Antimyasthenics

This chapter includes those drugs used for their anticholinesterase action in the treatment of myasthenia gravis and related neuromuscular disorders. Other groups of drugs playing an important role in the management of myasthenia are the corticosteroids (p.1490) and some drugs with immunosuppressant actions discussed in the chapters on Antineoplastics (p.635) and Immunosuppressants (p.1810).

Eaton-Lambert myasthenic syndrome

Eaton-Lambert myasthenic syndrome is a rare auto-immune disease of the neuromuscular junction. Unlike myasthenia gravis (below), in which autoantibodies affect acetylcholine receptors, antibodies in Eaton-Lambert syndrome act presynaptically to reduce release of acetylcholine. Weakness mostly affects the proximal muscles, particularly those of the limbs; respiratory and ocular muscles are usually spared. Autonomic symptoms including dry mouth, constipation, and impotence are common. Over half of patients also have small cell carcinoma of the lung. Successful treatment of the tumour often leads to some improvement in symptoms.

The symptomatic treatment of Eaton-Lambert syndrome involves the use of drugs that increase the availability of acetylcholine at the neuromuscular junction. Response to treatment with *anticholinesterases* alone is poor and treatment with *amifampridine*, which increases acetylcholine release, appears to be more effective, particularly when given with an anticholinesterase such as *pyridostigmine*. The use of similar drugs such as *guanidine* and *fampridine* is limited by severe adverse effects. Low-dose guanidine has been tried with pyridostigmine where amifampridine is not readily available. Although there has been some improvement with the combination, the incidence of adverse effects, especially gastrointestinal reactions, is still high. Immunosuppressants including *azathioprine* and *corticosteroids* are also used, and unlike in treatment for myasthenia gravis, corticosteroids do not appear to induce an initial exacerbation of symptoms. Plasma exchange or high-dose intravenous *normal immunoglobulin* have been tried in patients with severe weakness.

References.

1. Newsom-Davis J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers' J* 1993; **33:** 205–12.
2. Oh SJ, *et al.* Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1997; **20:** 1146–52.
3. Seneviratne U, de Silva R. Lambert-Eaton myasthenic syndrome. *Postgrad Med J* 1999; **75:** 516–20.
4. Pascuzzi RM. Myasthenia gravis and Lambert-Eaton syndrome. *Ther Apher* 2002; **6:** 57–68.
5. Sanders DB. Lambert-Eaton myasthenic syndrome: diagnosis and treatment. *Ann N Y Acad Sci* 2003; **998:** 500–8.
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Myasthenia gravis

Myasthenia gravis is an auto-immune disorder characterised by defective neuromuscular transmission and consequent muscular weakness. It is caused by the formation of autoantibodies to elements of the neuromuscular junction. In most patients, antibodies to the nicotinic acetylcholine receptor are present. However, about 10 to 15% of patients have so-called 'seronegative myasthenia', in whom antibodies to other elements such as muscle-specific tyrosine kinase (MuSK) may be present instead; the proportion of such patients is much higher among those with ocular myasthenia (disease confined to the extra-ocular muscles). The thymus appears to be involved in many patients and some have a thymoma. Classifications of the disease may be based on the distribution and severity of symptoms, on the age of onset, and on the presence or absence of thymoma. Other types of myasthenia include transient neonatal myasthenia due to transplacental passage of receptor antibodies, which may persist for 1 to 6 weeks in the infants of myasthenic mothers, penicillamine-induced myasthenia, and congenital myasthenia (see under Amifampridine, p.630).

Diagnosis of myasthenia gravis.

Antibody testing remains the gold standard for diagnosis of myasthenia gravis. Patients may often be tested first for their reaction to an anticholinesterase. Intravenous edrophonium preceded by atropine (Tensilon test) is the most commonly used anticholinesterase test because of its rapid onset and short duration of action. Severe adverse effects can occasionally occur so testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available. A positive result is considered to be a rapid but temporary increase in muscle strength. Repetitive nerve stimulation is also used as a diagnostic test but, like the anticholinesterase test, is not specific for myasthenia gravis. Computed tomography or magnetic resonance imaging may be used to detect thymoma.

Treatment of myasthenia gravis.

- Symptomatic treatment is with an *anticholinesterase*; pyridostigmine and neostigmine are those most commonly used. Most patients prefer pyridostigmine as it produces less muscarinic adverse effects and has a longer duration of action, although the quicker onset of action of neostigmine may offer an advantage at the beginning of the day. The dose must be adjusted to give the optimum therapeutic response but muscle strength may not be restored to normal and some patients must live with a degree of disability. The effect may vary for different muscles and the dosage should be adjusted so that the bulbar and respiratory muscles receive optimum treatment. Generally, anticholinesterases only provide partial remission and their effects tend to diminish with continued treatment. Overdosage may lead to a 'cholinergic crisis' (see Adverse Effects of Neostigmine, p.631). Edrophonium may be employed to establish whether the patient is underdosed or overdosed.
- *Corticosteroids* are the main immunosuppressive drugs used for treatment. They are also useful in patients with ocular myasthenia, who as a group respond poorly to anticholinesterases and to thymectomy, provided that their disability is severe enough to warrant long-term corticosteroid treatment with its attendant adverse effects. Many start with low doses such as 5 to 20 mg of prednisolone daily or on alternate days, to reduce the risk of steroid-induced exacerbations of weakness, and increase the dose slowly thereafter according to response; an improvement is usually seen after a few weeks. Others use more aggressive regimens to obtain a more rapid response and start with large doses such as 60 to 80 mg of prednisolone daily. Whichever method is used, once clinical benefit has been obtained the regimen should be modified to alternate-day dosage, with the dose being slowly tapered when the patient is in remission. Patients taking corticosteroids require less anticholinesterase therapy and, if the dosage of the anticholinesterase is not reduced, an initial deterioration in the myasthenia may occur in the first few weeks of treatment (see also under Interactions of Neostigmine, p.632). It is rarely possible to withdraw corticosteroids completely but some patients may be maintained satisfactorily on as little as 10 mg on alternate days. If remission cannot be maintained on low-dose prednisolone, addition of azathioprine at a dosage of 2 to 3 mg/kg daily may be considered.
- Addition of *azathioprine* to treatment may allow a reduction in the dose of both corticosteroids and anticholinesterases. Azathioprine may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient, but it has a much slower onset of action than corticosteroids and is not usually used alone. *Ciclosporin* is effective in some patients unresponsive to standard combinations but serious adverse effects including nephrotoxicity may limit its use; the time to response is similar to that with corticosteroids. Other drugs such as *cyclophosphamide* and *methotrexate* have also been tried and benefit has been reported with *mycophenolate mofetil* and *tacrolimus*. However, a recent systematic review has found that only a small number of randomised controlled studies have been conducted on the use of immunosuppressive drugs for myasthenia gravis and most have been short-term. The review of this limited evidence concluded that, apart from cyclophosphamide used alone or ciclosporin used alone or with corticosteroids, there was no clear evidence of benefit from use of other immunosuppressants.
- Plasma exchange provides a dramatic but short-lived improvement and is useful as a short-term measure in myasthenic crisis to improve ill patients while other therapies take effect, but there is no evidence that repeated plasma exchange combined with immunosuppression is superior to immunosuppression alone. A similar short-term benefit has been seen from the use of high-dose intravenous *normal immunoglobulins*; however, a systematic review considered further study to be warranted.
- Thymectomy may be offered to all patients sufficiently fit to undergo surgery unless they have minimal symptoms, purely ocular disease, or late onset or seronegative disease. Thymectomy is usually avoided in prepubertal children because of concern over the effect on growth and the developing immune system; it has been suggested that symptomatic treatment with anticholinesterases should be continued until adolescence, when the disease often improves spontaneously. After thymectomy, remission or improvement may be expected in about 80% of patients without thymomas, although this may take some years; the response is poorer in those with thymomas.

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5. Pascuzzi RM. Myasthenia gravis and Lambert-Eaton syndrome. *Ther Apher* 2002; **6:** 57–68.
6. Vincent A, Drachman DB. Myasthenia gravis. *Adv Neurol* 2002; **88:** 159–88.
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13. Schneider-Gold C, *et al.* Corticosteroids for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/02/06).
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15. Hart IK, *et al.* Immunosuppressive agents for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).
16. Gajdos P, *et al.* Intravenous immunoglobulin for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 28/05/08).

Ambenonium Chloride *(BAN, rINN)*

Ambenonii Chloridum; Ambénonium, Chlorure d'; Ambenoniumklorid; Ambenoniumkloridi; Ambestigmini Chloridum; Cloruro de ambenonio; Win-8077. *N,N'*-Oxalylbis(*N*-2-aminoethyl-*N*-2-chlorobenzyldiethylammonium) dichloride.

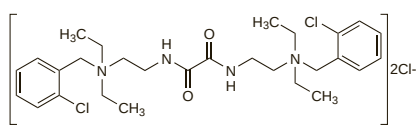
Амбенония Хлорид

$C_{28}H_{42}Cl_4N_4O_2$ = 608.5.

CAS — 7648-98-8 (ambenonium); 115-79-7 (anhydrous ambenonium chloride); 52022-31-8 (ambenonium chloride tetrahydrate).

ATC — N07AA30.

ATC Vet — QN07AA30.



Pharmacopoeias. In *Jpn.*

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631.

Ambenonium produces fewer muscarinic adverse effects than neostigmine. As there is only slight warning of overdosage, routine use of atropine with ambenonium is contra-indicated be-

cause the muscarinic symptoms of overdosage may be suppressed leaving only the more serious nicotinic effects (fasciculation and paralysis of voluntary muscle).

Pharmacokinetics
Ambenonium chloride is poorly absorbed from the gastrointestinal tract. It does not appear to be hydrolysed by cholinesterases.

Uses and Administration
Ambenonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632), but of longer duration. Ambenonium chloride is given orally in the treatment of myasthenia gravis (p.629) in usual doses of 5 to 25 mg three or four times daily, adjusted according to response. It may be of value in patients who cannot tolerate neostigmine or pyridostigmine.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Mytelase; ***Fr.:*** Mytelase; ***Gr.:*** Mytelase; ***Hung.:*** Mytelase; ***Pol.:*** Mytelase; ***Swed.:*** Mytelase; ***USA:*** Mytelase.

Amifampridine *(rINN)*

Amifampridina; Amifampridinum; 3,4-Diaminopyridine. Pyridine-3,4-diamine.

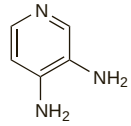
Амифампридин

$C_5H_7N_3$ = 109.1.

CAS — 54-96-6.

ATC — N07XX05.

ATC Vet — QN07XX05.



Profile
Amifampridine has similar actions and uses to fampridine (p.631) but is reported to be more potent in enhancing the release of acetylcholine from nerve terminals. It is used in the Eaton-Lambert myasthenic syndrome (below) and other myasthenic conditions. It has been tried in multiple sclerosis and in botulism. There have been isolated reports of seizures and amifampridine is therefore contra-indicated in patients with epilepsy.

Congenital myasthenia. Congenital or hereditary myasthenia is a heterogeneous group of rare disorders associated with various defects in neuromuscular transmission including presynaptic impairment of acetylcholinesterase release, postsynaptic abnormality of acetylcholine receptors, or a deficiency of acetylcholinesterase.[1] Symptoms may be similar to those of myasthenia gravis (p.629) but there are no immunological abnormalities. Although some forms may respond to anticholinesterases, therapy is usually unsatisfactory. Experience in 16 patients[2] has suggested that amifampridine used alone or with anticholinesterases may be of benefit. Clinical improvement was seen in 5 of 11 patients with congenital myasthenia who were given amifampridine as part of a placebo-controlled study; 3 of the 11 responded to placebo.[3] There have also been reports of benefit from the use of quinidine sulfate in patients with the slow-channel congenital myasthenic syndrome.[4]

1. Engel AG. Congenital myasthenic syndromes. *Neurol Clin North Am* 1994; **12:** 401–37.
2. Palace J, *et al.* 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. *J Neurol Neurosurg Psychiatry* 1991; **54:** 1069–72.
3. Anlar B, *et al.* 3,4-Diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial. *J Child Neurol* 1996; **11:** 458–61.
4. Harper CM, Engel AG. Quinidine sulfate therapy for the slow-channel congenital myasthenic syndrome. *Ann Neurol* 1998; **43:** 480–4.

Eaton-Lambert myasthenic syndrome. Daily doses of up to 100 mg of amifampridine by mouth have been found[1] to be effective in the treatment of both the motor and autonomic deficits of patients with Eaton-Lambert syndrome (p.629). A usual starting dose of 10 mg given three or four times daily increasing if necessary to a maximum of 20 mg given five times daily has been used.[2] However, some workers have recommended limiting the dose to 80 mg daily because of the increased risk of seizures with higher doses.[3] Adverse effects appear to be mainly mild and dose related,[1] although there is a report of cardiac arrest following toxicity.[4] Most patients experience some form of paraesthesia up to 60 minutes after a dose.[1-3] Amifampridine can produce mild excitatory effects and some patients may experience difficulty in sleeping.

1. McEvoy KM, *et al.* 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med* 1989; **321:** 1567–71.
2. Newsom-Davis J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers' J* 1993; **33:** 205–212.
3. Sanders DB, *et al.* A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* 2000; **54:** 603–7.
4. Boerma CE, *et al.* Cardiac arrest following an iatrogenic 3,4-diaminopyridine intoxication in a patient with Lambert-Eaton myasthenic syndrome. *J Toxicol Clin Toxicol* 1995; **33:** 249–51.

Multiple sclerosis. Amifampridine has been tried in the management of multiple sclerosis (p.892). In a crossover study[1] involving 36 patients with multiple sclerosis, amifampridine given in a dosage of up to 100 mg daily improved symptoms of leg weakness to a greater extent than placebo but paraesthesia and abdominal pain which occurred in most patients were dose-limiting in some. A systematic review[2] of the use of aminopyridines for symptomatic management of multiple sclerosis was unable to come to any conclusion, and commented on the problem of publication bias in this area.

1. Bever CT, *et al.* Treatment with oral 3,4-diaminopyridine improves leg strength in multiple sclerosis patients: results of a randomized, double-blind, placebo-controlled, crossover trial. *Neurology* 1996; **47:** 1457–62.
2. 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).

Distigmine Bromide *(BAN, rINN)*

BC-51; Bispyridostigmine Bromide; Bromuro de distigmina; Distigmiinibromidi; Distigminbromid; Distigmine, Bromure de; Distigmini Bromidum; Hexamarium Bromide. 3,3′-[*N,N*′-Hexamethylenebis(methylcarbamoyloxy)]bis(1-methylpyridinium bromide).

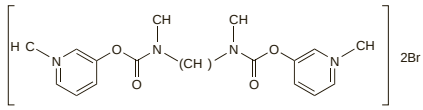
Дистигмина Бромид

$C_{22}H_{32}Br_2N_4O_4$ = 576.3.

CAS — 15876-67-2.

ATC — N07AA03.

ATC Vet — QN07AA03.



Pharmacopoeias. In *Jpn*.

Adverse Effects, Treatment, and Precautions
As for Neostigmine, p.631. The anticholinesterase action of distigmine, and hence its adverse effects, may be prolonged, and if treatment with atropine is required it should be maintained for at least 24 hours. Distigmine may stimulate uterine contractions and UK licensed product information has advised that it should be avoided in pregnancy.

Interactions
As for Neostigmine, p.632.

Pharmacokinetics
Distigmine is poorly absorbed from the gastrointestinal tract.

Uses and Administration
Distigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632) but more prolonged. Maximum inhibition of plasma cholinesterase occurs 9 hours after a single intramuscular dose, and persists for about 24 hours.

Although it is rarely used, distigmine bromide may be given orally with short-acting parasympathomimetics for the treatment of **myasthenia gravis** (p.629); patients being treated with parasympathomimetics tend to prefer pyridostigmine. The initial dose is 5 mg daily before breakfast, increased at intervals of 3 to 4 days if necessary to a maximum of 20 mg daily; children may be given up to 10 mg daily according to age.

Distigmine is one of several drugs that have been used in the prevention and treatment of **postoperative gastrointestinal atony** (see Decreased Gastrointestinal Motility, p.1694). It has also been used in **postoperative urinary retention** (p.2180), although it has been superseded by catheterisation. A dose of 500 micrograms of distigmine bromide was injected intramuscularly about 24 to 72 hours after surgery and repeated at intervals of 1 to 3 days until normal function was restored. Alternatively it has been given orally in a dose of 5 mg daily thirty minutes before breakfast. A similar oral dose, given daily or on alternate days, has been used in the management of **neurogenic bladder**.

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Ubretid; ***Cz.:*** Ubretid; ***Fin.:*** Ubretid†; ***Ger.:*** Ubretid; ***Gr.:*** Ubretid; ***Hong Kong:*** Ubretid; ***Hung.:*** Ubretid†; ***Neth.:*** Ubretid; ***Pol.:*** Ubretid; ***Port.:*** Tonus†; ***Rus.:*** Ubretid (Убретид); ***Singapore:*** Ubretid; ***Switz.:*** Ubretid; ***UK:*** Ubretid.

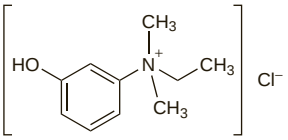
Edrophonium Chloride *(BAN, rINN)*

Cloruro de edrofonio; Edrofonio chloridas; Edrofonium-chlorid; Edrofoniumklorid; Edrofoniumkloridi; Edrofonyum Klorür; Edrophonii chloridum; Édrophonium, chlorure d'. Ethyl(3-hydroxyphenyl)dimethylammonium chloride.

Эдрофония Хлорид

$C_{10}H_{16}ClNO$ = 201.7.

CAS — 312-48-1 (edrophonium); 116-38-1 (edrophonium chloride).



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

Ph. Eur. 6.2 (Edrophonium Chloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Edrophonium Chloride). A white odourless crystalline powder. Soluble 1 in 0.5 of water and 1 in 5 of alcohol; insoluble in chloroform and in ether. A 10% solution in water is practically colourless and the pH is between 4.0 and 5.0.

Adverse Effects, Treatment, and Precautions
As for Neostigmine, p.631.

Interactions
As for Neostigmine, p.632.

Uses and Administration
Edrophonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity. It has actions similar to those of neostigmine (p.632) but its effect on skeletal muscle is claimed to be particularly prominent. It has a rapid onset but short duration of action. In patients with myasthenia gravis, there is immediate subjective improvement and muscle strength increases. This effect usually lasts only for about 5 to 15 minutes, after which time the typical signs and symptoms return; because of its brief action the drug is not suitable for the routine treatment of myasthenia gravis.

Edrophonium chloride is used in **myasthenia gravis** (p.629) both diagnostically and to distinguish between under- or over-treatment with other anticholinesterases.

- The usual *diagnostic procedure* is to inject 2 mg intravenously and, if no adverse reaction occurs within 30 to 45 seconds, to continue with the injection of a further 8 mg. In the UK the recommended total dose for children is 100 micrograms/kg, one-fifth of the dose being given initially, followed 30 seconds later by the remainder if no adverse effects develop; the *BNFC* suggests that this dose may be given to those aged from 1 month to 12 years. In the USA a total dose of 5 mg for children weighing less than 34 kg and 10 mg for heavier children is recommended, with one-fifth of the dose being given initially followed by increments of 1 mg every 30 to 45 seconds; the recommended total dose for infants is 500 micrograms.

  When intravenous injection is difficult edrophonium chloride may be given by intramuscular injection; the usual dose in adults is 10 mg while children below 34 kg in weight may be given 2 mg and heavier children 5 mg; a suggested dose for infants is 0.5 to 1 mg given intramuscularly or subcutaneously. Atropine should always be available when the test is carried out in order to treat any severe muscarinic reactions that may occur.
- To *detect under- or over-treatment*, test doses of 1 to 2 mg of edrophonium chloride are given intravenously to distinguish severe symptoms of myasthenia gravis due to inadequate therapy from the effects of overdosage with anticholinesterase drugs. If treat-