol* 1999; **106:** 736–9.
7. Lees CC, *et al.* Glyceryl trinitrate and ritodrine in tocolysis: an international multicenter randomized study. *Obstet Gynecol* 1999; **94:** 403–8.
8. Bisits A, *et al.* The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. *Am J Obstet Gynecol* 2004; **191:** 683–90.
9. El-Sayed YY, *et al.* Randomized comparison of intravenous nitroglycerin and magnesium sulfate for treatment of preterm labor. *Obstet Gynecol* 1999; **93:** 79–83.
10. Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 28/11/07).
11. Pittrof R, *et al.* Crossover study of glyceryl trinitrate patches for controlling pain in women with severe dysmenorrhoea. *BMJ* 1996; **312:** 884.
12. The Transdermal Nitroglycerine/Dysmenorrhoea Study Group. Transdermal nitroglycerine in the management of pain associated with primary dysmenorrhoea: a multinational pilot study. *J Int Med Res* 1997; **25:** 41–4.
13. Grunewald C, *et al.* Effects of nitroglycerin on the uterine and umbilical circulation in severe preeclampsia. *Obstet Gynecol* 1995; **86:** 600–4.
14. Thomson AJ, *et al.* Randomised trial of nitric oxide donor versus prostaglandin for cervical ripening before first-trimester termination of pregnancy. *Lancet* 1998; **352:** 1093–6.
15. Chen FC-K, *et al.* Isosorbide mononitrate vaginal gel versus misoprostol vaginal gel versus Dilapan-S for cervical ripening before first trimester curettage. *Eur J Obstet Gynecol Reprod Biol* 2008; **138:** 176–9.
16. Arteaga-Troncoso G, *et al.* Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomised controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception. *BJOG* 2005; **112:** 1615–19.

Oesophageal motility disorders. Achalasia is obstruction caused by failure of the lower oesophageal sphincter to relax and permit passage of food into the stomach. Nitrates such as isosorbide dinitrate have been reported to produce effective relaxation and to reduce symptoms when given sublingually. They have a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p.1702).

Nitrates may also be employed in oesophageal disorders such as variceal haemorrhage (see below).

Pain. Nitrates have been tried topically in the management of pain. Beneficial results have been reported with glyceryl trinitrate, applied as patches[1] or as a spray,[2] and isosorbide dinitrate spray,[3] in patients with painful diabetic neuropathy. Glyceryl trinitrate has also been used topically in musculoskeletal disorders[4] (see also Soft-tissue Rheumatism, below), and in surgical pain,[5] and intravenously as an adjunct to regional anaesthesia.[6]

Glyceryl trinitrate is also used topically to relieve pain in patients with anal fissure (above). For reference to its use in biliary colic, see Gallstones, above.

1. Rayman G, *et al.* Glyceryl trinitrate patches as an alternative to isosorbide dinitrate spray in the treatment of chronic painful diabetic neuropathy. *Diabetes Care* 2003; **26:** 2697–8.
2. Agrawal RP, *et al.* Glyceryl trinitrate spray in the management of painful diabetic neuropathy: a randomized double blind placebo controlled cross-over study. *Diabetes Res Clin Pract* 2007; **77:** 161–7.
3. Yuen KCJ, *et al.* Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. *Diabetes Care* 2002; **25:** 1699–1703.
4. Paoloni JA, *et al.* Topical nitric oxide application in the treatment of chronic extensor tendinosis at the elbow: a randomized, double-blinded, placebo-controlled clinical trial. *Am J Sports Med* 2003; **31:** 915–20.
5. McCabe JE, *et al.* A randomized controlled trial of topical glyceryl trinitrate before transrectal ultrasonography-guided biopsy of the prostate. *BJU Int* 2007; **100:** 536–8.
6. Sen S, *et al.* The analgesic effect of nitroglycerin added to lidocaine on intravenous regional anesthesia. *Anesth Analg* 2006; **102:** 916–20.

Peripheral vascular disease. In peripheral vascular disease (p.1178) nitrates have been tried as vasodilators and smooth muscle relaxants in order to improve resting blood flow. Glyceryl trinitrate has been applied topically in patients with Raynaud's syndrome[1-3] and in distal limb ischaemia[4] resulting in some benefit but this form of therapy is not widely used in these disorders.

1. Franks AG. Topical glyceryl trinitrate as adjunctive treatment in Raynaud's disease. *Lancet* 1982; **i:** 76–7.
2. Coppock JS, *et al.* Objective relief of vasospasm by glyceryl trinitrate in secondary Raynaud's phenomenon. *Postgrad Med J* 1986; **62:** 15–18.
3. Teh LS, *et al.* Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. *Br J Rheumatol* 1995; **34:** 636–41.
4. Fletcher S, *et al.* Locally applied transdermal nitrate patches for the treatment of ischaemic rest pain. *Int J Clin Pract* 1997; **51:** 324–5.

Pulmonary hypertension. Glyceryl trinitrate reduces total pulmonary resistance in most patients with pulmonary arterial hypertension (p.1179),[1,2] including when given by inhalation.[3] However, other vasodilators such as calcium-channel blockers, epoprostenol, or bosentan are generally preferred for long-term treatment.

1. Pearl RG, *et al.* Acute hemodynamic effects of nitroglycerin in pulmonary hypertension. *Ann Intern Med* 1983; **99:** 9–13.
2. Weir EK, *et al.* The acute administration of vasodilators in primary pulmonary hypertension. *Am Rev Respir Dis* 1989; **140:** 1623–30.
3. Goyal P, *et al.* Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease. *Br J Anaesth* 2006; **97:** 208–14.

Quinine oculotoxicity. Intravenous nitrate has been suggested for the management of quinine oculotoxicity (p.613) and its benefit may be due to an increase in retinal vascular bed flow.[1]

1. Moore D, *et al.* Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; **76:** 703.

Soft-tissue rheumatism. There is evidence from animal studies that nitric oxide plays an important role in tendon healing, and randomised studies in patients with tennis elbow (epicondylitis), Achilles tendinosis (tendinitis), and supraspinatus tendinosis showed enhanced subjective and objective recovery when a glyceryl trinitrate patch (releasing 1.25 mg over 24 hours) was applied over the area of tenderness once daily.[1] Glyceryl trinitrate has also been tried in musculoskeletal pain (see Pain, above). For the general management of soft-tissue rheumatism see p.13.

1. Murrell GAC. Using nitric oxide to treat tendinopathy. *Br J Sports Med* 2007; **41:** 227–31.

Variceal haemorrhage. The usual treatment in variceal haemorrhage (p.2346) is injection sclerotherapy or banding ligation which may be performed during the emergency endoscopy procedure. Where endoscopy is unavailable drug therapy may be used; it may also have a role when sclerotherapy fails and some have suggested that initial drug therapy may be preferable to sclerotherapy. Vasoconstrictors that are used include vasopressin and its analogue terlipressin, given with glyceryl trinitrate which counteracts the adverse cardiac effects of vasopressin while potentiating its beneficial effects on portal pressure; somatostatin is also used.

Prophylaxis of a first bleed in patients with portal hypertension is controversial since about 70% of patients who have varices will never bleed. It is postulated that a reduction in portal pressure to below 12 mmHg is necessary to reduce the incidence of variceal bleeding and that treatment with beta blockers alone does not achieve this. More effective drugs are being sought and isosorbide mononitrate (as adjunctive therapy with a beta blocker) is under investigation, both for prophylaxis of a first bleed[1,2] and in the prevention of rebleeding.[3] Early emergency treatment (before endoscopy) with terlipressin given intravenously and glyceryl trinitrate transdermally controlled bleeding and lowered mortality rates in patients with gastrointestinal bleeding and a history or clinical signs of cirrhosis.[4] However, use of oral isosorbide mononitrate with somatostatin infusion for acute variceal bleeding was less effective than somatostatin alone and induced more adverse effects.[5]

1. Angelico M, *et al.* Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. *Gastroenterology* 1993; **104:** 1460–5.
2. Merkel C, *et al.* Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Lancet* 1996; **348:** 1677–81.
3. Villanueva C, *et al.* Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996; **334:** 1624–9.
4. Levacher S, *et al.* Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* 1995; **346:** 865–8.
5. Junquera F, *et al.* Somatostatin plus isosorbide 5-mononitrate versus somatostatin in the control of acute gastro-oesophageal variceal bleeding: a double blind, randomised, placebo controlled clinical trial. *Gut* 2000; **46:** 127–32.

Venepuncture. Glyceryl trinitrate patches applied to skin adjacent to intravenous infusion sites are used in the prophylactic treatment of phlebitis and extravasation.[1]

Local application of glyceryl trinitrate 1 to 2 mg as ointment was found to be a useful aid to venepuncture in a study of 50 patients undergoing surgery,[2] but conflicting results have been reported in children and neonates.[3,4]

1. Tjon JA, Ansani NT. Transdermal nitroglycerin for the prevention of intravenous infusion failure due to phlebitis and extravasation. *Ann Pharmacother* 2000; **34:** 1189–92.
2. Hecker JF, *et al.* Nitroglycerine ointment as an aid to venepuncture. *Lancet* 1983; **i:** 332–3.
3. Vaksmann G, *et al.* Nitroglycerine ointment as aid to venous cannulation in children. *J Pediatr* 1987; **111:** 89–91.
4. Maynard EC, Oh W. Topical nitroglycerin ointment as an aid to insertion of peripheral venous catheters in neonates. *J Pediatr* 1989; **114:** 474–6.

Preparations

BP 2008: Glyceryl Trinitrate Sublingual Spray; Glyceryl Trinitrate Tablets; Glyceryl Trinitrate Transdermal Patches; ***USP 31:*** Nitroglycerin Injection; Nitroglycerin Ointment; Nitroglycerin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Dauxona; Enetege; Minitran†; Niglinar; Nitradisc†; Nitro-Dur; Nitroderm TTS; Nitrodom; Nitrogray; ***Austral.:*** Anginine; Lycinate; Minitran; Nitro-Dur; Nitrolingual; Rectogesic; Transiderm-Nitro; ***Austria:*** Cordiplast; Deponit; Minitran; Nitro; Nitro Mack; Nitro Pohl; Nitro-Dur; Nitroderm; Nitrolingual; Perlinganit; ***Belg.:*** Deponit; Diafusor; Minitran; Nitro-Dyl†; Nitroderm; Nitrolingual; Nysconitrine; Trinipatch; Willlong; ***Braz.:*** Nitradisc; Nitroderm TTS; Nitronal†; Tridil; ***Canad.:*** Gen-Nitro; Minitran; Nitro-Dur; Nitroject; Nitrol; Nitrolingual; Nitrong†; Nitrostat; Rho-Nitro; Transderm-Nitro; ***Chile:*** Angiolingual; Nitrocor; Nitroderm; Nitronal†; ***Cz.:*** Deponit†; Maycor Nitrospray†; Minitran†; Nit-Ret; Nitrangin†; Nitrilex†; Nitro Mack†; Nitro Pohl; Nitrolingual†; Nitromint; Perlinganit; Rectogesic; ***Denm.:*** Buccard; Discotrine; Glytrin; Nitrolingual; Nitromex; ***Fin.:*** Deponit; Minitran; Nitro; Nitromex; Perlinganit; Transiderm-Nitro; ***Fr.:*** Cordipatch; Diafusor; Discotrine; Epinitril; Lenitral†; Natispray; Nitriderm TTS; Rectogesic; Trinipatch; ***Ger.:*** Aquo-Trinitrosan; Corangin Nitrospray; Coro-Nitro†; Deponit; Gepan†; MinitranS; neos nitro OPT†; Nitrangin; Nitro Mack†; Nitro Solvay; Nitro-Pflaster-ratiopharm TL†; Nitroderm TTS; Nitrokor†; Nitrolingual; Perlinganit; Trinitrosan; ***Gr.:*** Cardiplast; Epinitril; Nitro Mack†; Nitrodyl; Nitrolingual; Nitrong; Nitroretard; Nitrosylon; Pancoran; Rectogesic; Sodemethin†; Supranitrin; Trinipatch; Trinitrine Simple Laleuf†; ***Hong Kong:*** Angised; Deponit; Lenitral†; Nitro Mack; Nitro Pohl†; Nitro-Dur; Nitrocine; Nitroderm TTS; Nitrolingual; Tridil†; ***Hung.:*** Nitro Pohl; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitromint; Perlinganit†; Sustac; ***India:*** Angised; Millisrol; Myonit; Myovin; Nitrocontin; Nitroderm TTS; Nitrogesic; Nitrolingual; ***Indon.:*** Nitrocine; Nitrokaf; ***Irl.:*** Deponit; Epinitril†; Glytrin; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin; Nitronal; Suscard; Sustac; Transiderm-Nitro; ***Israel:*** Angised†; Deponit; Nitrocine; Nitroderm TTS; Nitrolingual; Nitronal; Trinipatch†; ***Ital.:*** Adesitrin; Deponit; Dermatrans; Epinitril; Keritrina; Minitran; Natispray; Nitraket; Nitro-Dur; Nitrocor; Nitroderm TTS; Nitrosylon; Perganit; Top-Nitro; Triniplas; Trinitrina; Venitrin; ***Jpn:*** Millisrol; ***Malaysia:*** Deponit; Glytrin†; Nitrocine; Nitroderm; ***Mex.:*** Anglix; Cardinit; Minitran; Nitradisc; Nitro-Dur; Nitroder; Nitroderm TTS; ***Neth.:*** Deponit; Glytrin; Lenitral; Minitran; Nitro Pohl; Nitro-Dur; Nitrolingual; Transiderm-Nitro; Trinipatch; ***Norw.:*** Minitran; Nitro-Dur; Nitrolingual; Nitromex; Nitroven; Transiderm-Nitro; ***NZ:*** Anginine†; Glytrin; Lycinate; Minitran; Nitroderm; Nitrolingual; Nitronal; ***Philipp.:*** Deponit; Minitran; Nitrolingual; Nitronal; Nitrostat; Perlinganit; Transderm-Nitro; ***Pol.:*** Nitracor; Nitrocard; Nitroderm; Nitromint; Perlinganit; Sustonit; Trimonit; ***Port.:*** Dermatrans; Diafusor; Discotrine; Epinitril; Glytrin; Nitradisc; Nitro-Dur; Nitroderm TTS; Nitromint; Plastranit; Rectogesic; Trinipatch†; ***Rus.:*** Deponit (Депонит); Nirmin (Нирмин); Nitro (Нитро); Nitrocor (Нитрокор); Nitroject (Нитроджект); Nitromint (Нитроминт); Nitrong (Нитронг); Nitrospray (Нитроспрей); Perlinganit (Перлинганит); Sustac (Сустак); Sustonit (Сустонит); ***S.Afr.:*** Angised; Nitrocine; Nitrolingual; Tridil; ***Singapore:*** Angised; Deponit; Glytrin†; Nitro Mack†; Nitrocine; Rectogesic; ***Spain:*** Cordiplast; Dermatrans; Diafusor; Epinitril; Minitran; Nitradisc; Nitro-Dur; Nitroderm; Nitroplast; Solinitrina; Trinipatch; Trinispray; Vernies; ***Swed.:*** Glytrin; Minitran; Nitrolingual; Nitromex; Perlinganit†; Suscard; Transiderm-Nitro; ***Switz.:*** Deponit; Minitran; Nitro Mack; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitronal; Perlinganit; Trinitrine; ***Thai.:*** Amitacon†; Angised†; Glytrin; Nitro Mack†; Nitrocine; Nitroderm; Nitroject; ***Turk.:*** Deponit; Nitroderm TTS; Nitrolingual; Perlinganit; ***UAE:*** Cardispray†; ***UK:*** Coro-Nitro; Deponit; Glytrin; Minitran; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin; Nitronal; Percutol; Rectogesic; Suscard; Sustac†; Transiderm-Nitro; Trintek; ***USA:*** Minitran; Nitrek; Nitro-Bid; Nitro-Derm; Nitro-Dur; Nitro-Time; Nitrodisc; Nitrogard; Nitroglyn†; Nitrolingual; NitroMist; Nitrong†; NitroQuick; Nitrostat; NitroTab†; Transderm-Nitro; Transdermal-NTG; Tridil†; ***Venez.:*** Minitran†; Nitro Mack; Nitrocor; Nitroderm; Tridil†.

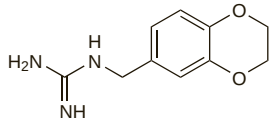
Multi-ingredient: ***Arg.:*** Trinitron; ***Austria:*** Myocardon; Percucor†; Spasmocor; ***Ger.:*** Nitrangin compositum†; ***Pol.:*** Pentaerythritol Compositum; ***Spain:*** Cafinitrina; ***USA:*** Emergent-Ez.

Guabenxan *(rINN)*

Guabenxán; Guabenxane; Guabenxanum. (1,4-Benzodioxan-6-ylmethyl)guanidine.

Гуабенксан

$C_{10}H_{13}N_3O_2$ = 207.2.
CAS — 19889-45-3.



Profile
Guabenxan is an antihypertensive with properties similar to guanethidine (below). It has been given orally as the sulfate.

Guanabenz Acetate *(USAN, rINNM)*

Acetato de guanabenzo; Guanabenz, Acétate de; Guanabenzi Acetas; NSC-68982 (guanabenz); Wy-8678 (guanabenz). (2,6-Dichlorobenzylideneamino)guanidine acetate.

Гуанабенза Ацетат

$C_8H_8Cl_2N_4,C_2H_4O_2$ = 291.1.
CAS — 5051-62-7 (guanabenz); 23256-50-0 (guanabenz acetate).