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.

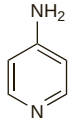
Proprietary Preparations (details are given in Part 3)
Canad.: Enlon; ***Gr.:*** Anticude; ***Spain:*** Anticude; ***USA:*** Enlon-Plus†; Enlon†; Reversol; Tensilon.

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.

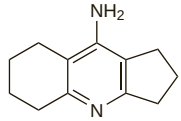
1. Velez L, *et al.* Opisthotonic posturing with neuromuscular irritability attributable to 4-aminopyridine ingestion by a healthy pediatric patient. Abstract: *Pediatrics* 2003; **111:** 192–3. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/1/e82 (accessed 15/02/06)

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.

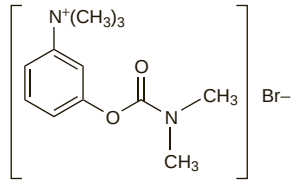
$C_{12}H_{19}N_2O_2$ = 223.3.
CAS — 59-99-4.
ATC — N07AA01; S01EB06.
ATC Vet — QA03AB93; QN07AA01; QS01EB06.

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-

cular weakness, which must be differentiated from the muscular weakness caused by an exacerbation of the disease itself (myasthenic crisis).

The adverse effects of parasympathomimetics applied topically for their miotic action are discussed under Pilocarpine on p.1885.

Treatment of Adverse Effects

If a life-threatening amount of neostigmine has been taken by mouth and the patient presents within 1 hour, the stomach may be emptied by lavage; giving activated charcoal to decrease absorption should also be considered. When necessary maintenance of respiration should take priority. Atropine sulfate should be given in usual doses of 1 to 2 mg, preferably intravenously, or else intramuscularly and repeated as necessary to control the muscarinic effects; doses of up to 4 mg have been suggested. Nicotinic effects, including muscle weakness and paralysis, are not antagonised by atropine; small doses of a competitive neuromuscular blocker have been suggested for the control of muscle twitching. Use of the cholinesterase reactivator pralidoxime as an adjunct to atropine has also been suggested (see p.1460). Further supportive treatment should be given as required.

Precautions

Neostigmine is contra-indicated in patients with mechanical gastrointestinal or urinary-tract obstruction, or peritonitis. It should be used with extreme caution in patients who have undergone recent intestinal or bladder surgery and in patients with bronchial asthma. It should be used with caution in patients with cardiovascular disorders including arrhythmias, bradycardia, recent myocardial infarction, and hypotension, as well as in patients with vagotonia, epilepsy, hyperthyroidism, parkinsonism, renal impairment, or peptic ulcer disease. When neostigmine is given by injection, atropine should always be available to counteract any excessive muscarinic reactions; atropine may also be given before, or with, neostigmine to prevent or minimise muscarinic adverse effects but this may mask the initial symptoms of overdosage and lead to cholinergic crisis.

UK licensed product information states that as the severity of myasthenia gravis often fluctuates considerably during pregnancy, particular care is needed to avoid cholinergic crisis caused by overdosage; it has also been reported that neonatal myasthenia may follow large doses during pregnancy. The amount of neostigmine distributed into breast milk is very small but breast-fed infants need to be monitored.

Large oral doses of neostigmine should be avoided in conditions where there may be increased absorption from the gastrointestinal tract. It should be avoided in patients known to be hypersensitive to neostigmine; the bromide ion from neostigmine bromide may contribute to any allergic reaction.

The precautions of parasympathomimetics applied topically for their miotic action are discussed under Pilocarpine on p.1885.

Neuromuscular disorders. Residual non-depolarising neuromuscular block in a patient with dystrophia myotonica was only partly reversed by neostigmine and atropine, and following a second dose of both drugs complete neuromuscular block developed.[1] In a second patient, with a history of progressive muscle dystrophy, the use of neostigmine to reverse residual non-depolarising blockade gave rise to a tonic response in the indirectly stimulated muscle. The type and degree of the response to neostigmine, and probably other anticholinesterases, cannot be predicted in patients with neuromuscular disease.

A patient with sero-negative ocular myasthenia gravis had exaggerated responses to both vecuronium and neostigmine.[2] The dose of neuromuscular blockers and their antagonists used in patients with myasthenia gravis should be titrated carefully regardless of the severity of the condition.

1. Buzello W, *et al.* Hazards of neostigmine in patients with neuromuscular disorders: report of two cases. *Br J Anaesth* 1982; **54:** 529–34.
2. Kim J-M, Mangold J. Sensitivity to both vecuronium and neostigmine in a sero-negative myasthenic patient. *Br J Anaesth* 1989; **63:** 497–500.

Interactions

Drugs with neuromuscular blocking activity, such as the aminoglycosides, clindamycin, colistin, cyclopropane, and the halogenated inhalational anaesthetics, may antagonise the effects of neostigmine. Those such as quinine, chloroquine, hydroxychloroquine, quinidine, procainamide, propafenone, lithium, and the beta blockers, that have the potential to aggravate myasthenia gravis, can reduce the effectiveness of treatment with parasympathomimetics. Prolonged bradycardia has also occurred in patients receiving beta blockers when given neostigmine. Anticholinesterases, such as neostigmine, can inhibit the metabolism of suxamethonium and enhance and prolong its action; combined use is not recommended.

Ophthalmic use of anticholinesterases, such as ecothiopate, should be undertaken with care in patients receiving neostigmine systemically for myasthenia gravis, because of possible additive toxicity.

Antimuscarinics such as atropine antagonise the muscarinic effects of neostigmine.

Beta blockers. There have been several reports of bradycardia and hypotension when neostigmine or physostigmine were given to patients receiving beta blockers[1-4] but no significant changes in heart rate were noted in a study of pyridostigmine given to 8 patients taking beta blockers.[5] Beta blockers have the potential to aggravate the symptoms of myasthenia gravis and may therefore reduce the effectiveness of parasympathomimetic treatment.

1. Sprague DH. Severe bradycardia after neostigmine in a patient taking propranolol to control paroxysmal atrial tachycardia. *Anesthesiology* 1975; **42:** 208–10.
2. Seidl DC, Martin DE. Prolonged bradycardia after neostigmine administration in a patient taking nadolol. *Anesth Analg* 1984; **63:** 365–7.
3. Baraka A, Dajani A. Severe bradycardia following physostigmine in the presence of beta-adrenergic blockade: a case report. *Middle East J Anesthesiol* 1984; **7:** 291–3.
4. Eldor J, *et al.* Prolonged bradycardia and hypotension after neostigmine administration in a patient receiving atenolol. *Anaesthesia* 1987; **42:** 1294–7.
5. Arad M, *et al.* Safety of pyridostigmine in hypertensive patients receiving beta blockers. *Am J Cardiol* 1992; **69:** 518–22.

Calcium-channel blockers. Use of calcium-channel blockers such as *verapamil* with neuromuscular blockers may produce an enhanced muscle block which is resistant to reversal with neostigmine[1] but which can be reversed by edrophonium.[2]

1. van Poorten JF, *et al.* Verapamil and reversal of vecuronium neuromuscular blockade. *Anesth Analg* 1984; **63:** 155–7.
2. Jones RM, *et al.* Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium. *Anesth Analg* 1985; **64:** 1021–5.

Corticosteroids. Although use of glucocorticoids alone may improve strength in myasthenic patients, use of *methylprednisolone* in patients receiving neostigmine or pyridostigmine has exacerbated symptoms and produced profound weakness needing assisted ventilation.[1] Since the adverse effects of combined therapy usually occur before any expected benefits it has been suggested that the glucocorticoid should be given on alternate days in small doses which are increased gradually until the optimal effect is achieved.[2]

1. Brunner NG, *et al.* Corticosteroids in management of severe, generalized myasthenia gravis: effectiveness and comparison with corticotrophin therapy. *Neurology* 1972; **22:** 603–10.
2. Jubiz W, Meikle AW. Alterations of glucocorticoid actions by other drugs and disease states. *Drugs* 1979; **18:** 113–21.

Pharmacokinetics

Neostigmine is a quaternary ammonium compound and, as the bromide, is poorly absorbed from the gastrointestinal tract. After parenteral doses as the metilsulfate, neostigmine is rapidly eliminated and is excreted in the urine both as unchanged drug and metabolites. Neostigmine undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Protein binding to human serum albumin is reported to range from 15 to 25%. Penetration into the CNS is poor. Neostigmine crosses the placenta and very small amounts are distributed into breast milk.

◊ Neostigmine appears to be poorly and variably absorbed when given orally. In 3 myasthenic patients peak plasma concentrations were obtained 1 to 2 hours after a single 30-mg dose by mouth and the mean plasma half-life was 0.87 hours; bioavailability was estimated to be 1 to 2%.[1] Mean plasma half-lives of 0.89 and 1.20 hours have been obtained after intravenous[1] and intramuscular[2] injections of neostigmine metilsulfate, respectively, although again only a few patients were studied. Metabolism and biliary excretion may play significant roles in the elimination of neostigmine.[2] About 80% of a dose may be excreted in the urine within 24 hours: about 50% of a dose as unchanged drug and 15% as 3-hydroxyphenyltrimethylammonium.[2] Mean plasma elimination half-lives for neostigmine have been found to be shorter in infants (0.65 hours) and children (0.80 hours) compared with adults (1.12 hours) but this does not appear to be related to its duration of effect in antagonising neuromuscular blockade.[3] For the half-life in anephric patients, see Administration in Renal Impairment, below.

1. Aquilonius S-M, *et al.* A pharmacokinetic study of neostigmine in man using gas chromatography–mass spectrometry. *Eur J Clin Pharmacol* 1979; **15:** 367–71.
2. Somani SM, *et al.* Kinetics and metabolism of intramuscular neostigmine in myasthenia gravis. *Clin Pharmacol Ther* 1980; **28:** 64–8.
3. Fisher DM, *et al.* The neuromuscular pharmacology of neostigmine in infants and children. *Anesthesiology* 1983; **59:** 220–5.

Uses and Administration

Neostigmine is a quaternary ammonium compound that inhibits cholinesterase activity and thus prolongs and intensifies the physiological actions of acetylcholine (p.1877). It probably also has direct effects on skeletal muscle fibres. The anticholinesterase actions of neostigmine are reversible.

Neostigmine is used in the treatment of myasthenia gravis, and has been used as an alternative to edrophonium in the diagnosis of myasthenia gravis (p.629). It is used in anaesthesia to reverse the neuromuscular blockade produced by competitive neuromuscular blockers (see below). It is also used in the management of paralytic ileus. Neostigmine has been used in the management of postoperative urinary retention (p.2180) but has generally been superseded by catheterisation. It has also been used to lower intra-ocular pressure in the management of glaucoma and to reduce rises in intra-ocular pressure associated with ophthalmic surgery, although other parasympathomimetics are usually used when such miotics are required.

Neostigmine is given as the bromide and as the metilsulfate. Neostigmine bromide is given orally and has been used topically as eye drops; the metilsulfate is given by intramuscular, intravenous, or subcutaneous injection.

Licensed product information states that 500 micrograms of neostigmine metilsulfate by intravenous injection is equivalent in effect to about 1 to 1.5 mg of neostigmine metilsulfate by intramuscular or subcutaneous injection, or 15 mg of neostigmine bromide orally.

In the treatment of **myasthenia gravis**, neostigmine bromide is given orally in a total daily dose usually between 75 and 300 mg, divided throughout the day, and if necessary the night, according to response; larger portions of the total dose may be given at times of greater fatigue. The maximum daily dose that most patients can tolerate is 180 mg. A usual total daily oral dose in children is 15 to 90 mg. In patients in whom oral therapy is impractical neostigmine metilsulfate may be given in doses of 0.5 to 2.5 mg by intramuscular or subcutaneous injection at intervals, giving a total daily dose usually in the range 5 to 20 mg. Single doses in children have ranged from 200 to 500 micrograms.

In the treatment of neonatal myasthenia gravis doses in the range 50 to 250 micrograms of the metilsulfate by intramuscular or subcutaneous injection, or 1 to 5 mg of the bromide orally, have been given usually every 4 hours (30 minutes before feeds); treatment is rarely needed beyond 8 weeks of age.

To **reverse neuromuscular blockade** produced by competitive neuromuscular blockers, the usual adult dose in the UK is 50 to 70 micrograms/kg given by intravenous injection over a period of 60 seconds; in the USA lower doses of 0.5 to 2 mg are used. Additional neostigmine may be given until the muscle power is normal but a total of 5 mg should not be exceeded. Similar doses may be used in children; the *BNFC* recommends a dose of 50 to 80 micrograms/kg in neonates and children, to a maximum of 2.5 mg in those under 12 years of age. The patient should be well ventilated until complete recovery of normal respiration is assured. To counteract any muscarinic effects in adults 0.6 to 1.2 mg of atropine sulfate is given by intravenous injection with or before the dose of neostigmine;

neonates and children up to 18 years of age may be given 20 micrograms/kg of atropine sulfate (to a maximum of 600 micrograms in those aged 1 month and over). It has been suggested that in the presence of bradycardia atropine sulfate should be given several minutes before neostigmine. Glycopyrronium bromide has been used as an alternative to atropine sulfate.

In the treatment of paralytic **ileus** and postoperative **urinary retention**, oral doses of 15 to 30 mg of the bromide, or more usually 500 micrograms of the metilsulfate by subcutaneous or intramuscular injection, have been used.

Administration in renal impairment. The dosage of neostigmine may need to be adjusted in patients with renal impairment. The mean serum elimination half-life of 79.8 minutes obtained in patients with normal renal function was found to be prolonged to 181.1 minutes in anephric patients.[1]

1. Cronnelly R, *et al.* Renal function and the pharmacokinetics of neostigmine in anesthetized man. *Anesthesiology* 1979; **51:** 222–6.

Decreased gastrointestinal motility. Parasympathomimetics enhance gastric contractions and increase intestinal motility and have been used in conditions associated with decreased gastrointestinal motility (p.1694). Good results have been reported with intravenous neostigmine in the treatment of acute colonic pseudo-obstruction,[1,2] a condition that appears to be due to parasympathomimetic dysfunction. These results have been confirmed in a randomised double-blind study.[3] It has therefore been suggested that parasympathomimetics should be tried before colonic decompression or surgery when conservative management has failed or a rapid resolution is required.[3] Neostigmine has also been used in the treatment of severe constipation due to disrupted intestinal motility.[4,5]

1. Hutchinson R, Griffiths C. Acute colonic pseudo-obstruction: a pharmacological approach. *Ann R Coll Surg Engl* 1992; **74:** 364–7.
2. Stephenson BM, *et al.* Parasympathomimetic decompression of acute colonic pseudo-obstruction. *Lancet* 1993; **342:** 1181–2.
3. Ponec RJ, *et al.* Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999; **341:** 137–41.
4. Miller LS. Neostigmine for severe constipation with spinal cord lesions. *Ann Intern Med* 1984; **101:** 279.
5. Thurtle OA, *et al.* Intractable constipation in malignant phaeochromocytoma: combined treatment with adrenergic blockade and cholinergic drugs. *J R Soc Med* 1984; **77:** 327–8.

Local anaesthesia. Intrathecal neostigmine has been added to spinal local anaesthetics or opioids as an adjunct to prolong regional analgesia and improve haemodynamic stability. A systematic review[1] of studies of such use found that although neostigmine in doses up to 500 micrograms produced a very modest increase in analgesia in the perioperative and peripartum setting, it did not appear to improve haemodynamic stability and the incidence of adverse effects was greatly increased, even at low doses. The disadvantages were felt to outweigh whatever benefits such therapy might have.

1. Ho, KM, *et al.* Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta-analysis. *Anaesth Intensive Care* 2005; **33:** 41–53.

Reversal of neuromuscular blockade. Anticholinesterases have often been used after surgery to antagonise residual neuromuscular block induced by long-acting competitive neuromuscular blockers. However, there has been continuing debate[1-3] on whether anticholinesterases can be used in reduced doses or even omitted for intermediate-acting blockers such as atracurium and vecuronium and shorter-acting blockers such as mivacurium.

Decreasing the anticholinesterase dose may reduce adverse effects. Although it is not clear whether omitting neostigmine reversal reduces nausea and vomiting,[3,4] it avoids any adverse effects neostigmine may have on gut anastomoses. One commentator[1] considered that the wide variation in recovery time with aminosteroid blockers such as rocuronium was an indication for always using at least a small dose of anticholinesterase when these drugs were used. However, it was suggested that, if the block was being carefully monitored and recovery was established, a reduced dose of 1.25 mg of neostigmine might be preferable after a benzylisoquinolinium blocker such as atracurium or mivacurium. In children, smaller doses of an anticholinesterase could be used, even after an aminosteroid blocker, and after a blocker such as mivacurium, they might not be needed at all.

Others have preferred to reserve neostigmine reversal for cases where it was deemed clinically necessary: in a study[4] using such a protocol, 68% of those receiving rocuronium were given neostigmine, against 10% of those receiving mivacurium.

It has been suggested that because of its shorter duration of action edrophonium might be more suitable than neostigmine to antagonise residual block for neuromuscular blockers with shorter actions and in particular, that edrophonium might be more appropriate than neostigmine for use with mivacurium. Neostigmine inhibits the plasma cholinesterase responsible for the metabolism of mivacurium and its use can in theory delay rather than speed recovery, although in practice there is considered to be little evidence for such an effect.[1] Edrophonium also has lesser effects on the vagus, a more rapid onset of action, and may be associated with a lower incidence of nausea and vomiting than neostigmine.[5] Neostigmine can cause clinically significant neuromuscular blockade if it is given to a patient who has already recovered a large degree of neuromuscular function[6,7] but edrophonium appears not to have this effect.[8] However, the antagonism produced by edrophonium is not adequately and reliably sustained especially after profound block.[9,10]

1. Hunter JM. Is it always necessary to antagonize residual neuromuscular block? Do children differ from adults? *Br J Anaesth* 1996; **77:** 707–9.
2. Fawcett WJ. Neuromuscular block in children. *Br J Anaesth* 1997; **78:** 627.
3. Fuchs-Buder T, Mencke T. Use of reversal agents in day care procedures (with special reference to postoperative nausea and vomiting). *Eur J Anaesthesiol* 2001; **18** (suppl 23): 53–9.
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9. Caldwell JE, *et al.* Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium: comparison of neostigmine with edrophonium. *Br J Anaesth* 1986; **58:** 1285–9.
10. Mirakhur RK, *et al.* Antagonism of vecuronium-induced neuromuscular blockade with edrophonium or neostigmine. *Br J Anaesth* 1987; **59:** 473–7.

Snake bite. The general management of snake bites is discussed on p.2239. Numerous reports from India have claimed benefit for anticholinesterases in the treatment of neurotoxic snake bites but failure to distinguish between cobra and krait bites, lack of controls, and inadequate information about other therapy weaken the claims.[1] However, edrophonium has been shown in 2 double-blind studies to be more effective than placebo[2] and antivenom[3] in the treatment of snake bite due to the Philippine cobra (*Naja naja philippinensis*). Neostigmine has also been reported[4] to have been effective in reversing paralysis in 2 patients bitten by *Micrurus frontalis* (a coral snake). Similarly, another patient made a remarkable recovery when treated with neostigmine after being bitten by an Asiatic cobra (*Naja naja kaouthia*).[5] Anticholinesterases would be expected to be of little value for bites from snakes whose venom contains neurotoxins which act presynaptically, including the Asian krait, the Australian tiger snake, and the taipan[6] and, although beneficial results have been reported in individual patients,[7] overall results are considered to be inconsistent.[2,8] However, it is recommended that a test dose of edrophonium preceded by atropine should be given to patients with neurological signs after a snake bite by any species and if improvement occurs, a longer acting anticholinesterase such as neostigmine can be given.[2,3]

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3. Watt G, *et al.* Comparison of Tensilon and antivenom for the treatment of cobra-bite paralysis. *Trans R Soc Trop Med Hyg* 1989; **83:** 570–3.
4. Vital Brazil O, Vieira RJ. Neostigmine in the treatment of snake accidents caused by Micrurus frontalis: report of two cases. *Rev Inst Med Trop Sao Paulo* 1996; **38:** 61–7.
5. Gold BS. Neostigmine for the treatment of neurotoxicity following envenomation by the Asiatic cobra. *Ann Emerg Med* 1996; **28:** 87–9.
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7. Warrell DA, *et al.* Severe neurotoxic envenoming by the Malayan krait Bungarus candidus (Linnaeus): response to antivenom and anticholinesterase. *BMJ* 1983; **286:** 678–80.
8. Trevett AJ, *et al.* Failure of 3,4-diaminopyridine and edrophonium to produce significant clinical benefit in neurotoxicity following the bite of Papuan taipan (Oxyuranus scutellatus carini). *Trans R Soc Trop Med Hyg* 1995; **89:** 444–6.

Tetrodotoxin poisoning. For reference to the use of neostigmine in the treatment of tetrodotoxin poisoning caused by eating puffer fish, see under Uses and Administration of Edrophonium Chloride, p.631.

Preparations

BP 2008: Neostigmine Injection; Neostigmine Tablets;
USP 31: Neostigmine Bromide Tablets; Neostigmine Methylsulfate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Fadastigmina; Prostigmin; ***Austral.:*** Prostigmin; ***Austria:*** Normastigmin; Prostigmin; ***Belg.:*** Prostigmine; Robinul-Neostigmine; ***Braz.:*** Normastig; Prostigmine; ***Canad.:*** Prostigmin; ***Chile:*** Prostigmine†; ***Cz.:*** Syntostigmin; ***Denm.:*** Robinul-Neostigmin; ***Fin.:*** Glycostigmin; Robinul-Neostigmin; ***Fr.:*** Prostigmine; ***Ger.:*** Neostig; ***Gr.:*** Prostigmine; ***Hong Kong:*** Prostigmin†; ***Hung.:*** Stigmosan; ***India:*** Tilstigmin; ***Indon.:*** Prostigmin; ***Israel:*** Prostigmine†; ***Ital.:*** Intrastigmina; Prostigmina; ***Malaysia:*** Prostigmin†; ***Mex.:*** Prostigmine; ***Neth.:*** Prostigmin; ***Norw.:*** Robinul-Neostigmin; ***Philipp.:*** Prostigmin; ***Pol.:*** Polstigminum; ***Port.:*** Intrastigmina; Prostigmine; ***Spain:*** Prostigmine; ***Swed.:*** Robinul-Neostigmin; ***Switz.:*** Prostigmin; Robinul-Neostigmine; ***Thai.:*** Prostigmin; ***UK:*** Robinul-Neostigmine; ***USA:*** Neostigmine Min-I-Mix; Prostigmin.

Multi-ingredient: ***Austria:*** Normastigmin mit Pilocarpin; Pilostigmin Puroptal; ***Ger.:*** Syncarpin-N†.

Pyridostigmine Bromide *(BAN, rINN)*

Bromuro de piridostigmina; Piridostigmin Bromür; Piridostigmino bromidas; Piridosztigmin-bromid; Pyridostig. Brom.; Pyridostigmiinibromidi; Pyridostigminbromid; Pyridostigmine, bromure de; Pyridostigmini bromidum; Pyridostigminii Bromidum; Pyridostigminium-bromid. 3-Dimethylcarbamoyloxy-1-methylpyridinium bromide.

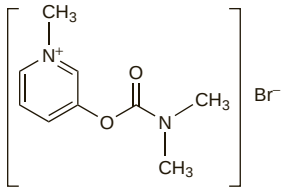
Пиридостигмина Бромид

$C_9H_{13}BrN_2O_2$ = 261.1.

CAS — 155-97-5 (pyridostigmine); 101-26-8 (pyridostigmine bromide).

ATC — N07AA02.

ATC Vet — QN07AA02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Pyridostigmine Bromide). A white or almost white deliquescent crystalline powder. Very soluble in water and in alcohol. Store in airtight containers. Protect from light.
USP 31 (Pyridostigmine Bromide). A white or practically white, hygroscopic, crystalline powder, having an agreeable characteristic odour. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether; slightly soluble in petroleum spirit. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631. It has been stated that muscarinic adverse effects occur less frequently with pyridostigmine treatment than with neostigmine.

Breast feeding. Pyridostigmine was present in the breast milk of 2 nursing mothers, receiving maintenance therapy for myasthenia gravis, in a concentration between 36 and 113% of that in maternal plasma,[1] but in both cases the dose ingested per kg body-weight by the nursing infant was 0.1% or less of that ingested by the mother. Maternal medication with pyridostigmine should be no obstacle to breast feeding, at least with doses in the range of 180 to 300 mg daily.

On the basis of this study, the American Academy of Pediatrics considers[2] that pyridostigmine is usually compatible with breast feeding.

1. Hardell L-I, *et al.* Pyridostigmine in human breast milk. *Br J Clin Pharmacol* 1982; **14:** 565–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/02/06)

Effects on the joints. Several years after starting oral pyridostigmine bromide 60 mg five times daily, a middle-aged woman had episodes of bilateral arthralgia and hyperalgesia of her hips, knees, toes, and shoulders.[1] Symptoms resolved when pyridostigmine was stopped and rechallenge was positive on several occasions.

1. Rostedt A, Stålberg E. Joint pain and hyperalgesia due to pyridostigmine bromide in a patient with myasthenia gravis. *Neurology* 2004; **62:** 835–6.

Psychosis. Postoperative psychosis in a patient with myasthenia gravis who received large doses of pyridostigmine bromide was attributed to bromide intoxication,[1] but this diagnosis has been challenged.[2]

1. Rothenberg DM, *et al.* Bromide intoxication secondary to pyridostigmine bromide therapy. *JAMA* 1990; **263:** 1121–2.
2. Senecal P-E, Osterloh J. Confusion from pyridostigmine bromide: was there bromide intoxication? *JAMA* 1990; **264:** 454–5.

Renal impairment. During use of pyridostigmine for the reversal of neuromuscular blockade produced by competitive neuromuscular blockers, pyridostigmine kinetics were not significantly different after renal transplantation in 5 patients compared with those in 5 patients with normal renal function. However, in 4 anephric patients the elimination half-life was significantly in-