ment has been inadequate, edrophonium chloride will produce an immediate amelioration of symptoms, whereas in cholinergic crises due to over-treatment the symptoms will be temporarily aggravated. In the UK, the *BNFC* recommends that edrophonium chloride may be used in children aged from 1 month to 12 years to detect under- or over-treatment in a dose of 20 micrograms/kg. Licensed product information suggests testing one hour after the last dose of treatment but the *BNF* and the *BNFC* recommend testing just before the next dose is due. Testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available.

Edrophonium chloride was originally introduced for the **reversal of neuromuscular blockade** in anaesthesia. In the UK, the recommended dose in adults and children for the reversal of the effects of competitive neuromuscular blockers is 500 to 700 micrograms/kg given by intravenous injection over several minutes either with or after atropine sulfate 7 micrograms/kg; the *BNFC* suggests that this dose may be given to children as young as 1 month of age. In the USA, a dose of 10 mg of edrophonium chloride is given over 30 to 45 seconds and repeated as required up to a maximum of 40 mg. The brevity of its action limits its value. Prolonged apnoea may occur in patients treated with a depolarising neuromuscular blocker, such as suxamethonium; to determine if this is caused by a phase II block (see p.1912), edrophonium chloride 10 mg may be given intravenously with atropine.

Edrophonium bromide has been used similarly to edrophonium chloride.

Reversal of neuromuscular blockade. For a discussion of whether edrophonium might be more suitable than neostigmine for reversal of residual block after the use of the shorter-acting competitive neuromuscular blockers, see under Uses and Administration of Neostigmine, p.633.

Snake bite. For the use of anticholinesterases in the treatment of snake bite, see under Uses and Administration of Neostigmine, p.633.

Tetrodotoxin poisoning. Management of poisoning due to tetrodotoxin, a heat stable neuromuscular blocking toxin found in various marine animals, such as puffer fish, is mainly symptomatic and supportive. Reports[1,2] on the effectiveness of intravenous anticholinesterases such as edrophonium or neostigmine in reversing muscle weakness in tetrodotoxin poisoning have been conflicting. Although it appears that anticholinesterases may only be effective during partial block produced by tetrodotoxin, some consider[3] that, as there is no specific antidote, any measure that brings about improvement may be tried.

1. Chew SK, *et al*. Anticholinesterase drugs in the treatment of tetrodotoxin poisoning. *Lancet* 1984; **ii:** 108.
2. Tibballs J. Severe tetrodotoxic fish poisoning. *Anaesth Intensive Care* 1988; **16:** 215–17.
3. Karalliedde L. Management of puffer fish poisoning. *Br J Anaesth* 1995; **75:** 500.

Preparations

BP 2008: Edrophonium Injection;
USP 31: Edrophonium Chloride Injection.

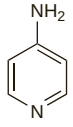
Proprietary Preparations (details are given in Part 3)
Canad.: Enlon; ***Gr.:*** Anticude; ***Spain:*** Anticude; ***USA:*** Enlon-Plus†; Enlon†; Reversol; Tensilon.

Fampridine *(USAN, rINN)*

EL-970; Fampridina; Fampridinum. 4-Aminopyridine; 4-Pyridinamine.

Фампридин

$C_5H_6N_2$ = 94.11.
CAS — 504-24-5.



Profile

Fampridine enhances the release of acetylcholine from nerve terminals and has been used intravenously to reverse the effects of competitive neuromuscular blockers. It has also been tried orally and intravenously in the management of neurological disorders such as Eaton-Lambert myasthenic syndrome (p.629), Guillain-Barré syndrome (p.2228), multiple sclerosis (p.892), spinal cord injury, and Alzheimer's disease (see Dementia, p.362), and for the reversal of neuromuscular blockade in patients with botulism (p.2207). Typical oral doses appear to be around 30 to 50 mg daily.

Fampridine has also been considered as a specific antidote in poisoning with calcium-channel blockers (see Overdosage under Treatment of Adverse Effects of Nifedipine, p.1352).

Adverse effects seen in clinical trials include insomnia, seizures, paraesthesia, dizziness, and nausea; these effects, especially seizures, may limit its use.

◊ References.

1. Ter Wee PM, *et al.* 4-Aminopyridine and haemodialysis in the treatment of verapamil intoxication. *Hum Toxicol* 1985; **4:** 327–9.
2. Davidson M, *et al.* 4-Aminopyridine in the treatment of Alzheimer's disease. *Biol Psychiatry* 1988; **23:** 485–90.
3. Hansebout RR, *et al.* 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients. *J Neurotrauma* 1993; **10:** 1–18.
4. Hayes KC, *et al.* Pharmacokinetics of an immediate-release oral formulation of fampridine (4-aminopyridine) in normal subjects and patients with spinal cord injury. *J Clin Pharmacol* 2003; **43:** 379–85.

Multiple sclerosis. Fampridine has potassium-channel blocking activity and has been tried in the treatment of multiple sclerosis to improve conduction in demyelinated fibres. Improvements have been reported in walking, dexterity, and vision, but only small numbers of patients have been studied. A systematic review[1] was unable to come to a conclusion about its safety and efficacy, noting that publication bias posed a problem in this area.

1. Solari A, *et al.* Aminopyridines for symptomatic treatment in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 15/02/06).

Overdosage. An 8-month-old boy experienced dramatic opisthotonic posturing and vermiform tongue fasciculations after ingestion of up to 20 mg of fampridine;[1] the child was also noted to be tachycardic and tachypnoeic. His symptoms resolved after treatment with benzodiazepines.

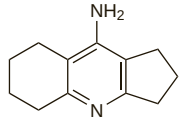
1. Velez L, *et al.* Opisthotonic posturing with neuromuscular irritability attributable to 4-aminopyridine ingestion by a healthy pediatric patient. Abstract: *Pediatrics* 2003; **111:** 192–3. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/1/e82 (accessed 15/02/06)

Ipidacrine *(rINN)*

Amiridin (base or hydrochloride); Ipidacrina; Ipidacrinum; NIK-247 (hydrochloride). 9-Amino-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta[*b*]quinoline.

Ипидакрин

$C_{12}H_{16}N_2$ = 188.3.
CAS — 62732-44-9 (ipidacrine); 90043-86-0 (ipidacrine hydrochloride); 118499-70-0 (ipidacrine hydrochloride monohydrate).



Profile

Ipidacrine, an analogue of tacrine (p.370), is a cholinesterase inhibitor. It is used in the management of various neurological disorders including CNS and peripheral nervous system disorders, demyelinating disease, myasthenia gravis (p.629) and other myasthenic syndromes, Alzheimer's disease (see Dementia, p.362), and gastrointestinal atony. For myasthenic syndromes an oral dose of 20 to 40 mg has been given up to 5 times daily. A usual dosage in Alzheimer's disease is 10 to 20 mg given 2 or 3 times daily but this may be increased gradually up to 200 mg daily given in divided doses.

Ipidacrine has also been given by injection as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Part 3)
Rus.: Ахатоп (Аксамон).

Neostigmine *(BAN)*

Neostigmiini; Neostigmin; Neostigmina; Neostigminum. 3-(Dimethylcarbamoyloxy)trimethylanilinium ion.

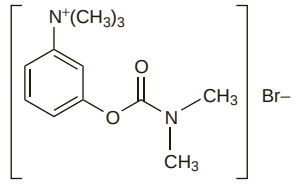
$C_{12}H_{19}N_2O_2$ = 223.3.
CAS — 59-99-4.
ATC — N07AA01; S01EB06.
ATC Vet — QA03AB93; QN07AA01; QS01EB06.

Neostigmine Bromide *(BANM, pINN)*

Bromuro de neostigmina; Neostig. Brom.; Neostigmiinibromidi; Neostigminbromid; Néostigmine, bromure de; Neostigmini bromidum; Neostigminii Bromidum; Neostigminium-bromid; Neostigmino bromidas; Neostigminum Bromatum; Neosztigminbromid; Synstigminium Bromatum.

Неостигмина Бромид

$C_{12}H_{19}BrN_2O_2$ = 303.2.
CAS — 114-80-7.
ATC — N07AA01; S01EB06.
ATC Vet — QN07AA01; QS01EB06.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Neostigmine Bromide). Hygroscopic, colourless crystals or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Protect from light.
USP 31 (Neostigmine Bromide). Store in airtight containers.

Stability. References.

1. Porst H, Kny L. Kinetics of the degradation of neostigmine bromide in aqueous solution. *Pharmazie* 1985; **40:** 713–17.

Neostigmine Metilsulfate *(BANM)*

Neostig. Methylsulph.; Neostigmiinimetilsulfaatti; Neostigmina, metilsulfato de; Neostigmine Methylsulfate; Neostigmine Methylsulphate; Néostigmine, métilsulfate de; Neostigmini metilsulfas; Neostigminii Metilsulfas; Neostigminium-methylsulfát; Neostigminmetilsulfat; Neostigminmetylsulfat; Neostigmino metilsulfatas; Neostygminy metylosiarczan; Neosztigmin-metilszulfát; Proserinum.

$C_{13}H_{22}N_2O_6S$ = 334.4.
CAS — 51-60-5.
ATC — N07AA01; S01EB06.
ATC Vet — QN07AA01; QS01EB06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Neostigmine Metilsulfate). Hygroscopic, colourless crystals or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers. Protect from light.
USP 31 (Neostigmine Methylsulfate). Store in airtight containers.

Adverse Effects

The adverse effects of neostigmine are chiefly due to excessive cholinergic stimulation and most commonly include increased salivation, nausea and vomiting, abdominal cramps, and diarrhoea. Allergic reactions have been reported; rashes have been associated with the use of the bromide salt. Neostigmine penetrates the blood-brain barrier poorly and CNS effects are usually only seen with high doses.

Overdosage may lead to a 'cholinergic crisis', characterised by both muscarinic and nicotinic effects. These effects may include excessive sweating, lachrymation, increased peristalsis, involuntary defaecation and urination or desire to urinate, miosis, ciliary spasm, nystagmus, bradycardia and other arrhythmias, hypotension, muscle cramps, fasciculations, weakness and paralysis, tight chest, wheezing, and increased bronchial secretion combined with bronchoconstriction. CNS effects include ataxia, convulsions, coma, slurred speech, restlessness, agitation, and fear. Death may result from respiratory failure, due to a combination of the muscarinic, nicotinic, and central effects, or cardiac arrest.

It has been reported that a paradoxical increase in blood pressure and heart rate may result from nicotinic stimulation of sympathetic ganglia, especially where atropine has been given to reverse the muscarinic effects (see Treatment of Adverse Effects, below).

In patients with myasthenia gravis, in whom other symptoms of overdosage may be mild or absent, the major symptom of cholinergic crisis is increased mus-