Diprenorphine Hydrochloride *(BANM, rINNM)*

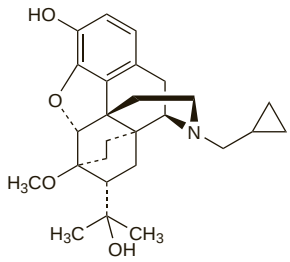
Diprénorphine, Chlorhydrate de; Diprenorphini Hydrochloridum; Hidrocloruro de diprenorfina; M-5050. (6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-(1-hydroxy-1-methylethyl)-6-*O*-methyl-6,14-ethano-17-normorphine hydrochloride; 2-[(–)-(5*R*,6*R*,7*R*,14*S*)-9a-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]propan-2-ol hydrochloride.

Дипренорфина Гидрохлорид

$C_{26}H_{35}NO_4$,HCl = 462.0.

CAS — 14357-78-9 (diprenorphine); 16808-86-9 (diprenorphine hydrochloride).

ATC Vet — QV03AB92.



(diprenorphine)

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Diprenorphine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 4.5 to 6.0. Protect from light.

Profile

Diprenorphine hydrochloride is an opioid antagonist used in veterinary medicine to reverse the effects of etorphine hydrochloride.

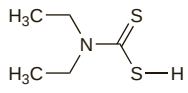
Ditiocarb Sodium *(rINN)*

DDTC; Dithiocarb Sodium; Ditiocarbe Sodique; Ditiocarbo sódico; Ditiocarbum Natricum; DTC; Sodium Diethyldithiocarbamate; Sodu dietyloditiokarbaminian; U-14624.

Дитиокарб Натрий

$C_5H_{10}NNaS_2$ = 171.3.

CAS — 148-18-5.



(ditiocarb)

Profile

Ditiocarb sodium is a chelator that has been used in nickel carbonyl poisoning. Disulfiram (p.2296), which is rapidly metabolised to ditiocarb, has been used as an alternative. Ditiocarb has also been used in the destruction of cisplatin wastes (see Handling and Disposal, p.699). It also has immunomodulating properties and has been investigated in HIV infection.

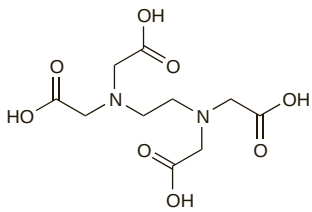
Edetic Acid *(BAN, rINN)*

Acide Édétique; Ácido edético; Acidum edeticum; Edathamil; Edetiinihappo; Edetinsyra; Edeto rūgštis; EDTA; Etiléndiamintetraecetsav; Kwas edetynowy; Kyselina edetová; Tetracemic Acid. Ethylenediaminetetra-acetic acid.

Эдетовая Кислота

$C_{10}H_{16}N_2O_8$ = 292.2.

CAS — 60-00-4.



Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF*.

Ph. Eur. 6.2 (Edetic Acid). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 26 (Edetic Acid). A white crystalline powder. Very slightly soluble in water; soluble in solutions of alkali hydroxides.

Incompatibility. Edetic acid and its salts chelate bivalent and trivalent metals and may affect the activity of drugs such as zinc insulin that contain such ions. Although edetates may enhance the antimicrobial efficacy of some disinfectants (see Chloroxylenol, p.1640), other preservatives may be inactivated. For reference to the inactivation of phenylmercuric salts by disodium edetate, see Incompatibility, under Phenylmercuric Nitrate, p.1657. For a report of edetates reducing the antimicrobial efficacy of thiomersal, see Incompatibility, p.1664.

Adverse Effects and Precautions

Edetic acid, used as a pharmaceutical excipient, is generally well tolerated. Adverse effects have been reported after inhalation of solutions containing edetic acid.

Asthma. Inhalation of an ipratropium nebuliser solution that contained edetic acid as one of the preservatives caused bronchoconstriction in 6 of 22 patients with asthma.[1] Inhalation of edetic acid alone produced dose-related bronchoconstriction that persisted for more than 1 hour.

1. Beasley CRW, *et al*. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *BMJ* 1987; **294:** 1197–8.

Blood testing. Pseudothrombocytopenia due to platelet clumping is a recognised complication of the use of edetates as anticoagulants for blood sampling and may lead to diagnostic errors.[1] The mechanism appears to be antibody-mediated. Alternative anticoagulants have been suggested.[1,2]

1. Bizzaro N. EDTA-dependent pseudothrombocytopenia: a clinical and epidemiological study of 112 cases, with 10-year follow-up. *Am J Hematol* 1995; **50:** 103–9.
2. Lippi U, *et al.* EDTA-induced platelet aggregation can be avoided by a new anticoagulant also suitable for automated complete blood count. *Haematologica* 1990; **75:** 38–41.

Uses

Edetic acid and its salts are chelators and are used in pharmaceutical manufacturing as well as having other industrial applications. They are also used as anticoagulants for blood taken for haematological investigations. Salts of edetic acid that are used clinically include sodium edetate (p.1463), sodium calcium edetate (p.1462), dicobalt edetate (p.1443), and sodium feredetate (p.1962).

Gallstones. Edetic acid has been suggested as a possible solvent for non-cholesterol gallstones (p.2409).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***USA:*** Clear Eyes Contact Lens Relief; Summers Eve Post-Menstrual; Triv; Zonite.

Flumazenil *(BAN, USAN, rINN)*

Flumatseniili; Flumazénil; Flumazenilis; Flumazenilum; Flumazepil; Ro-15-1788; Ro-15-1788/000. Ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate.

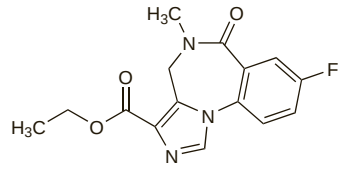
Флумазенил

$C_{15}H_{14}FN_3O_3$ = 303.3.

CAS — 78755-81-4.

ATC — V03AB25.

ATC Vet — QV03AB25.



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

Ph. Eur. 6.2 (Flumazenil). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in dichloromethane; sparingly soluble in methyl alcohol.

USP 31 (Flumazenil). A white to off-white powder. Practically insoluble in water; slightly soluble in acidic aqueous solutions. Store in airtight containers.

Adverse Effects and Precautions

The adverse effects experienced during use of flumazenil are generally due to the reversal of benzodiazepine effects and resemble benzodiazepine withdrawal symptoms (see p.987). Nausea, vomiting, dizziness, blurred vision, headache, and flushing may occur. Anxiety, fear, and agitation have been reported after too rapid reversal of sedation. There have been reports of seizures, especially in epileptics. Transient increases in blood pressure and heart rate have been observed. Hypersensitivity reactions have occurred rarely. Patients who have received benzodiazepines for prolonged periods are particularly at risk of experiencing withdrawal symptoms and rapid injection of flumazenil should be avoided in such patients.

Because of its short duration of action, patients given flumazenil to reverse benzodiazepine-induced sedation should be kept under close observation; further doses of flumazenil may be necessary. Flumazenil is contra-indicated in patients who are receiving benzodiazepines to control potentially life-threatening conditions and should not be given to epileptic patients who have been receiving benzodiazepines for a prolonged period to control seizures.

In cases of mixed overdose, flumazenil may unmask adverse effects of other psychotropic drugs. In particular, it should not be used in the presence of severe intoxication with tricyclic and related antidepressants.

Flumazenil should not be given to patients who have received neuromuscular blockers until the effects of neuromuscular blockade have fully cleared. Dosage should be adjusted individually; in high-risk or anxious patients, and after major surgery, it may be preferable to maintain some sedation during the early postoperative period. Flumazenil should be used with caution in patients with head injury since it may precipitate seizures or alter cerebral blood flow.

Careful titration of dosage is recommended in hepatic impairment.

◊ Cardiac arrhythmias,[1] sometimes preceded by tonic-clonic (grand mal) seizures[2,3] and occasionally fatal,[2] have been reported in several patients after the use of flumazenil for mixed overdoses with benzodiazepines and other psychotropics. Heart block has also been reported[4] after flumazenil use in a patient who had taken benzodiazepines, paracetamol, nifedipine, and atenolol. Death from refractory tonic-clonic seizures has been reported in a patient[5] after the use of flumazenil for a mixed overdose with a benzodiazepine and a tricyclic antidepressant.

Death from respiratory failure occurred in an 83-year-old woman after sedation with midazolam[6] despite use of flumazenil, although some[7] considered that this did not represent a failure by flumazenil to reverse the depressive effects on respiration of midazolam. Ventricular fibrillation followed by asystole and death has been reported in a patient given flumazenil during weaning from assisted ventilation (a period during which diazepam had been given).[8]

1. Short TG, *et al.* Ventricular arrhythmia precipitated by flumazenil. *BMJ* 1988; **296:** 1070–1.
2. Burr W, *et al.* Death after flumazenil. *BMJ* 1989; **298:** 1713.
3. Marchant B, *et al.* Flumazenil causing convulsions and ventricular tachycardia. *BMJ* 1989; **299:** 860.
4. Herd B, Clarke F. Complete heart block after flumazenil. *Hum Exp Toxicol* 1991; **10:** 289.
5. Haverkos GP, *et al.* Fatal seizures after flumazenil administration in a patient with mixed overdose. *Ann Pharmacother* 1994; **28:** 1347–9.
6. Lim AG. Death after flumazenil. *BMJ* 1989; **299:** 858–9. Correction. *ibid.*: 1531.
7. Birch BRP, Miller RA. Death after flumazenil? *BMJ* 1990; **300:** 467–8.
8. Katz Y, *et al.* Cardiac arrest associated with flumazenil. *BMJ* 1992; **304:** 1415.

Effects on mental function. Although flumazenil is considered to lack agonist properties, a study[1] in healthy subjects found that intravenous flumazenil resulted in impairment of some measures of cognition and alertness. A severe acute psychotic disorder, which developed during treatment with flumazenil in a patient with hepatic encephalopathy, resolved when flumazenil was discontinued.[2]

1. Neave N, *et al.* Dose-dependent effects of flumazenil on cognition, mood, and cardio-respiratory physiology in healthy volunteers. *Br Dent J* 2000; **189:** 668–74.
2. Seebach J, Jost R. Flumazenil-induced psychotic disorder in hepatic encephalopathy. *Lancet* 1992; **339:** 488–9.

Pharmacokinetics

Flumazenil is well absorbed from the gastrointestinal tract but undergoes extensive first-pass hepatic metabolism and has a systemic bioavailability of about 20%. It is about 50% bound to plasma proteins. After intravenous administration it is extensively metabolised in the liver to the inactive carboxylic acid form, which is excreted mainly in the urine. The elimination half-life