reduced by urinary alkalinisers, which may enhance or prolong their effects; excretion is increased by urinary acidifiers.

Amfetamines may delay the absorption of ethosuximide, phenobarbital, and phenytoin. The stimulant effects of amfetamines are inhibited by chlorpromazine, haloperidol, and lithium. Disulfiram may inhibit the metabolism and excretion of amfetamines.

Use of sympathomimetics with volatile liquid anaesthetics such as halothane is associated with an increased risk of cardiac arrhythmias.

Pharmacokinetics

Amfetamines are readily absorbed from the gastrointestinal tract and are distributed into most body tissues with high concentrations in the brain and CSF. They are partially metabolised in the liver but a considerable fraction may be excreted in the urine unchanged. Urinary elimination is pH-dependent and enhanced in acid urine. Amfetamines are distributed into breast milk.

◊ References.

1. Steiner E, *et al*. Amphetamine secretion in breast milk. *Eur J Clin Pharmacol* 1984; **27:** 123–4.
2. de la Torre R, *et al*. Clinical pharmacokinetics of amfetamine and related substances: monitoring in conventional and non-conventional matrices. *Clin Pharmacokinet* 2004; **43:** 157–85.
3. Ilett KF, *et al*. Transfer of dexamphetamine into breast milk during treatment for attention deficit hyperactivity disorder. *Br J Clin Pharmacol* 2007; **63:** 371–5.

Uses and Administration

Dexamfetamine, the dextrorotatory isomer of amfetamine, is an indirect-acting sympathomimetic with alpha- and beta-adrenergic agonist activity. It has a marked stimulant effect on the CNS, particularly the cerebral cortex.

Dexamfetamine is used in the treatment of narcolepsy (p.2148). It is also used in the treatment of attention deficit hyperactivity disorder (p.2148); in the UK, this use is limited to refractory hyperactivity disorders in children. Dexamfetamine has been given in the treatment of obesity (p.2149), although amfetamines are no longer recommended for this indication. Amfetamines have also been used to overcome fatigue but, again, such use is considered undesirable. In some countries dexamfetamine has been tried for motion sickness (p.1700), but safer drugs are available.

Dexamfetamine is generally used as the sulfate and is given by mouth.

In the treatment of **narcolepsy**, the usual initial dose is 5 to 10 mg daily in divided doses, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily. The lower initial dose of 5 mg daily is recommended for the elderly and any weekly increments should also be restricted to 5 mg in such patients.

In children with **hyperactivity** individualisation of treatment is especially important. Children aged 6 years and over usually start with a dose of 5 mg once or twice daily; the dose may be increased if necessary by 5 mg at weekly intervals to an upper limit of 20 mg daily, although older children might require up to 40 mg or more daily. Although dexamfetamine is licensed for the treatment of children younger than 6 years of age in some countries, including the UK and the USA, many authorities consider that stimulants should not be used in young children.

In the USA, an immediate-release, combination preparation containing dexamfetamine sulfate and saccharate, with amfetamine sulfate and amfetamine aspartate monohydrate (*Adderall*, *Shire*), is licensed for the treatment of narcolepsy and attention deficit hyperactivity disorder. This formulation is given by mouth in doses similar to those for dexamfetamine (see above). A modified-release formulation is also available for the treatment of attention deficit hyperactivity disorder in adults and children. The initial dose in adults is 20 mg of total amfetamine salts once daily. In children, it is given as for dexamfetamine in initial doses of 10 mg of total amfetamine salts once daily increased gradually up to a maximum of 30 mg daily; in older children aged 13 to 17 years the dose may be increased to a maximum of 20 mg once daily after 1 week if necessary.

Preparations

BP 2008: Dexamfetamine Tablets.

Proprietary Preparations (details are given in Part 3)
Canad.: Dexedrine; ***Switz.:*** Dexamin†; ***UK:*** Dexedrine; ***USA:*** Dexedrine; Dextrostat.

Multi-ingredient: ***Canad.:*** Adderall; ***USA:*** Adderall.

Dexfenfluramine Hydrochloride ⊗

(BANM, USAN, rINNM) ⊗

Deksfenfluramiinihydrokloridi; Dexfenfluramine, Chlorhydrate de; Dexfenfluraminhydroklorid; Dexfenfluramini Hydrochloridum; Hidrocloruro de dexfenfluramina; S-5614 (dexfenfluramine). (*S*)-*N*-Ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride.

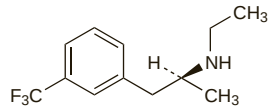
Дексфенфлурамина Гидрохлорид

$C_{12}H_{16}F_3N$,HCl = 267.7.

CAS — 3239-44-9 (dexfenfluramine); 3239-45-0 (dexfenfluramine hydrochloride).

ATC — A08AA04.

ATC Vet — QA08AA04.



(dexfenfluramine)

Profile

Dexfenfluramine is the *S*-isomer of fenfluramine (p.2156). It stimulates the release of serotonin and selectively inhibits its reuptake, but differs from fenfluramine in not possessing any catecholamine agonist activity.

Dexfenfluramine was formerly given orally as the hydrochloride in the treatment of obesity but, like fenfluramine, was withdrawn worldwide after reports of valvular heart defects.

Porphyria. Dexfenfluramine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Isolipan†; ***Hung.:*** Isolipan†.

Dexmethylphenidate Hydrochloride

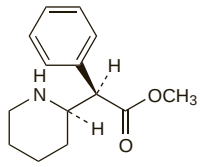
(USAN, rINNM) ⊗

Dexméthylphénidate, Chlorhydrate de; Dexmethylphenidati Hydrochloridum; d-MPH; Hidrocloruro de dexmetilfenidato; *d-threo*-Methylphenidate; *d*-Methylphenidate Hydrochloride. Methyl (2*R*)-phenyl[(2*R*)-piperidin-2-yl]acetate hydrochloride.

Дексметилфенидата Гидрохлорид

$C_{14}H_{19}NO_2$,HCl = 269.8.

CAS — 40431-64-9 (dexmethylphenidate); 19262-68-1 (dexmethylphenidate hydrochloride).



(dexmethylphenidate)

Profile

Dexmethylphenidate hydrochloride is the *d-threo*-enantiomer of racemic methylphenidate hydrochloride (p.2159). It is used as a central stimulant in the treatment of attention deficit hyperactivity disorders.

Dexmethylphenidate hydrochloride is licensed for use in children aged 6 years and older. For patients new to methylphenidate the starting dose of dexmethylphenidate hydrochloride is 2.5 mg twice daily. Each dose should be given at least four hours apart. Dosage may be adjusted in 2.5 to 5 mg increments weekly to a maximum of 10 mg twice daily.

For patients currently using methylphenidate the starting dose of dexmethylphenidate hydrochloride is half the dose of the racemic substance. The maximum recommended dose is 10 mg twice daily.

A modified-release formulation is also available for once-daily dosing.

Dexmethylphenidate should be stopped if there is no improvement in symptoms after appropriate adjustments in dosage over one month. It also needs to be stopped from time to time in those who do respond to assess the patient's condition.

◊ References.

1. Robinson DM, Keating GM. Dexmethylphenidate extended release: in attention-deficit hyperactivity disorder. *Drugs* 2006; **66:** 661–8.

Preparations

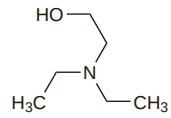
Proprietary Preparations (details are given in Part 3)
USA: Focalin.

Diethylaminoethanol ⊗

Dietilaminoetanol. 2-Diethylaminoethanol.

$C_6H_{15}NO$ = 117.2.

CAS — 100-37-8.



Profile

Diethylaminoethanol is an analogue of deanol (p.2152) and has been used similarly as the malate. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Gr.: Durobion.

Multi-ingredient: ***Austria:*** Barokaton.

Diethylpropion Hydrochloride *(BANM)* ⊗

Amfepramone Hydrochloride *(pINNM)*; Amfépramone, Chlorhydrate d'; Amfepramoni Hydrochloridum; Hidrocloruro de anfepramona. *N*-(1-Benzoylethyl)-*NN*-diethylammonium chloride; 2-Diethylaminopropiophenone hydrochloride; (*RS*)-α-Diethylaminopropiophenone hydrochloride.

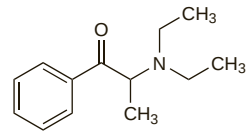
Амфепрамона Гидрохлорид

$C_{13}H_{19}NO$,HCl = 241.8.

CAS — 90-84-6 (diethylpropion); 134-80-5 (diethylpropion hydrochloride).

ATC — A08AA03.

ATC Vet — QA08AA03.



(diethylpropion)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of diethylpropion: Blue; Blues.

Pharmacopoeias. In *US*.
USP 31 (Diethylpropion Hydrochloride). A white to off-white, fine crystalline powder. Is odourless or has a slight characteristic odour. It may contain tartaric acid as a stabilising agent. Soluble 1 in 0.5 of water, 1 in 3 of alcohol, and 1 in 3 of chloroform; practically insoluble in ether. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Dexamfetamine Sulfate, p.2153. In addition gynaecomastia has been reported rarely. The incidence of central adverse effects may be lower with diethylpropion than with dexamfetamine. Diethylpropion should not be given to patients with emotional instability or a history of psychiatric illness. It should be avoided in children and the elderly. Diethylpropion hydrochloride is subject to abuse.

Porphyria. Diethylpropion is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

Diethylpropion is an indirect-acting sympathomimetic and, similarly to dexamfetamine (p.2153), may interact with a number of other drugs.

Pharmacokinetics

Diethylpropion is readily absorbed from the gastrointestinal tract. It is extensively metabolised in the liver and possibly the gastrointestinal tract and is excreted in the urine. Diethylpropion crosses the blood-brain barrier and the placenta. Diethylpropion and its metabolites are distributed into breast milk.

Uses and Administration

Diethylpropion hydrochloride is a central stimulant and indirect-acting sympathomimetic with the actions of dexamfetamine (p.2154). It is used as an oral anorectic in the short-term treatment of obesity (p.2149), although stimulants are not generally recommended for this indication.

Doses of 25 mg three times daily 1 hour before meals or 75 mg once daily in mid-morning as a modified-release preparation, are given. To reduce the risk of dependence, diethylpropion should not be given for more than a few weeks at a time.

Regulatory authorities in the EU have called for the withdrawal of diethylpropion from the market (see under Effects on the Cardiovascular System in Fenfluramine, p.2156).

Preparations

USP 31: Diethylpropion Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Tenuate; ***Braz.:*** Dualid S; Hipofagin S; Inibex S; ***Canad.:*** Tenuate; ***Chile:*** Sacin; ***Denm.:*** Regenon; ***Ger.:*** Regenon; ***Hong Kong:*** Atractil; Prothin; ***Mex.:*** Ifa Norex; Neobes; ***NZ:*** Tenuate Dospan; ***S.Afr.:*** Tenuate Dospan; ***Switz.:*** Prefamone†; Regenon; ***Thai.:*** Atractil; Dietil; Regenon†; ***USA:*** Tenuate†.

Multi-ingredient: ***Arg.:*** Tratobes; ***Indon.:*** Apisate.

Dimefline Hydrochloride *(BANM, USAN, rINNM)*

Dimépline, Chlorhydrate de; Dimeflini Hydrochloridum; DW-62; Hidrocloruro de dimeflina; NSC-114650; Rec-7/0267. 8-Dimethylaminomethyl-7-methoxy-3-methyl-2-phenylchromen-4-one hydrochloride.

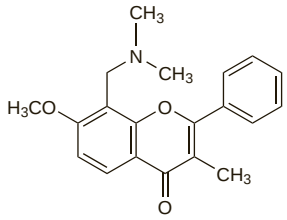
Димефлина Гидрохлорид

$C_{20}H_{21}NO_3,HCl$ = 359.8.

CAS — 1165-48-6 (dimefline); 2740-04-7 (dimefline hydrochloride).

ATC — R07AB08.

ATC Vet — QR07AB08.



(dimefline)

Profile

Dimefline has actions similar to those of doxapram (below) and has been used orally as the hydrochloride and parenterally as a respiratory stimulant.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Remeflin.

Doxapram Hydrochloride *(BANM, USAN, rINNM)*

AHR-619; Doksapraamihydrokloridi; Doksapram Hidroklorür; Doksapramo hidrochloridas; Doxapram, chlorhydrate de; Doxaprám-hidroklorid; Doxapram-hydrochlorid monohydrát; Doxapramhydroklorid; Doxaprami hydrochloridum; Doxaprami Hydrochloridum Monohydricum; Hidrocloruro de doxapram. 1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride monohydrate.

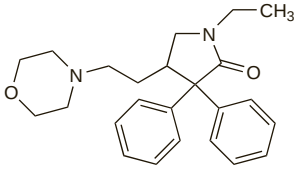
Доксапрама Гидрохлорид

$C_{24}H_{30}N_2O_2,HCl,H_2O$ = 433.0.

CAS — 309-29-5 (doxapram); 113-07-5 (anhydrous doxapram hydrochloride); 7081-53-0 (doxapram hydrochloride monohydrate).

ATC — R07AB01.

ATC Vet — QR07AB01.



(doxapram)

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

Ph. Eur. 6.2 (Doxapram Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water, in alcohol and in dichloromethane. A 1% solution in water has a pH of 3.5 to 5.0.

USP 31 (Doxapram Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 50 of water; soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether. pH of a 1% solution in water is between 3.5 and 5.0. Store in airtight containers.

Incompatibility. The commercial injection of doxapram hydrochloride is reported to be incompatible with alkaline solutions such as aminophylline, furosemide, or thiopental sodium.

Adverse Effects

As with other respiratory stimulants, there is a risk that doxapram will produce adverse effects due to general stimulation of the CNS.

Doxapram may produce dyspnoea and other respiratory problems such as coughing, bronchospasm, laryngospasm, hiccup, hyperventilation, and rebound hypoventilation. Muscle involvement may range from fasciculations to spasticity. Convulsions, headache, dizziness, hyperactivity, and confusion can occur as can sweating, flushing, fever or a sensation of warmth, particularly in the genital or perineal regions. Hallucinations may occur rarely. There may be nausea, vomiting, diarrhoea, and problems with urination. Cardiovascular effects include hypertension and various arrhythmias although sudden hypotension may also occur.

Thrombophlebitis may follow extravasation of doxapram during injection.

Effects on the heart. Second-degree AV block caused by prolongation of the QT interval has been associated with doxapram use in 3 neonates.[1] Although the preparation used contained benzyl alcohol this was not considered to play a role in the adverse effect. A prospective study[2] involving 40 premature infants given doxapram for apnoea of prematurity also found QT interval lengthening at 48 and 72 hours of treatment, even when the drug plasma concentrations were kept within therapeutic ranges. In 6 infants, the QT interval lengthened to a degree considered to be life-threatening. There was also a trend towards moderate increases in blood pressure. The authors recommended heart monitoring when doxapram was given to premature infants.

1. De Villiers GS, *et al.* Second-degree atrioventricular heart block after doxapram administration. *J Pediatr* 1998; **133:** 149–50.
2. Maillard C, *et al.* QT interval lengthening in premature infants treated with doxapram. *Clin Pharmacol Ther* 2001; **70:** 540–5.

Effects on the liver. Acute hepatic necrosis in a patient was attributed to a 24-hour infusion of doxapram.[1] Liver function tests returned to normal over 3 weeks.

1. Fancourt GJ, *et al*. Hepatic necrosis with doxapram hydrochloride. *Postgrad Med J* 1985; **61:** 833–5.

Precautions

Doxapram should not be given to patients with epilepsy or other convulsive disorders, cerebral oedema, cerebrovascular accident, head injury, acute severe asthma, physical obstruction of the airway, severe hypertension, ischaemic heart disease, hyperthyroidism, or phaeochromocytoma. Caution is also advisable if doxapram is used in patients with less severe degrees of hypertension or impaired cardiac reserve. It should be given with care to patients with significant hepatic or renal impairment.

Patients should be carefully supervised during use of doxapram; special attention should be paid to changes in blood gas measurements. Doxapram should be given with oxygen in severe irreversible airways obstruction or severely decreased lung compliance because of the increased work of breathing. A $beta_2$ agonist should also be given to patients with bronchoconstriction.

Interactions

Additive pressor effects may occur when doxapram is used with sympathomimetics or MAOIs. Cardiac arrhythmias may occur when doxapram is given with anaesthetics known to sensitise the myocardium, such as halothane, enflurane, and isoflurane; it has been recommended that doxapram should not be given for at least 10 minutes after stopping these anaesthetics. Doxapram may temporarily mask the residual effects of neuromuscular blockers. The manufacturers have reported that there may be an interaction between doxapram and aminophylline manifested by agitation and increased skeletal muscle activity.

Pharmacokinetics

After intravenous doses doxapram is rapidly distributed into the tissues. Onset of respiratory stimulation usually occurs in 20 to 40 seconds, with a peak effect achieved in 1 to 2 minutes. Duration of effect following a single dose varies from 5 to 12 minutes. Doxapram is extensively metabolised in the liver. The major route of excretion of metabolites and a small amount of unchanged drug is thought to be via bile to the faeces. It is also excreted in the urine.

Some absorption occurs when doxapram is given orally.

◊ References.

1. Robson RH, Prescott LF. A pharmacokinetic study of doxapram in patients and volunteers. *Br J Clin Pharmacol* 1978; **7:** 81–7.
2. Baker JR, *et al*. Normal pharmacokinetics of doxapram in a patient with renal failure and hypothyroidism. *Br J Clin Pharmacol* 1981; **11:** 305–6.

Uses and Administration

Doxapram hydrochloride is a central and respiratory stimulant with a brief duration of action. It acts by stimulation of peripheral chemoreceptors and central respiratory centres; at higher doses, it stimulates other parts of the brain and spinal cord. Doxapram has a pressor action and may also increase catecholamine release.

Doxapram has limited uses in the treatment of acute respiratory failure (for example where this is superimposed on chronic obstructive pulmonary disease), and of postoperative respiratory depression (see Respiratory Failure under Oxygen, p.1691).

Doxapram hydrochloride may be infused at a rate of 1.5 to 4 mg/minute in the treatment of acute respiratory failure.

For postoperative respiratory depression it has been given in a dose of 0.5 to 1.5 mg/kg by intravenous injection over a period of at least 30 seconds. This dose may be repeated at hourly intervals. It may also be given by intravenous infusion, initially at a rate of 2 to 5 mg/minute and then reduced, according to response, to 1 to 3 mg/minute; a recommended maximum total dosage is 4 mg/kg.

Doxapram hydrochloride has also been used to treat respiratory and CNS depression following drug overdose but its use for this indication is no longer recommended.

Chronic obstructive pulmonary disease. Respiratory stimulants such as doxapram have a limited and short-term role in hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease (p.1112). Benefit has been reported in such patients in whom doxapram was used as an alternative to intubation.[1,2] However, a systematic review suggested that despite short-term improvements in blood-gas exchange with doxapram, techniques such as non-invasive ventilation might be more effective.[3]

1. Hirshberg AJ, *et al.* Use of doxapram hydrochloride injection as an alternative to intubation to treat chronic obstructive pulmonary disease patients with hypercapnia. *Ann Emerg Med* 1994; **24:** 701–3.
2. Kerr HD. Doxapram in hypercapnic chronic obstructive pulmonary disease with respiratory failure. *J Emerg Med* 1997; **15:** 513–15.
3. Greenstone M, Lasserson TJ. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/05/05).

Neonatal apnoea. Doxapram is effective in neonatal apnoea (p.1118) and may be considered as an alternative, or in addition, to xanthines in infants with apnoea that does not respond to xanthine therapy alone. However, it is less convenient to use as it must be given by continuous intravenous infusion and blood pressure must be monitored (although it has also been suggested that the oral route may be used after the initial intravenous dose—see *BNFC* doses below). Additionally, some preparations may contain benzyl alcohol as a preservative making them unsuitable for use in neonates. It has been used in intravenous doses of 2.5 mg/kg per hour.[1-3] Adverse CNS effects have been reported.[3] Lower doses of 0.25 or 1.5 mg/kg per hour have been shown to be effective.[4,5] However, use of low doses of 500 micrograms/kg per hour in very low birth-weight premature infants produced higher than expected plasma-doxapram concentrations and a greater increase in systolic blood pressure compared with controls.[6] A systematic review[7] concluded that the place of doxapram in the management of neonatal apnoea had not yet been properly established.

Although unlicensed, the *BNFC* suggests giving neonates doxapram hydrochloride intravenously in an initial dose of 2.5 mg/kg over 5 to 10 minutes followed by 300 micrograms/kg per hour by continuous infusion, adjusted according to response, to a maximum dose of 1.5 mg/kg per hour; alternatively, 6 mg/kg may be given orally 4 times daily after the initial intravenous dose.

1. Sagi E, *et al.* Idiopathic apnoea of prematurity treated with doxapram and aminophylline. *Arch Dis Child* 1984; **59:** 281–3.
2. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; **75:** 709–13.
3. Dear PRF, Wheeler D. Doxapram and neonatal apnoea. *Arch Dis Child* 1984; **59:** 903–4.
4. Bairam A, Vert P. Low-dose doxapram for apnoea of prematurity. *Lancet* 1986; **i:** 793–4.
5. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; **116:** 648–53.
6. Huon C, *et al.* Low-dose doxapram for treatment of apnoea following early weaning in very low birthweight infants: a randomized, double-blind study. *Acta Paediatr* 1998; **87:** 1180–4.
7. Henderson-Smart DJ, Steer PA. Doxapram treatment for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/10/07).

Respiratory depression. References to the use of doxapram in postoperative respiratory depression.

1. Jansen JE, *et al.* Effect of doxapram on postoperative pulmonary complications after upper abdominal surgery in high-risk patients. *Lancet* 1990; **335:** 936–8.
2. Thangathurai D, *et al.* Doxapram for respiratory depression after epidural morphine. *Anaesthesia* 1990; **45:** 64–5.
3. Sajjad T. Comparison of the effects of doxapram or carbon dioxide on ventilatory frequency and tidal volume during induction of anaesthesia with propofol, *Br J Anaesth* 1994; **73:** 266P.
4. Alexander-Williams M, *et al.* Doxapram and the prevention of postoperative hypoxaemia. *Br J Anaesth* 1995; **75:** 233P.

Shivering. Doxapram is one of a number of drugs that have been used in postoperative shivering, see p.1779.

References.

1. Sarma V, Fry ENS. Doxapram after general anaesthesia: its role in stopping shivering during recovery. *Anaesthesia* 1991; **46:** 460–1.
2. Singh P, *et al.* Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. *Br J Anaesth* 1993; **71:** 685–8.
3. Wrench IJ, *et al.* The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia* 1997; **52:** 32–6.