Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US*.
Ph. Eur. 6.2 (Isoprenaline Sulphate). A white or almost white crystalline powder. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.3 to 5.5. Store in airtight containers. Protect from light.
USP 31 (Isoproterenol Sulfate). A white to practically white, odourless, crystalline powder. It gradually darkens on exposure to light and air. Soluble 1 in 4 of water; very slightly soluble in alcohol, in chloroform, in ether, and in benzene. A 1% solution in water has a pH of about 5. Solutions become pink to brownish-pink on standing exposed to air, and almost immediately so when made alkaline. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407. Isoprenaline has almost exclusively beta-agonist properties but also stimulates the CNS; its main adverse effects include tachycardia and cardiac arrhythmias, palpitations, hypotension, tremor, headache, sweating, and facial flushing. Prolonged use of isoprenaline has been associated with swelling of the parotid glands.

Prolonged use of sublingual tablets may also cause severe damage to the teeth due to the acidic nature of the drug. Sublingual use or inhalation may colour the saliva or sputum red.

Increased mortality. For a discussion of the increased mortality and morbidity that has sometimes been observed in asthmatic patients using beta agonists and reference to an early epidemic associated with isoprenaline inhalers, see Fenoterol, p.1121.

Interactions

As for Sympathomimetics, p.1407. Due to the risk of arrhythmias, isoprenaline should not be used with other potent beta$_1$ agonists such as adrenaline.

Theophylline. For reports of increased theophylline clearance following use of isoprenaline, see p.1145.

Pharmacokinetics

As a result of sulfate conjugation in the gut, isoprenaline is considerably less active orally than after parenteral doses. It is absorbed through the oral mucosa and has accordingly been given sublingually, but absorption by this route remains very erratic. Isoprenaline in the body is resistant to metabolism by monoamine oxidase, but is metabolised by catechol-*O*-methyltransferase in the liver, lungs, and other tissues, the metabolite then being conjugated before excretion in the urine. Whereas the sulfate conjugate of isoprenaline is inactive the methylated metabolite exhibits weak activity.

After intravenous injection isoprenaline has a plasma half-life of about one to several minutes according to whether the rate of injection is rapid or slow; it is almost entirely excreted in the urine as unchanged drug and metabolites within 24 hours. A much slower onset of action and a more extended initial half-life has been found after oral dosage. Isoprenaline is reported to have a duration of action of up to about 2 hours after inhalation; it has been shown that a large proportion of an inhaled dose is swallowed.

◊ References.

1. Blackwell EW, *et al.* The fate of isoprenaline administered by pressurized aerosols. *Br J Pharmacol* 1970; **39:** 194P–195P.
2. Conolly ME, *et al.* Metabolism of isoprenaline in dog and man. *Br J Pharmacol* 1972; **46:** 458–72.
3. Blackwell EW, *et al.* Metabolism of isoprenaline after aerosol and direct intrabronchial administration in man and dog. *Br J Pharmacol* 1974; **50:** 587–91.
4. Reyes G, *et al.* The pharmacokinetics of isoproterenol in critically ill pediatric patients. *J Clin Pharmacol* 1993; **33:** 29–34.

Uses and Administration

Isoprenaline is a sympathomimetic (p.1408) that acts almost exclusively on beta-adrenergic receptors. It has a powerful stimulating action on the heart and increases cardiac output, excitability, and rate; it also causes peripheral vasodilatation and produces a fall in diastolic blood pressure and usually maintains or slightly increases systolic blood pressure. In addition, isoprenaline has bronchodilating properties. It also stimulates the CNS.

Isoprenaline has been used in a variety of cardiac disorders. It may be used for the temporary prevention or control of Stokes-Adams attacks and in severe bradycardia unresponsive to atropine, but use of a pacemaker is preferred. It has also been advocated as an adjunct for other cardiac disorders including shock (p.1183) and torsade de pointes (see Cardiac Arrhythmias, p.1160). It has been used in the diagnosis of congenital heart defects.

In the management of **cardiac disorders**, isoprenaline is usually given as the hydrochloride by slow intravenous infusion under ECG control. Infusion rates may range from 0.5 to 10 micrograms/minute depending on the clinical condition of the patient; 1 to 4 micrograms/minute may be adequate to correct bradycardia but rates of 4 to 8 micrograms/minute may be required for acute Stokes-Adams attacks. Isoprenaline hydrochloride can be given by intracardiac injection in extreme cases. It has also been given subcutaneously or intramuscularly in initial doses of 200 micrograms (as 1 mL of a 0.02% solution) and by slow intravenous injection in initial doses of 20 to 60 micrograms (as 1 to 3 mL of a 0.002% solution); doses are subsequently adjusted according to ventricular rate. Tablets of isoprenaline hydrochloride have been given orally or sublingually.

Isoprenaline has been used as a bronchodilator in the management of **reversible airways obstruction** but sympathomimetics with a selective action on beta$_2$ receptors, such as salbutamol, are now preferred (see Asthma, p.1108). It has been given as the sulfate or hydrochloride, usually by inhalation; sublingual tablets and intravenous injections have also been used.

Preparations

BP 2008: Isoprenaline Injection;
USP 31: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol; Isoproterenol Hydrochloride Inhalation Aerosol; Isoproterenol Hydrochloride Injection; Isoproterenol Hydrochloride Tablets; Isoproterenol Inhalation Solution; Isoproterenol Sulfate Inhalation Aerosol; Isoproterenol Sulfate Inhalation Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciapar†; Proterenal†; ***Austral.:*** Isuprel; ***Austria:*** Ingelan; ***Belg.:*** Isuprel; ***Cz.:*** Isuprel; ***Fr.:*** Isuprel; ***Ger.:*** Ingelan†; ***Gr.:*** Isuprel†; Saventrine†; ***Hung.:*** Isuprel†; ***India:*** Autohaler†; Isolin; ***Indon.:*** Isuprel; ***Irl.:*** Saventrine†; ***Israel:*** Isuprel; ***NZ:*** Isuprel; ***S.Afr.:*** Imuprel; Lenoprel†; ***Singapore:*** Isuprel†; Saventrine†; ***Spain:*** Aleudrina; ***Thai.:*** Isuprel; ***USA:*** Isuprel; Medihaler-Iso.

Multi-ingredient: ***Arg.:*** Zantril†; ***Austria:*** Ingelan; ***Ger.:*** Ingelan†; ***Mex.:*** Isobutil†; ***Port.:*** Prelus†; ***Spain:*** Aldo Asma; Frenal Compositum; ***USA:*** Norisodrine with Calcium Iodide.

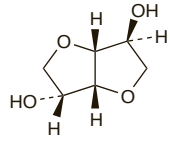
Isosorbide *(BAN, USAN, rINN)* ⊗

AT-101; Isosorbida; Isosorbidum; NSC-40725. 1,4:3,6-Dianhydro-D-glucitol.

Изосорбид

$C_6H_{10}O_4$ = 146.1.

CAS — 652-67-5.



Pharmacopoeias. In *Jpn.*
US includes Isosorbide Concentrate.
USP 31 (Isosorbide Concentrate). An aqueous solution containing 70.0 to 80.0% w/w of isosorbide. A colourless to slightly yellow liquid. Soluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Isosorbide is an osmotic diuretic with properties similar to those of mannitol (p.1330). It is reported to cause less nausea and vomiting than other oral osmotic diuretics.

Isosorbide is used for short-term reduction of intra-ocular pressure in acute glaucoma or prior to surgery (p.1873). The usual oral dose is 1 to 3 g/kg 2 to 4 times daily. The onset of action is usually within 30 minutes and lasts for up to 5 or 6 hours.

Preparations

USP 31: Isosorbide Concentrate; Isosorbide Oral Solution.

Proprietary Preparations (details are given in Part 3)
Mex.: Biordyn; ***USA:*** Ismotic.

Isosorbide Dinitrate *(BAN, USAN, rINN)*

Dinitrato de isosorbida; ISDN; Isosorbid dinitrát; Isosorbiddinitrat; Isosorbide, dinitrate d'; Isosorbidi dinitras; Isosorbididinitraatti; Izosorbid Dinitrat; Izosorbido dinitratas; Izosorbidu diazotan; Izoszorbid-dinitrát; Sorbide Nitrate. 1,4:3,6-Dianhydro-D-glucitol 2,5-dinitrate.

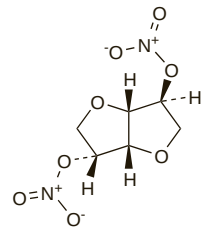
Изосорбида Динитрат

$C_6H_8N_2O_8$ = 236.1.

CAS — 87-33-2.

ATC — C01DA08; C05AE02.

ATC Vet — QC01DA08; QC05AE02.



Pharmacopoeias. In *Chin.* and *Jpn.*
Eur. (see p.vii), *Int.*, and *US* include diluted isosorbide dinitrate.
Ph. Eur. 6.2 (Isosorbide Dinitrate, Diluted). A dry mixture of isosorbide dinitrate and lactose monohydrate or mannitol. The solubility of the diluted product depends on the diluent and its concentration. Protect from light.
Undiluted isosorbide dinitrate is a fine, white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone.
USP 31 (Diluted Isosorbide Dinitrate). A dry mixture of isosorbide dinitrate (usually about 25%) with lactose, mannitol, or other suitable inert excipients, the latter being added to minimise the risk of explosion. It may contain up to 1% of a suitable stabiliser such as ammonium phosphate. It is an ivory-white, odourless powder. Store in airtight containers.
Undiluted isosorbide dinitrate occurs as white crystalline rosettes. Very slightly soluble in water; sparingly soluble in alcohol; very soluble in acetone; freely soluble in chloroform.

Handling. Undiluted isosorbide dinitrate may explode if subjected to percussion or excessive heat.

Stability. The loss of isosorbide dinitrate from solution during infusion was found to be 30% with PVC plastic intravenous infusion sets but negligible when polyolefin or glass delivery systems were used.[1] Another study reported a 23% decrease in isosorbide dinitrate concentration after 24 hours of storage at 21° in PVC containers; most of the loss occurred in the first 6 hours. Loss of potency was not noted when isosorbide dinitrate was stored under similar conditions in glass bottles or polyethylene, nylon, and polypropylene laminated bags.[2]

1. Kowaluk EA, *et al.* Drug loss in polyolefin infusion systems. *Am J Hosp Pharm* 1983; **40:** 118–19.
2. 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.

Adverse Effects, Treatment, and Precautions

As for Glyceryl Trinitrate, p.1296.

Effects on the blood. Haemolysis occurred in 2 patients with G6PD deficiency during treatment with isosorbide dinitrate.[1]

1. Aderka D, *et al.* Isosorbide dinitrate-induced hemolysis in G6PD-deficient subjects. *Acta Haematol (Basel)* 1983; **69:** 63–4.

Headache. The most common adverse effect of nitrate therapy is headache which usually decreases after a few days. There has been a report[1] of a severe continuous unilateral headache with an oculosympathetic paresis on the same side associated with isosorbide dinitrate therapy.

1. Mueller RA, Meienberg O. Hemicrania with oculosympathetic paresis from isosorbide dinitrate. *N Engl J Med* 1983; **308:** 458–9.

Hypersensitivity. Laryngeal oedema developed on two occasions in a woman after the use of isosorbide dinitrate spray;[1] nifedipine was also given sublingually which on the second occasion caused a noticeable increase in the laryngeal swelling induced by the nitrate.

1. Silfvast T, *et al.* Laryngeal oedema after isosorbide dinitrate spray and sublingual nifedipine. *BMJ* 1995; **311:** 232.

Nitrate tolerance. Continuous use of organic nitrates is associated with tolerance to their haemodynamic effects; for an overview of nitrate tolerance, see under Precautions for Glyceryl Trinitrate, p.1297.