Tocainide Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tocainida; Tocaïnide, Chlorhydrate de; Tocainidi Hydrochloridum.

Токаинида Гидрохлорид

$C_{11}H_{16}N_2O,HCl$ = 228.7.

CAS — 35891-93-1.

ATC — C01BB03.

ATC Vet — QC01BB03.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Tocainide Hydrochloride). A fine, white, odourless powder. Freely soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Profile

Tocainide is a class Ib antiarrhythmic (p.1153) with similar properties to mexiletine (p.1339); like mexiletine it is structurally related to lidocaine (p.1862). Tocainide hydrochloride has been given orally and intravenously in the management of ventricular arrhythmias but severe haematological and pulmonary toxicity limit its use.

◊ General references.

1. Holmes B, *et al.* Tocainide: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1983; **26:** 93–123.

Preparations

USP 31: Tocainide Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Ger.: Xylotocan†; ***USA:*** Tonocard†.

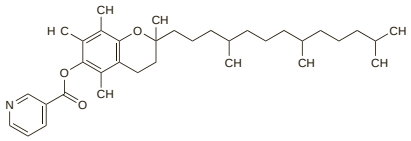
Tocoferil Nicotinate

Tocoferilo, nicotinato de; Tocopheryl Nicotinate; Vitamin E Nicotinate. (±)-α-Tocopherol nicotinate.

Токоферола Никотинат

$C_{35}H_{53}NO_3$ = 535.8.

CAS — 51898-34-1; 16676-75-8.



Pharmacopoeias. In *Jpn.*

Profile

Tocoferil nicotinate is a lipid regulating drug and a vasodilator. It is used in the treatment of hyperlipidaemias (p.1169), and in peripheral (p.1178) and cerebral vascular disorders (p.1165). The usual oral dose is 100 to 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: Hijuven; ***Indon.:*** Enico; ***Jpn:*** Juvela; ***Malaysia:*** Hijuven; ***Philipp.:*** Hijuven; ***Port.:*** Nicojuvel†; Reoferol.

Multi-ingredient: ***Arg.:*** Anaphase; ***Fr.:*** Anaphase; ***Ital.:*** Evitex; ***Spain:*** Evitex A E Fuerte.

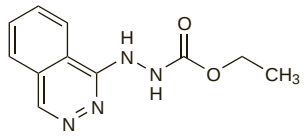
Todralazine Hydrochloride *(BANM, pINNM)*

BT-621; CEPH; Ecarazine Hydrochloride; Hidrocloruro de todralazina; Todralazine, Chlorhydrate de; Todralazini Hydrochloridum; Todralazyny chlorowodorek. Ethyl 3-(phthalazin-1-yl)carbazate hydrochloride monohydrate.

Тодралазина Гидрохлорид

$C_{11}H_{12}N_4O_2,HCl,H_2O$ = 286.7.

CAS — 14679-73-3 (todralazine); 3778-76-5 (anhydrous todralazine hydrochloride).



(todralazine)

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Todralazine hydrochloride is an antihypertensive structurally related to hydralazine (p.1305) and with similar properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Pol.: Binazin.

Tolazoline Hydrochloride *(BANM, rINNM)*

Benzazoline Hydrochloride; Hidrocloruro de tolazolina; Tolazol. Hydrochlor;; Tolazoline, Chlorhydrate de; Tolazolini Hydrochloridum; Tolazolinium Chloratum. 2-Benzyl-2-imidazoline hydrochloride.

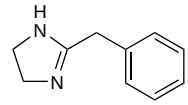
Толазолина Гидрохлорид

$C_{10}H_{12}N_2,HCl$ = 196.7.

CAS — 59-98-3 (tolazoline); 59-97-2 (tolazoline hydrochloride).

ATC — C04AB02; M02AX02.

ATC Vet — QC04AB02; QM02AX02.



(tolazoline)

NOTE. Do not confuse with benazoline (see Metizoline, p.1565), which is a sympathomimetic vasoconstrictor, or with benazolin, which is a herbicide.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Tolazoline Hydrochloride). A white to off-white, crystalline powder. Its solutions are slightly acid to litmus. Soluble 1 in less than 1 of water, 1 in 2 of alcohol, 1 in 3 of chloroform, and 1 in 10 000 of ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects

Adverse effects of tolazoline include piloerection, headache, flushing, tachycardia, cardiac arrhythmias, tingling, chilliness, shivering, sweating, nausea, vomiting, diarrhoea, and epigastric pain. Orthostatic hypotension or marked hypertension may occur, especially with large doses. Tolazoline stimulates gastric acid and may exacerbate peptic ulcer disease. Oliguria, haematuria, myocardial infarction, gastrointestinal haemorrhage, thrombocytopenia and other blood dyscrasias have been reported.

Intra-arterial injection has been followed by a burning sensation in the limb.

Effects in the neonate. Hypochloraemic metabolic alkalosis,[1] acute renal failure,[2] and duodenal perforation[3] have been reported in neonates given tolazoline.

1. Adams JM, *et al.* Hypochloremic metabolic alkalosis following tolazoline-induced gastric hypersecretion. *Pediatrics* 1980; **65:** 298–300.
2. Trompeter RS, *et al.* Tolazoline and acute renal failure in the newborn. *Lancet* 1981; **i:** 1219.
3. Wilson RG, *et al.* Duodenal perforation associated with tolazoline. *Arch Dis Child* 1985; **60:** 878–9.

Treatment of Adverse Effects

In the event of overdosage hypotension is best treated by keeping the patient recumbent with the head lowered. If necessary the circulation may be maintained by infusion of suitable electrolyte solutions. Hypotension may be treated with ephedrine. Adrenaline is not suitable for the reversal of hypotension induced by alpha blockers since it may exacerbate the hypotension by stimulating beta receptors.

Precautions

Tolazoline should not be given to patients with hypotension and when used for peripheral vascular disease should be avoided in ischaemic heart disease or after a cerebrovascular accident. Since tolazoline stimulates gastric secretion of hydrochloric acid it may activate stress ulcers and may cause significant hypochloraemic alkalosis. Pretreatment of infants with antacids may prevent gastrointestinal bleeding, although use of intravenous ranitidine is not recommended (see below under Interactions). Tolazoline should not be used in the presence of peptic ulcer disease and should be used with caution in patients with mitral stenosis.

Interactions

Tolazoline should not be used with sympathomimetics such as adrenaline since the hypotensive effect may be potentiated due to unopposed beta-adrenoceptor stimulation. Tolazoline may cause a disulfiram-like reaction if given with alcohol.

Ranitidine. Intravenous ranitidine reversed the falls in pulmonary and systemic vascular resistances in 12 children who had been given tolazoline as a pulmonary vasodilator.[1]

1. Bush A, *et al.* Cardiovascular effects of tolazoline and ranitidine. *Arch Dis Child* 1987; **62:** 241–6.

Sympathomimetics. For a report of fatal hypotension associated with the use of tolazoline with *dopamine*, see Vasodilators under the Interactions of Sympathomimetics, p.1408.

Pharmacokinetics

Tolazoline is absorbed from the gastrointestinal tract. It is more rapidly absorbed after intramuscular injection. An elimination half-life in neonates of 3 to 13 hours has been reported after intravenous use, although it may be as high as about 40 hours and is inversely related to urine output. Tolazoline is rapidly excreted in the urine, largely unchanged.

Uses and Administration

Tolazoline hydrochloride is a vasodilator that has a direct dilator action on the peripheral blood vessels. It has some alpha-adrenoceptor blocking activity and also stimulates smooth muscle in the gastrointestinal tract, increases gastrointestinal secretion, can cause mydriasis, and has a stimulant effect on the heart.

Tolazoline hydrochloride is used intravenously to reduce pulmonary artery pressure in persistent pulmonary hypertension in neonates with persistent fetal circulation (see below). It has been used orally and by subcutaneous, intramuscular, intravenous, or slow intra-arterial injection in the treatment of peripheral vascular disease. It has also been given in some ophthalmic conditions.

Pulmonary hypertension. Tolazoline and other vasodilators have been tried in persistent pulmonary hypertension in the newborn (p.1179) in an attempt to induce selective pulmonary vasodilatation and improve gas exchange. The response is variable and often unsuccessful due to concomitant systemic hypotension, a failure to achieve or sustain pulmonary vasodilatation, and adverse effects, and other therapies such as high-frequency oscillatory ventilation, extracorporeal membrane oxygenation, and inhaled nitric oxide are now more widely used.

The loading dose for pulmonary hypertension in neonates that has been recommended by licensed product information is 1 to 2 mg/kg over 5 to 10 minutes by intravenous infusion; this is then followed by doses of up to 1 to 2 mg/kg per hour. Infants with reduced urine output may require lower maintenance doses. The high incidence of adverse effects has, however, led to several studies investigating the use of lower doses. One group suggested that a loading dose of 500 micrograms/kg given intravenously followed by a continuous infusion of 500 micrograms/kg per hour was more appropriate and safer than standard doses.[1] In a retrospective study[2] of extremely preterm infants (mean gestational age 24 weeks) with severe hypoxaemia (possibly attributable to persistent pulmonary hypertension), tolazoline was given as a slow bolus infusion, with most patients receiving a dose of 0.5 to 1 mg/kg; some required further doses.

Tolazoline has also been given via the endotracheal route,[3,4] although as it is acid in solution it may contribute to alveolar injury. In a study[4] of 12 neonates with gestational age ranging from 25 to 42 weeks, endotracheal tolazoline at doses from 1 to 2.5 mg/kg was found to cause no adverse systemic effects.

The *BNFC* gives a dose of 1 mg/kg by slow intravenous injection, followed by 200 micrograms/kg per hour by infusion if necessary. It warns that doses in excess of 300 micrograms/kg per hour are associated with cardiotoxicity and renal failure. A suggested dose for endotracheal use is 200 micrograms/kg diluted in 0.5 to 1 mL of sodium chloride 0.9%.

1. Monin P, *et al.* Treatment of persistent fetal circulation syndrome of the newborn: comparison of different doses of tolazoline. *Eur J Clin Pharmacol* 1987; **31:** 569–73.
2. Nuntnarumit P, *et al.* Efficacy and safety of tolazoline for treatment of severe hypoxemia in extremely preterm infants. *Pediatrics* 2002; **109:** 852–6.
3. Welch JC, *et al.* Endotracheal tolazoline for severe persistent pulmonary hypertension of the newborn. *Br Heart J* 1995; **73:** 99–100.
4. Parida SK, *et al.* Endotracheal tolazoline administration in neonates with persistent pulmonary hypertension. *J Perinatol* 1997; **17:** 461–4.

Preparations

USP 31: Tolazoline Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Cz.: Divascol; ***Gr.:*** Priscol†; Priscoline†.

Multi-ingredient: ***Switz.:*** Lunadon.

Torasemide *(BAN, rINN)* ⊗

AC-4464; BM-02015; Torasemid; Torasemid bezvodý; Torasemid, vattenfri; Torasemida; Torasémide; Torasémide anhydre; Torasemidi; Torasemidi, vedetön; Torasemidum; Torasemidum anhydricum; Torazemidas, bevandenis; Torsemide *(USAN).* 1-Isopropyl-3-(4-*m*-toluidinopyridine-3-sulphonyl)urea.

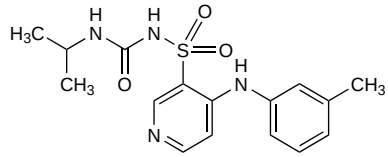
Торасемид

$C_{16}H_{20}N_4O_3S$ = 348.4.

CAS — 56211-40-6 (torasemide); 72810-59-4 (torasemide sodium).

ATC — C03CA04.

ATC Vet — QC03CA04.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Torasemide, Anhydrous). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol. It is sparingly soluble in dilute solu-