could be fatal in the absence of ventilatory support. To avoid the risk of secondary infection from an indwelling intraspinal catheter intermittent intrathecal baclofen has also been used.[7,8]

1. Müller H, *et al.* Intrathecal baclofen in tetanus. *Lancet* 1986; **i:** 317–18.
2. Dressnandt J, *et al.* Intrathecal baclofen in tetanus: four cases and a review of reported cases. *Intensive Care Med* 1997; **23:** 896–902.
3. Engrand N, *et al.* The efficacy of intrathecal baclofen in severe tetanus. *Anesthesiology* 1999; **90:** 1773–6.
4. Boots RJ, *et al.* The treatment of tetanus with intrathecal baclofen. *Anaesth Intensive Care* 2000; **28:** 438–42.
5. Santos ML, *et al.* Intrathecal baclofen for the treatment of tetanus. *Clin Infect Dis* 2004; **38:** 321–8.
6. Romijn JA, *et al.* Reversible coma due to intrathecal baclofen. *Lancet* 1986; **ii:** 696.
7. Demaziere J, *et al.* Intermittent intrathecal baclofen for severe tetanus. *Lancet* 1991; **337:** 427.
8. Saissy JM, *et al.* Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. *Intensive Care Med* 1992; **18:** 241–4.

Tourette's syndrome. Improvement was noted in children with Tourette's syndrome (see Tics, p.954) treated with baclofen compared with placebo in a small study.[1]

1. Singer HS, *et al.* Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial. *Neurology* 2001; **56:** 599–604.

Urinary incontinence. Baclofen has been used with some benefit in the management of urinary incontinence and retention (p.2180) secondary to lesions of the spinal cord.

References.

1. Hachen HJ, Krucker V. Clinical and laboratory assessment of the efficacy of baclofen (Lioresal) on urethral sphincter spasticity in patients with traumatic paraplegia. *Eur Urol* 1977; **3:** 237–40.
2. Leyson JFJ, *et al.* Baclofen in the treatment of detrusor-sphincter dyssynergia in spinal cord injury patients. *J Urol (Baltimore)* 1980; **124:** 82–4.
3. Kums JJM, Delhaas EM. Intrathecal baclofen infusion in patients with spasticity and neurogenic bladder disease. *World J Urol* 1991; **9:** 153–6.

Preparations

BP 2008: Baclofen Oral Solution; Baclofen Tablets;
USP 31: Baclofen Oral Suspension; Baclofen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Baclodox; Lioresal; ***Austral.:*** Baclo; Baclohexal†; Clofen; Lioresal; Stelax; ***Austria:*** Lioresal; ***Belg.:*** Lioresal; ***Braz.:*** Baclon; Lioresal; ***Canad.:*** Lioresal; Liotec†; Nu-Baclo; ***Chile:*** Cetril; Lioresyl; ***Denm.:*** Lioresal; ***Fin.:*** Baclon; Baclopar; Lioresal; ***Fr.:*** Lioresal; ***Ger.:*** Lebic; Lioresal; ***Gr.:*** Jofen†; Lioresal; Miorel; Vioridon; ***Hong Kong:*** Lioresal; Stelax; ***Hung.:*** Lioresal; ***India:*** Lioresal; ***Indon.:*** Lioresal; ***Irl.:*** Baclopar; Lioresal; ***Israel:*** Baclosal; Lioresal; ***Ital.:*** Lioresal; ***Malaysia:*** Clofen; Lioresal; ***Neth.:*** Lioresal; ***Norw.:*** Lioresal; ***NZ:*** Pacifen; ***Philipp.:*** Lioresal; Onelaxant-R; ***Port.:*** Lioresal; ***Rus.:*** Baclosan (Баклосан); ***S.Afr.:*** Lioresal; ***Singapore:*** Lioresal†; ***Spain:*** Lioresal; ***Swed.:*** Lioresal; ***Switz.:*** Lioresal; ***Thai.:*** Baclosal; Fenisal; Liobac; Lioresal; ***Turk.:*** Lioresal; ***UK:*** Baclospas†; Lioresal; Lyflex; ***USA:*** Kemstro; Lioresal; ***Venez.:*** Lioresal.

Botulinum Toxins

Toxinas botulínicas.
ATC — M03AX01.
ATC Vet — QM03AX01.

Description. Botulinum toxins A and B are neurotoxins produced by *Clostridium botulinum*. They are proteins comprising a heavy chain thought to be responsible for binding to the target cells and translocation of the toxin across the cell membrane, linked by a disulfide bond to a light chain responsible for the toxic activity.

Botulinum A Toxin

Botuliinitoksiini tyyppi A; Botulinum A Toksini; Toxin typ A mot botulism; Toxina botulínica A; Toxine botulinique type A; Toxinum botulinicum typum A.

Pharmacopoeias. *Eur.* (see p.vii) includes the injection.
Ph. Eur. 6.2 (Botulinum Toxin Type A for Injection; Toxinum Botulinicum Typum A ad Iniectabile). A dried preparation containing purified botulinum neurotoxin type A, which may be present in the form of a complex with haemagglutinins and non-toxic proteins, prepared from a suitable strain of *Clostridium botulinum* type A.

Botulinum B Toxin

Botulinum B Toksini; Toxina botulínica B.

Units

The dose of preparations containing botulinum toxins A or B is expressed in terms of units, but the available preparations are used at different doses for the same indications, and the units of one preparation cannot be considered to apply to another.

Adverse Effects

Injections of botulinum toxins have been associated with a transient burning sensation, bruising at the injection site, and local weakness. Adverse reactions related to the spread of botulinum toxins distant to the site of injection have been reported and sometimes this was associated with significant debility or a fatal outcome in very rare cases. Exaggerated muscle weakness may occur with therapeutic doses. Deep or misplaced injections may paralyse nearby muscle groups and excessive doses may paralyse distant muscles. Overdosage can produce a widespread paralysis.

There have been occasional reports of hypersensitivity reactions such as skin rashes and flu-like symptoms. There have also been rare reports of cardiovascular adverse effects, including arrhythmia and myocardial infarction, and of seizures or convulsions, particularly in predisposed patients.

- The most common adverse effects **after injection into muscles around the eye**, such as in the management of blepharospasm, hemifacial spasm, or strabismus, are ptosis, lachrymation, photophobia, ocular irritation, and facial swelling. Some patients may be unable to close the eyelid completely. Other adverse effects that have been reported include ectropion and entropion, and diplopia. Patients experience a reduction in blinking and this can lead to dry eye, keratitis, and corneal damage. Angle-closure glaucoma has been reported. Vertical deviation has also occurred in patients treated for horizontal strabismus. Needle penetrations of the eye during treatment of strabismus have resulted in vitreous and retrobulbar haemorrhages.
- Dysphagia is the most common adverse effect **after injection into neck muscles** in the treatment of spasmodic torticollis and there may be pooling of saliva with risk of aspiration in severely affected patients (*important*, see also Precautions, below). Dry mouth, paralysis of the vocal cords, and weakness of the neck muscles may also occur. Generalised weakness, malaise, nausea, and visual disturbances have occasionally been reported. Other effects which have occurred rarely include drowsiness, numbness, stiffness, ptosis, and headache. Respiratory difficulties, associated with the use of large doses, have occurred on rare occasions.
- Adverse effects most frequently associated with **injection into the lower limbs** in the treatment of cerebral palsy include falling, leg pain, and local and general weakness; lethargy and leg cramps have also been reported.
- Common adverse effects **after injection into the upper limb** in the treatment of spasticity associated with stroke are arm pain, dysphagia, muscle weakness, and hypertonia. A perceived increase in non-axillary sweating, within one month of the injection, has been reported after treatment for hyperhidrosis of the axillae; rarely, mild transient weakness of the arms has also occurred.
- Headache is the most frequent adverse effect **after injection into the muscles around the forehead** in the treatment of glabellar (frown) lines. Other adverse effects frequently reported include ptosis, facial pain, muscle weakness, and nausea.

◊ Reviews.

1. Klein AW. Complications and adverse reactions with the use of botulinum toxin. *Dis Mon* 2002; **48:** 336–56.

Incidence of adverse effects. It has been suggested that the difference between botulinum A toxin preparations may not be confined to just a numerical dosage adjustment.[1] Reviews of the literature have suggested that there may also be a difference in the incidence of adverse effects. The reported frequency of dysphagia for *Dysport* (28% and 44%) in patients with spasmodic torticollis was greater than that for *Botox* (9.5 to 17%). This variation might relate to differences in bioactivity not recognised by the mouse lethality bioassay which is used to determine the potency of preparations.

1. Borodic G. Therapeutic botulinum toxin. *Lancet* 1994; **344:** 1370.

Angiosarcoma. It has been suggested[1] that botulinum A toxin injection might have acted as a triggering factor for angiosarcoma in a 66-year-old patient being treated for blepharospasm.

1. Kárpáti S, *et al.* Human herpesvirus type 8-positive facial angiosarcoma developing at the site of botulinum toxin injection for blepharospasm. *Br J Dermatol* 2000; **143:** 660–2.

Antibody formation. Neutralising antibodies that reduce or abolish the beneficial effects of treatment have been found after prolonged treatment with botulinum A toxin.[1] A review[2] in 1994 considered that there was growing concern over the development of antibodies after repeated injections, as many of the conditions for which botulinum toxin is indicated require indefinite treatment. Antibody formation was reported to be more common with high doses (as in spasmodic torticollis) than after low doses (as for blepharospasm). The occurrence of antibodies appeared to correlate with the dose per injection, the quantity of botulinum protein given per injection, the number of injections given, and the frequency of injections.

Antibodies have also developed after the use of botulinum B toxin. However, botulinum toxin B is antigenically distinct from botulinum A toxin, and may be of value in patients who develop resistance to treatment associated with antibody formation to type A toxin.[3] Botulinum F toxin is also antigenically distinct and is being studied in a similar way.

1. Hambleton P, *et al.* Antitoxins and botulinum toxin treatment. *BMJ* 1992; **304:** 959–60.
2. Borodic GE, Pearce LB. New concepts in botulinum toxin therapy. *Drug Safety* 1994; **11:** 145–52.
3. Brin MF, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1431–8.

Biliary colic. A 43-year-old woman with no history of gallbladder disease had single episodes of biliary colic after each of 3 sessions of treatment with botulinum A toxin for blepharospasm.[1] Botulinum A toxin might have exerted a systemic effect to block acetylcholine release leading to gallbladder hypomotility with delayed emptying and stasis.

1. Schnider P, *et al.* Gallbladder dysfunction induced by botulinum A toxin. *Lancet* 1993; **342:** 811–12.

Dysphagia. By November 1993, the UK CSM had received 4 reports of severe dysphagia with choking in patients given injections of botulinum A toxin into the neck muscles as a treatment for torticollis.[1] The dysphagia developed 5 to 7 days after the injection and in one patient it was persisting 6 weeks after the injection. The dysphagia led to aspiration of the stomach contents into the lungs and one patient with a history of poor lung function died from bronchopneumonia. Dysphagia is also reported to be a common adverse effect in patients with spasmodic torticollis being treated with Botulinum B toxin.[2]

See also Incidence of Adverse Effects, above for further reference to dysphagia as an adverse effect.

1. Committee on Safety of Medicines/Medicines Control Agency. Reminder: botulinum type A toxin (Dysport)—severe dysphagia with unlicensed route of administration. *Current Problems* 1993; **19:** 11. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Lew MF, *et al.* The safety and efficacy of botulinum toxin type B in the treatment of patients with cervical dystonia: summary of three controlled clinical trials. *Neurology* 2000; **55** (suppl 5): S29–S35.

Effects on the eyes. Acute angle-closure glaucoma has been reported[1] in an 83-year-old woman after a series of injections of botulinum A toxin for the treatment of blepharospasm. Permanent extra-ocular muscle damage after botulinum A toxin injection into the left inferior rectus muscle has been reported[2] in a 70-year-old man.

1. Corridan P, *et al.* Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm. *Br J Ophthalmol* 1990; **74:** 309–10.
2. Mohan M, *et al.* Permanent extraocular muscle damage following botulinum toxin injection. *Br J Ophthalmol* 1999; **83:** 1309–10.

Treatment of Adverse Effects

The use of artificial tears may relieve keratitis and dry eye. In the event of overdosage general supportive care is required. The patient should be monitored for several days for signs of paralysis and artificial respiration may be necessary. Since the effects of botulinum toxins are irreversible once bound to nerve terminals, it is doubtful that specific botulinum antitoxin (p.2207) will be of value unless given very rapidly after overdosage.

Precautions

Botulinum toxin is contra-indicated in generalised disorders of muscle activity such as myasthenia gravis. As with other biological products, the potential for botulinum toxin to cause anaphylaxis should be considered. Botulinum toxins should be given with extreme caution to patients with neurological disorders or a history of dysphagia or aspiration. Patients or their carers should be advised to seek immediate medical attention if problems with swallowing or speech, or respiratory disorders develop.

Botulinum toxins should only be used by appropriately qualified and trained specialists. Injections must be made with great care, especially those into the neck, to

avoid unintended paralysis; the relevant anatomy, and any alterations due to previous surgery, must be understood before injection. Botulinum toxins should not be given if there is any infection at the proposed injection site.

The effects of botulinum toxins in pregnancy are unknown; fetal malformations and abortion have been reported in *rabbits*, and licensed product information recommends that botulinum toxins should not be given to pregnant women. Breast feeding is also considered a contra-indication: it is not clear whether the toxin is distributed into breast milk.

When **injected into the muscles around the eyes**, as for the treatment of blepharospasm, hemifacial spasm, or strabismus, reduced blinking can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with seventh cranial nerve disorders. Corneal sensation should be carefully tested in previously treated eyes, injection into the lower eyelid area avoided, and any resulting epithelial defect vigorously treated.

Handling. Residual botulinum A toxin or spillages should be inactivated by autoclaving or use of a dilute hypochlorite solution (0.5%). Botulinum B toxin may be decontaminated in a similar manner; a strong caustic solution may also be used.

Interactions

The effect of botulinum toxins may theoretically be potentiated by aminoglycosides or spectinomycin. Interactions may also occur with other drugs that have neuromuscular blocking activity, including lincosamides, polymyxins, tetracyclines, and muscle relaxants.

Uses and Administration

Botulinum toxins cause neuromuscular blockade by inhibiting the calcium-ion mediated release of acetylcholine at the motor nerve terminals, resulting in a diminished endplate potential and subsequent flaccid paralysis of the affected muscles. The paralysis persists until new nerve terminals form, usually within 2 to 4 months.

Botulinum A toxin is given as a complex usually with haemagglutinin by local injection in the treatment of hemifacial spasm, blepharospasm, spasmodic torticollis, lower limb spasticity in children with cerebral palsy, and upper limb spasticity associated with stroke in adults. Botulinum A toxin is also used for the management of strabismus and hyperhidrosis, and has also been approved for the treatment of glabellar (frown) lines in adults up to 65 years of age. It is being investigated for use in the management of several other disorders. Botulinum B toxin is also used in the management of spasmodic torticollis and, being antigenically distinct, it has the potential for use in patients who develop resistance to treatment due to the development of antibodies to type A toxin.

Doses of botulinum toxins A and B are expressed in terms of units, which have not been standardised between preparations (see under Units, above). Doses are therefore specific to each individual preparation; details are given below.

Botulinum F toxin is under investigation for the treatment of similar neuromuscular disorders.

◊ Reviews.

1. Borodic GE, Pearce LB. New concepts in botulinum toxin therapy. *Drug Safety* 1994; **11:** 145–52.
2. Hughes AJ. Botulinum toxin in clinical practice. *Drugs* 1994; **48:** 888–93.
3. Cheng CM, *et al.* Unlabeled uses of botulinum toxins: a review, part 1. *Am J Health-Syst Pharm* 2006; **63:** 145–52.
4. Cheng CM, *et al.* Unlabeled uses of botulinum toxins: a review, part 2. *Am J Health-Syst Pharm* 2006; **63:** 225–32.

Achalasia. The treatment of choice for achalasia (see Oesophageal Motility Disorders, p.1702) is mechanical dilatation of the lower oesophageal sphincter, or if necessary surgery, but more recently injection of botulinum A toxin[1-3] has been found to be effective. However, one year after treatment only 7 of 22 (32%) patients who received botulinum A toxin were in symptomatic remission compared with 14 of 20 (70%) patients treated with mechanical dilatation.[4] It was recommended that its use would be better reserved for patients thought to be at risk from mechanical dilatation or surgery.[3-5] Another study[6] showed that intrasphincteric injection of botulinum toxin A was safe and effective for the treatment of achalasia in the short and medium term, although only a weak correlation with dose emerged.

1. Pasricha PJ, *et al.* Intrasphincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995; **332:** 774–8. Correction. *ibid.*; **333:** 75.
2. Cuillière C, *et al.* Achalasia: outcome of patients treated with intrasphincteric injection of botulinum toxin. *Gut* 1997; **41:** 87–92.
3. da Silveira EBV, Rogers AI. Treatment of achalasia with botulinum A toxin. *Am J Ther* 2002; **9:** 157–61.
4. Vaezi MF, *et al.* Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut* 1999; **44:** 231–9.
5. Spiess AE, Kahrilas PJ. Treating achalasia: from whalebone to laparoscope. *JAMA* 1998; **280:** 638–42.
6. Annesse V, *et al.* A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. *Gut* 2000; **46:** 597–600.

Anal fissure. Anal fissure is a superficial tear in the mucosa of the distal anal canal characterised by pain on defaecation, rectal bleeding, and spasm of the anal sphincter. Healing, which is usually uneventful, may be helped by conservative management with bran and bulk laxatives and topical local anaesthetics for pain relief. Surgical treatment has been used for patients who develop a chronic condition but has been associated with high rates of long-term incontinence and recurrence. Although systematic reviews considered that surgery was more effective than alternative medical therapies,[1,2] a number of these have been investigated.[3] As hypertonicity of the internal anal sphincter may be involved in the pathophysiology of chronic anal fissure, local injections of botulinum A toxin have been used to produce paresis of this sphincter.[4-6] The duration of the effect appears to be long enough to allow complete healing of the fissure in most patients although some may relapse; a long-term, follow-up trial[7] involving 57 completely healed patients, noted a high recurrence rate (41.5%) once the effects of botulinum toxin disappeared. Temporary incontinence had been the only adverse effect reported during treatment.

Topical application of nitrates can relax the anal sphincter; numerous studies[8-10] have reported benefit from topical application of glyceryl trinitrate, although a high rate of spontaneous resolution with placebo has cast doubt over the degree of advantage in some studies.[1,9] Follow-up[11] of patients treated with glyceryl trinitrate indicated that after 24 to 38 months most had not experienced further problems or had had occasional recurrences which in the majority of cases had responded to further topical treatment. Isosorbide dinitrate ointment has also been tried, and may be of benefit with botulinum A toxin.[12]

Topical calcium antagonists also seem to be effective. Both diltiazem[13-15] and nifedipine[16,17] seem to be of benefit and there is evidence that they may be a better choice than topical glyceryl trinitrate.[16,17] Nifedipine has been combined with botulinum toxin;[17] it has also been given orally.[18]

1. Nelson R. A systematic review of medical therapy for anal fissure. *Dis Colon Rectum* 2004; **47:** 422–31.
2. Nelson R. Non surgical therapy for anal fissure. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 08/05/08).
3. Cook TA, *et al.* The pharmacology of the internal anal sphincter and new treatments of ano-rectal disorders. *Aliment Pharmacol Ther* 2001; **15:** 887–98.
4. Jost WH, Schimrigk K. Botulinum toxin in therapy of anal fissure. *Lancet* 1995; **345:** 188–9.
5. Maria G, *et al.* A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *N Engl J Med* 1998; **338:** 217–20.
6. Jost WH. Ten years' experience with botulin toxin in anal fissure. *Int J Colorectal Dis* 2002; **17:** 298–302.
7. Minguez M, *et al.* Long-term follow-up (42 months) of chronic anal fissure after healing with botulinum toxin. *Gastroenterology* 2002; **123:** 112–17.
8. Lund JN, Scholefield JH. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate ointment in treatment of anal fissure. *Lancet* 1997; **349:** 11–14. Correction. *ibid.*: 656.
9. Bailey HR, *et al.* Fissure Study Group. A study to determine the nitroglycerin ointment dose and dosing interval that best promote the healing of chronic anal fissures. *Dis Colon Rectum* 2002; **45:** 1192–9.
10. Scholefield JH, *et al.* A dose finding study with 0.1%, 0.2%, and 0.4% glyceryl trinitrate ointment in patients with chronic anal fissures. *Gut* 2003; **52:** 264–9.
11. Lund JN, Scholefield JH. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet* 1998; **352:** 1681.
12. Lysy J, *et al.* Topical nitrates potentiate the effect of botulinum toxin in the treatment of patients with refractory anal fissure. *Gut* 2001; **48:** 221–4.
13. Jonas M, *et al.* A randomized trial of oral vs topical diltiazem for chronic anal fissures. *Dis Colon Rectum* 2001; **44:** 1074–8.
14. Jonas M, *et al.* Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. *Dis Colon Rectum* 2002; **45:** 1091–5.
15. Bielecki K, Kolodziejczak M. A prospective randomized trial of diltiazem and glyceryltrinitrate ointment in the treatment of chronic anal fissure. *Colorectal Dis* 2003; **5:** 256–7.
16. Ezri T, Susmallian S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; **46:** 805–8.
17. Tranqui P, *et al.* Nonsurgical treatment of chronic anal fissure: nitroglycerin and dilatation versus nifedipine and botulinum toxin. *Can J Surg* 2006; **49:** 41–5.
18. Cook TA, *et al.* Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br J Surg* 1999; **86:** 1269–73.

Anismus. Anismus is a condition in which inappropriate contraction of the anal sphincters occurs when bowel evacuation is attempted; it seems to be a form of dystonia.

Treatment with botulinum A toxin was investigated in 7 patients with intractable constipation due mainly to anismus.[1] The toxin was injected bilaterally into the puborectalis muscle using an electromyographically guided needle; patients were allowed to continue with their laxatives throughout the study if required. Symptoms improved in all but one of the patients, although two patients could not be regarded as treatment successes because they developed faecal incontinence; four patients had an excellent clinical outcome. However, another study involving 24 patients found the clinical effectiveness of botulinum A toxin to be limited, and further studies are needed to determine its role in the treatment of anismus.[2]

1. Hallan RI, *et al.* Treatment of anismus in intractable constipation with botulinum A toxin. *Lancet* 1988; **ii:** 714–17.
2. Ron Y, *et al.* Botulinum toxin type-A in therapy of patients with anismus. *Dis Colon Rectum* 2001; **44:** 1821–6.

Blepharospasm. Blepharospasm is a focal dystonia characterised by repeated involuntary blinking caused by spasms of the orbicularis oculi muscle of the eye, and can result in functional blindness. Blepharospasm is often associated with other dystonias of the head and neck, such as Meige syndrome, in which patients also suffer from involuntary contractures of the muscles around the mouth. Oral drug treatment as used for dystonias in general (see p.809) is usually ineffective, and surgery (facial nerve avulsion) is often followed by recurrent spasm.[1] Local injections of botulinum A toxin into the orbicularis oculi muscle mimic the effect of surgical denervation of the muscle and are reported[2-6] to have been effective in over 70% of patients. Symptomatic improvement has been reported to last from about 9 to 15 weeks; no increase in duration of effect is apparent following multiple injections. In one retrospective study in patients with blepharospasm and Meige syndrome, treatment with botulinum A toxin was still effective in most patients 11 years after the start of therapy.[4]

For blepharospasm botulinum A toxin is injected into the orbicularis oculi of the upper and lower lids; injection into additional sites in the brow area and upper facial area may be indicated if the spasms interfere with vision. Doses of botulinum A toxin are expressed in terms of units, which have not been standardised between preparations. Doses are therefore *specific to each individual preparation*:

- The preparation *Botox* (*Allergan, UK*) is injected intramuscularly in an initial dose of 1.25 to 2.5 units at each site to a total of up to 25 units per eye. An effect is usually obtained within 3 days and reaches a peak after 1 to 2 weeks; each treatment lasts for about 3 months. If the response lasts less than 2 months the dose may be increased up to 5 units at each site but the total dose given in a 12-week period should not exceed 100 units. Giving more often than every 3 months confers no additional benefit. *Botox* (*Allergan*) is also available in the USA and given in similar doses, although higher cumulative doses of up to 200 units are allowed in a 30-day period
- The preparation *Xeomin (Merz, UK)* is injected intramuscularly in an initial dose of 1.25 to 2.5 units at each site to a total of up to 25 units per eye. An effect is usually obtained within 4 days; each treatment lasts for about 3 to 4 months. If the response lasts less than 2 months the dose may be increased up to 5 units at each site but the total dose given in a 12-week period should not exceed 100 units. Giving more often than every 3 months confers no additional benefit.
- For the preparation *Dysport* (*Ipsen, UK*) the initial dose is a total of 120 units per eye given as subcutaneous injections of 20 and 40 units per site. Subsequently the total dose may need to be reduced to 60 to 80 units per eye. With this preparation the relief of symptoms may begin within 2 to 4 days with a maximum effect being obtained within 2 weeks. Injections of *Dysport* should be repeated every 12 weeks or as required.

1. Kennedy RH, *et al.* Treatment of blepharospasm with botulinum toxin. *Mayo Clin Proc* 1989; **64:** 1085–90.
2. Grandas F. Blepharospasm: a review of 264 patients. *J Neurol Neurosurg Psychiatry* 1988; **51:** 767–72.
3. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol* 1992; **239:** 5–8.
4. Mauriello JA, *et al.* Treatment selections of 239 patients with blepharospasm and Meige syndrome over 11 years. *Br J Ophthalmol* 1996; **80:** 1073–6.
5. Defazio G, Livrea P. Primary blepharospasm: diagnosis and management. *Drugs* 2004; **64:** 237–44.
6. Costa J, *et al.* Botulinum toxin type A therapy for blepharospasm. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 28/03/06).

Cosmetic use. Botulinum A toxin has been used for the cosmetic treatment of facial lines and wrinkles and age-related neck degeneration.[1-5]

For the temporary improvement in appearance of moderate to severe glabellar (frown) lines two doses of botulinum A toxin are injected into each of the corrugator muscles and one dose into the procerus muscle. Doses of botulinum A toxin are expressed in terms of units, which have not been standardised between preparations. Doses are therefore *specific to each individual preparation*: the preparation *Botox Cosmetic* (*Allergan, USA*) is injected intramuscularly, not closer than 1 cm above the central eyebrow. A dose of 4 units is given into each of 5 sites to a total dose of

20 units. An effect is obtained in 1 to 2 days which increases in intensity in the first week; each treatment lasts for about 3 to 4 months. More frequent dosing is not recommended as safety and effectiveness have not been evaluated.

A preparation with a similar dosage regimen (*Vistabel; Allergan, UK*) is available in the UK.

1. Olver JM. Botulinum toxin A treatment of overactive corrugator supercilii in thyroid eye disease. *Br J Ophthalmol* 1998; **82:** 528–33.
2. Song KH. Botulinum toxin type A injection for the treatment of frown lines. *Ann Pharmacother* 1998 **32:** 1365–7.
3. Anonymous. Cosmetic use of botulinum toxin. *Med Lett Drugs Ther* 1999; **41:** 63–4.
4. Anonymous. Botulinum toxin (Botox Cosmetic) for frown lines. *Med Lett Drugs Ther* 2002; **44:** 47–8.
5. Carruthers A. Botulinum toxin type A: history and current cosmetic use in the upper face. *Dis Mon* 2002; **48:** 299–322.

Gastric motility disorders. Some benefit has been reported from the use of botulinum A toxin injection in gastric motility disorders (p.1694). In an open-label study[1] 6 diabetic patients with gastroparesis experienced an improvement in gastric emptying after treatment with botulinum A toxin.

1. Ezzeddine D, *et al.* Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 2002; **55:** 920–3.

Hand dystonia. Hand dystonia, or hand cramp, is a type of focal dystonia (p.809). It is more commonly reported in people who perform repetitive movements with their hands, such as writers, keyboard operators, and musicians. Treatment was traditionally with antimuscarinics, although with limited success, but botulinum toxin has increasingly become the first-line option.[1] A double-blind study reported that 8 out of 10 patients had greater subjective improvement in focal hand dystonia, compared with placebo, after treatment with botulinum A toxin given by the intramuscular route; objective improvement in muscle strength was seen in 6 patients.[2] However, pain and severe weakness in the shoulder region resembling neuralgic amyotrophy has been reported[3] in 2 patients injected with botulinum A toxin for writer's cramp. It was considered that if unexplained pain occurred in the shoulder or upper arm after a first injection of botulinum A toxin further injections were contra-indicated.

1. Karp BI. Botulinum toxin treatment of occupational and focal hand dystonia. *Mov Disord* 2004; **19** (suppl 8): S116–S119.
2. Cole R, *et al.* Double-blind trial of botulinum toxin for treatment of focal hand dystonia. *Mov Disord* 1995; **10:** 466–71.
3. Sheean GL, *et al.* Pain and remote weakness in limbs injected with botulinum toxin A for writer's cramp. *Lancet* 1995; **346:** 154–6.

Headache. The therapeutic effect of botulinum A toxin in headache was first seen as a coincidental adverse effect in patients receiving the drug for hyperfunctional facial lines. A review[1] of subsequent studies concluded that efficacy could be demonstrated for the prophylaxis of migraine (p.616); a small number of patients who received treatment during the acute phase of a migraine attack also experienced pain relief. Contradictory results had been reported in the studies evaluating tension-type headache (p.617) and continue to be reported.[2-4] However, in the original review[1] it was emphasised that an important finding had been the need to inject botulinum A toxin at the site of the pain or trigger points and not on a standardised basis, and that this should be considered in future studies. Improvement had been noted in individual cases of cluster headache (p.616) and in some patients with headache attributed to disorders of the neck.

Some benefit has also been seen with botulinum B toxin in the treatment of migraine and tension-type headaches.[5]

1. Göbel H, *et al.* Evidence-based medicine: botulinum toxin A in migraine and tension-type headache. *J Neurol* 2001; **248** (suppl 1): 34–8.
2. Ondo WG, *et al.* Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalalgia* 2004; **24:** 60–5.
3. Schulte-Mattler WJ, *et al.* Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. *Pain* 2004; **109:** 110–14.
4. Rozen D, Sharma J. Treatment of tension-type headache with Botox: a review of the literature. *Mt Sinai J Med* 2006; **73:** 493–8.
5. Fadeyi MO, Adams QM. Use of botulinum toxin type B for migraine and tension headaches. *Am J Health-Syst Pharm* 2002; **59:** 1860–2.

Hemifacial spasm. Hemifacial spasm is characterised by involuntary unilateral synchronous contractions of muscles innervated by the facial nerve. The spasms usually begin with twitching of muscles around the eye or mouth but as the disease progresses their frequency increases and they spread to involve the rest of the facial muscles. Hemifacial spasm may be improved by surgery but there is a risk of irreversible paralysis. Few drugs are effective for hemifacial spasm but carbamazepine has been reported to have been of help on occasions. Reports suggest that injections of botulinum A toxin may be effective in relieving symptoms in at least 75% of patients but there do not appear to be any studies comparing it against other treatments. Repeat injections are required by most patients every 3 to 4 months but long-term efficacy appears to be maintained. Dosage regimens of botulinum A toxin used in hemifacial spasm are similar to those used for blepharospasm (see above) although an electromyographically guided needle may be required to identify small muscles around the mouth.

References.

1. Elston JS. The management of blepharospasm and hemifacial spasm. *J Neurol* 1992; **239:** 5–8.
2. Chen R-S, *et al.* Botulinum toxin A injection in the treatment of hemifacial spasm. *Acta Neurol Scand* 1996; **94:** 207–11.
3. Boghen DR, Lesser RL. Blepharospasm and hemifacial spasm. *Curr Treat Options Neurol* 2000; **2:** 393–400.
4. Jost WH, Kohl A. Botulinum toxin: evidence-based medicine criteria in blepharospasm and hemifacial spasm. *J Neurol* 2001; **248** (suppl 1): 21–4.
5. Defazio G, *et al.* Botulinum toxin A treatment for primary hemifacial spasm: a 10-year multicenter study. *Arch Neurol* 2002; **59:** 418–20.
6. Costa J, *et al.* Botulinum toxin type A therapy for hemifacial spasm. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 28/03/06).

Hyperhidrosis. A number of drugs and surgical techniques have been used in the treatment of hyperhidrosis (p.1580). Botulinum A toxin is used in the management of focal hyperhidrosis because of its ability to block cholinergic transmission at nerve terminals innervating the sweat glands. Encouraging results have been obtained in patients with severe resistant focal hyperhidrosis using intradermal[1,2] or subcutaneous[3,4] injections and results from two larger multicentre studies[5,6] confirm that intradermal injection of botulinum A is effective and well-tolerated for the treatment of axillary hyperhidrosis. In the UK, it is given for this purpose as the preparation *Botox* (*Allergan, UK*), by intradermal injection in doses of 50 units to each axilla, evenly distributed in multiple sites approximately 1 to 2 cm apart. Clinical improvement generally occurs within a week of injection, and may last for 4 to 7 months; repeat injections may be given once the effects of the previous injection have subsided. *Botox* (*Allergan*) is also available in the USA for the treatment of axillary hyperhidrosis; it is given in similar doses.

Some workers[7] prefer to use intradermal injections for palmar hyperhidrosis in order to minimise the risk of reversible weakness of the small muscles of the hand reported with subcutaneous injection.

1. Naumann M, *et al.* Focal hyperhidrosis: effective treatment with intracutaneous botulinum toxin. *Arch Dermatol* 1998; **134:** 301–4.
2. Schnider P, *et al.* Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients. *Br J Dermatol* 2001; **145:** 289–93.
3. Schnider P, *et al.* Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. *Br J Dermatol* 1997; **136:** 548–52.
4. Schnider P, *et al.* Uses of botulinum toxin. *Lancet* 1997; **349:** 953.
5. Heckmann M, *et al.* Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001; **344:** 488–93.
6. Naumann M, *et al.* Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. *BMJ* 2001; **323:** 596–9.
7. Heckmann M, *et al.* Optimizing botulinum toxin therapy for hyperhidrosis. *Br J Dermatol* 1998; **138:** 553–4.

Hyperlachrymation. Botulinum A toxin may be of benefit[1,2] in the management of hyperlachrymation ('crocodile tears').

1. Riemann R, *et al.* Successful treatment of crocodile tears by injection of botulinum toxin into the lacrimal gland: a case report. *Ophthalmology* 1999; **106:** 2322–4.
2. Keegan DJ, *et al.* Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. *Br J Ophthalmol* 2002; **86:** 43–6.

Laryngeal dystonias. Botulinum A toxin has been tried in the treatment of spasmodic dysphonia,[1-3] focal laryngeal dystonia,[4] and dysfunctional spasm after total laryngectomy.[5] Botulinum B toxin has also been used.[6]

1. Whurr R, *et al.* Meta-analysis of botulinum toxin treatment of spasmodic dysphonia: a review of 22 studies. *Int J Lang Commun Disord* 1998; **33** (suppl): 327–9.
2. Gibbs SR, Blitzer A. Botulinum toxin for the treatment of spasmodic dysphonia. *Otolaryngol Clin North Am* 2000; **33:** 879–94.
3. Watts CCW, *et al.* Botulinum toxin injections for the treatment of spasmodic dysphonia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 07/05/08).
4. Marion M-H, *et al.* Stridor and focal laryngeal dystonia. *Lancet* 1992; **339:** 457–8.
5. Crary MA, *et al.* Using botulinum toxin A to improve speech and swallowing function following total laryngectomy. *Arch Otolaryngol Head Neck Surg* 1996; **122:** 760–3.
6. Sataloff RT, *et al.* Botulinum toxin type B for treatment of spasmodic dysphonia: a case report. *J Voice* 2002; **16:** 422–4.

Micturition disorders. Preliminary results[1] suggest that injection of botulinum A toxin into the detrusor muscle can increase functional bladder capacity and restore continence in patients with urinary incontinence (p.2180) after spinal cord injury who are resistant to antimuscarinics. Similar results[2] have been found in children with detrusor hyperreflexia caused by myelomeningocele.

Botulinum A toxin has also been tried in other bladder dysfunctions.[3,4] Reviews[5,6] have concluded that although there is some evidence that injection of botulinum toxins into the detrusor wall can improve symptoms of overactive bladder syndrome, further studies are warranted.

In a few small studies[7,8] the injection of botulinum A toxin into the prostate gland has been reported to relieve the symptoms of urinary retention associated with benign prostatic hyperplasia (p.2178).

1. Schurch B, *et al.* Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol (Baltimore)* 2000; **164:** 692–7.
2. Schulte-Baukloh H, *et al.* Efficacy of botulinum-A toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. *Urology* 2002; **59:** 325–7.
3. Phelan MW, *et al.* Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. *J Urol (Baltimore)* 2001; **165:** 1107–10.
4. Smith CP, *et al.* Botulinum toxin in urology: evaluation using an evidence-based medicine approach. *Nat Clin Pract Urol* 2004; **1:** 31–7.
5. Schurch B. Botulinum toxin for the management of bladder dysfunction. *Drugs* 2006; **66:** 1301–18.
6. Duthie J, *et al.* Botulinum toxin injections for adults with overactive bladder syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/05/08).
7. Maria G, *et al.* Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology* 2003; **62:** 259–65.
8. Kuo H-C. Prostate botulinum A toxin injection—an alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology* 2005; **65:** 670–4.

Nystagmus. Surgery, corrective spectacles, and drug therapy have all been tried for the treatment of nystagmus (rapid involuntary movement of the eyeball). Retrobulbar injection of botulinum A toxin has produced improvement in patients with acquired or congenital nystagmus.[1-4] In 6 patients with acquired nystagmus visual acuity was improved, and the amplitude of the nystagmus was reduced, but the frequency was generally unchanged and the need for repeated injections and adverse effects such as diplopia limited patient acceptability.[1]

1. Repka MX, *et al.* Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol* 1994; **112:** 1320–4.
2. Carruthers J. The treatment of congenital nystagmus with Botox. *J Pediatr Ophthalmol Strabismus* 1995; **32:** 306–8.
3. Lennerstrand G, *et al.* Treatment of strabismus and nystagmus with botulinum toxin type A: an evaluation of effects and complications. *Acta Ophthalmol Scand* 1998; **76:** 27–37.
4. Stahl JS, *et al.* Medical treatment of nystagmus and its visual consequences. *J R Soc Med* 2002; **95:** 235–7.

Ocular surgery. Ptosis is a common adverse effect of botulinum A toxin but therapeutic ptosis induced with botulinum toxin has been described as a useful adjunct in the management of patients undergoing epikeratoplasty since it promoted stabilisation of the epithelium on the graft.[1]

1. Freegard T, *et al.* Therapeutic ptosis with botulinum toxin in epikeratoplasty. *Br J Ophthalmol* 1993; **77:** 820–2.

Pain. There have been anecdotal reports of the use of botulinum A toxin in the treatment of painful disorders such as postcholecystectomy pain associated with sphincter of Oddi dysfunction,[1] and relief of orofacial pain associated with temporomandibular joint dysfunction[2] and facial arthromyalgia.[3] Promising results have been obtained from an open study[4] investigating botulinum toxin as a treatment for chronic refractory tennis elbow in 14 patients. Its efficacy in relieving pain in other chronic conditions such as low back pain, and myofascial pain, in addition to improving function, has also been shown in individual studies.[5] The general management of pain is discussed on p.2 with separate sections on biliary and renal colic (p.5), low back pain (p.7), orofacial pain (p.8), and soft-tissue rheumatism (p.13).

1. Pasricha PJ, *et al.* Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. *Gut* 1994; **35:** 1319–21.
2. Girdler NM. Use of botulinum toxin to alleviate facial pain. *Br J Hosp Med* 1994; **52:** 363.
3. Girdler NM. Uses of botulinum toxin. *Lancet* 1997; **349:** 953.
4. Morré HHE, *et al.* Treatment of chronic tennis elbow with botulinum toxin. *Lancet* 1997; **349:** 1746.
5. Lang AM. Botulinum toxin therapy for myofascial pain disorders. *Curr Pain Headache Rep* 2002; **6:** 355–60.

Sialorrhoea. Botulinum toxins may be effective in the treatment of sialorrhoea and drooling associated with conditions such as cerebral palsy[1] and Parkinson's disease.[2] A review[3] found botulinum toxin A to be safe and effective in the treatment of sialorrhoea; however, further studies are warranted.

1. Jongerius PH, *et al.* Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. *Pediatrics* 2004; **114:** 620–7.
2. Ondo WG, *et al.* A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. *Neurology* 2004; **62:** 37–40.
3. Benson J, Daugherty KK. Botulinum toxin A in the treatment of sialorrhea. *Ann Pharmacother* 2007; **41:** 79–85.

Spasmodic torticollis. Spasmodic torticollis (cervical dystonia) is a focal dystonia (p.809) characterised by spasmodic rotation of the head as a result of dystonic spasm of the neck muscles. The head may turn to one side (torticollis), extend (retrocollis), or flex (antecollis). Spasms may be repetitive or sustained. Response of spasmodic torticollis to drug therapy is usually poor and surgery has been associated with potentially serious complications. Intramuscular injections of botulinum toxins can be effective but dysphagia, which can have severe consequences (see under Adverse Effects, above) occurs in a significant number of patients. Other adverse effects have included lethargy, local weakness, vertigo, and dysphonia.

When injecting botulinum toxins localisation of the involved muscles with electromyographic guidance may be useful. Multiple injection sites allow more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. Bilateral injection of the sternocleidomastoid muscle is not recommended as there is an increased risk of adverse effects, especially dysphagia. Reduced doses may be required for patients with reduced muscle mass.

Doses of botulinum toxins, which are expressed in terms of units, have not been standardised between preparations. Doses are therefore *specific to each individual preparation.*

In the UK the usual initial dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 500 units injected in divided doses into the two or three most active neck muscles:

- for *rotational torticollis,* 350 units is given initially into the splenius capitis muscle (ipsilateral to the direction of the chin/head rotation) and 150 units into the sternocleidomastoid muscle (contralateral to rotation)
- for *laterocollis,* 350 units is given initially into the ipsilateral splenius capitis muscle and 150 units into the ipsilateral sternocleidomastoid muscle; if associated with *shoulder elevation,* ipsilateral trapezoid or levator scapulae muscles may also require treatment; if 3 muscles need treatment, 300 units are injected into the splenius capitis muscle, 100 units into the sternocleidomastoid muscle, and 100 units into the third muscle
- for *retrocollis,* 250 units is given into each of the splenius capitis muscles which may be followed after 6 weeks by bilateral trapezius injections in a dose of up to 250 units per muscle; bilateral splenii injections may increase the risk of neck muscle weakness

Subsequent doses may range from 250 to 1000 units, although the higher doses may be accompanied by an increase in adverse effects such as dysphagia; doses above 1000 units are not recommended. An initial effect is usually observed within 1 week; injections usually need to be repeated every 12 weeks or as required.

In the UK, botulinum A toxin as the preparation *Xeomin (Merz, UK)* is indicated for spasmodic torticollis. Licensed product information recommends that doses should be tailored to meet individual patient requirements. In practice, the maximum total dose is usually not more than 200 units but up to 300 units may be given. No more than 50 units should be given at any one injection site; limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may reduce the risk of dysphagia. An initial effect is usually observed within 1 week; each treatment lasts for about 3 to 4 months and injections may be repeated if necessary after at least 10 weeks.

Recommended doses in the UK for botulinum A toxin as the preparation *Botox* (*Allergan, UK*) are listed below but licensed product information states that in practice the maximum total dose is not usually more than 200 units. No more than 50 units should be given at any one injection site; limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may reduce the risk of dysphagia.

- *Type I* (head rotated toward side of shoulder elevation)—sternocleidomastoid muscle: total dosage of 50 to 100 units divided amongst at least 2 sites; levator scapulae: total of 50 units amongst 1 or 2 sites; scalene: total of 25 to 50 units amongst 1 or 2 sites; splenius capitis: total of 25 to 75 units amongst 1 to 3 sites; trapezius: total of 25 to 100 units amongst 1 to 8 sites
- *Type II* (head rotation only)—sternocleidomastoid muscle: total dosage of 25 to 100 units divided amongst at least 2 sites if more than 25 units is given
- *Type III* (head tilted toward side of shoulder elevation)—sternocleidomastoid muscle: total dosage of 25 to 100 units at posterior border divided amongst at least 2 sites if more than 25 units is given; levator scapulae: total of 25 to 100 units amongst at least 2 sites; scalene: total of 25 to 75 units amongst at least 2 sites; trapezius: total of 25 to 100 units amongst 1 to 8 sites
- *Type IV* (bilateral posterior cervical muscle spasm with elevation of the face)—splenius capitis and splenius cervicis: a total dosage of 50 to 200 units divided amongst 2 to 8 sites and which include both sides of the neck

Botulinum A toxin as the preparation *Botox* (*Allergan, USA*) is also available in the USA for the treatment of spasmodic torticollis. Licensed product information recommends that doses should be tailored to meet individual patient requirements.

In the UK the usual initial dose of botulinum B toxin as the preparation *NeuroBloc* (*Zeneus Pharma, UK*) is 5000 to 10 000 units given by intramuscular injection in divided doses into the two to four most affected muscles.

Botulinum B toxin as the preparation *Myobloc* (*Solstice, USA*) is also available in the USA. The initial dose is 2500 to 5000 units given by intramuscular injection divided between the affected muscles. Licensed product information recommends that patients with no history of tolerating botulinum injections should be started on a lower initial dose.

References.

1. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* 1990; **53:** 640–3.
2. Greene P, *et al.* Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990; **40:** 1213–18.
3. Anderson TJ, *et al.* Botulinum toxin treatment of spasmodic torticollis. *J R Soc Med* 1992; **85:** 524–9.
4. Brans JWM, *et al.* Botulinum toxin versus trihexyphenidyl in cervical dystonia: a prospective, randomized, double-blind controlled trial. *Neurology* 1996; **46:** 1066–72.
5. Brin MF, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1431–8.
6. Brashear A, *et al.* Safety and efficacy of NeuroBloc (botulinum toxin B) in type A-resistant cervical dystonia. *Neurology* 1999; **53:** 1439–46.
7. Velickovic M, *et al.* Cervical dystonia: pathophysiology and treatment options. *Drugs* 2001; **61:** 1921–43.
8. Figgitt DP, Noble S. Botulinum toxin B: a review of its therapeutic potential in the management of cervical dystonia. *Drugs* 2002; **62:** 705–22.
9. Dressler D, *et al.* Botulinum toxin type B in antibody-induced botulinum toxin type A therapy failure. *J Neurol* 2003; **250:** 967–9. Correction. *ibid.*; 1263–5.
10. Walker FO. Botulinum toxin therapy for cervical dystonia. *Phys Med Rehabil Clin N Am* 2003; **14:** 749–66.
11. Lew MF. Duration of effectiveness of botulinum toxin type B in the treatment of cervical dystonia. *Adv Neurol* 2004; **94:** 211–15.
12. Jankovic J. Treatment of cervical dystonia with botulinum toxin. *Mov Disord* 2004; **19** (suppl 8): S109–S115.
13. Costa J, *et al.* Botulinum toxin type B for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 28/03/06).
14. Costa J, *et al.* Botulinum toxin type A therapy for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 28/03/06).
15. Comella CL, *et al.* Comparison of botulinum toxin serotypes A and B for the treatment of cervical dystonia. *Neurology* 2005; **65:** 1423–9.
16. Costa J, *et al.* Botulinum toxin type A versus anticholinergics for cervical dystonia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 07/05/08).

Spasticity. The mainstay of management of spasticity, as discussed on p.1887, is physiotherapy together with antispastic drugs. Chemical neurolysis should only be considered when there is intractable continuous pain. Local injections of botulinum A toxin, as an alternative to chemical neurolysis, have been used in the management of limb spasticity in multiple sclerosis,[1] and in post-stroke patients,[1-5] and children with cerebral palsy.[6-12] However, systematic reviews[13,14] have found insufficient evidence to support or refute such use in children with cerebral palsy. Botulinum B toxin has also been tried.[11,15]

Doses of botulinum A toxin, which are expressed in terms of units, have not been standardised between preparations. Doses are therefore *specific to each individual preparation:* Botulinum A toxin is used in the management of dynamic equinus foot deformity associated with spasticity in children with cerebral palsy.

- For children over 2 years of age the recommended total dose of botulinum A toxin as the preparation *Botox* (*Allergan, UK*) is 4 units/kg injected into each of 2 sites in the medial and lateral heads of the gastrocnemius muscle. When both lower limbs are to be injected on the same occasion this total dose should be divided between the 2 limbs. Clinical improvement generally occurs within the first 2 weeks. Repeat doses should not be given more frequently than every 2 months.
- For children over 2 years of age the recommended total dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 10 to 30 units/kg divided between both calf muscles, primarily targeted to the gastrocnemius muscle. The maximum dose administered should not exceed 1000 units per patient. Clinical improvement generally occurs within the first 2 weeks. Repeat doses should not be given more frequently than every 12 weeks.

Botulinum A toxin is also used in the treatment of upper limb spasticity in adults.

- In the treatment of upper limb spasticity associated with stroke, the exact dosage and number of injection sites of botulinum A toxin as the preparation *Botox* (*Allergan, UK*) should be tailored to the individual based on the muscles involved, the severity of the spasticity, and the presence of local weakness. The manufacturer recommends a total dose of 50 units into the flexor digitorum profundus, the flexor digitorum sublimis, the flexor carpi radialis, or the flexor carpi ulnaris, and a total dose of 20 units into the adductor pollicis or flexor pollicis longus. In clinical studies, cumulative doses did not exceed 360 units at any treatment session.
- In the treatment of focal spasticity of the arm, the recommended total dose of botulinum A toxin as the preparation *Dysport* (*Ipsen, UK*) is 1000 units divided into: a dose of 150 units into the flexor digitorum profundus, the flexor carpi ulnaris, and the flexor carpi radialis; 150 to 250 units into the flexor digitorum superficialis; and 300 to 400 units into the biceps brachii. All muscles should be injected at one site except the biceps brachii which should be injected at 2 sites. Lower doses are recommended in patients whose target muscles are small, where the biceps brachii is not to be injected, or in patients receiving multi-level injections. Clinical improvement generally occurs within the first 2 weeks.

1. Sheean G. Botulinum toxin treatment of adult spasticity : a benefit-risk assessment. *Drug Safety* 2006; **29:** 31–48.
2. Simpson DM, *et al.* Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996; **46:** 1306–10.
3. Bhakta BB, *et al.* Use of botulinum toxin in stroke patients with severe upper limb spasticity. *J Neurol Neurosurg Psychiatry* 1996; **61:** 30–5.
4. Burbaud P, *et al.* A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. *J Neurol Neurosurg Psychiatry* 1996; **61:** 265–9.
5. Brashear A, *et al.* Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002; **347:** 395–400.
6. Zelnik N, *et al.* The role of botulinum toxin in the treatment of lower limb spasticity in children with cerebral palsy—a pilot study. *Isr J Med Sci* 1997; **33:** 129–33.
7. Carr LJ, *et al.* Position paper on the use of botulinum toxin in cerebral palsy. *Arch Dis Child* 1998; **79:** 271–3.
8. Fehlings D, *et al.* An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. *J Pediatr* 2000; **137:** 331–7.
9. Ubhi T, *et al.* Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. *Arch Dis Child* 2000; **83:** 481–7.
10. Koman LA, *et al.* Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. *Pediatrics* 2001; **108:** 1062–71.
11. Berweck S, Heinen F. Use of botulinum toxin in pediatric spasticity (cerebral palsy). *Mov Disord* 2004; **19** (suppl 8): S162–S167.
12. Bjornson K, *et al.* Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. *Pediatrics* 2007; **120:** 49–58.
13. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 07/05/08).
14. Wasiak J, *et al.* Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 07/05/08).
15. Brashear A, *et al.* Botulinum toxin type B in upper-limb post-stroke spasticity: a double-blind, placebo-controlled trial. *Arch Phys Med Rehabil* 2004; **85:** 705–9.

Stiff-man syndrome. A patient with stiff-man syndrome (see Muscle Spasm, p.993) had marked improvement of ambulation and cessation of pain after injection of botulinum A toxin into affected paraspinal muscles.[1] In another case report, improvement in rigidity and muscle spasm was reported[2] in 2 patients after botulinum treatment; muscle spasms reduced within 3 days of treatment. It was also found that there was an increase in the duration of effect of botulinum A toxin after each subsequent injection and only a gradual return of painful spasm.

1. Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A. *Mov Disord* 1993; **8:** 371–3.
2. Liguori R, *et al.* Botulinum toxin A improves muscle spasms and rigidity in stiff-person syndrome. *Mov Disord* 1997; **12:** 1060–3.

Strabismus. Botulinum A toxin has been used to weaken overactive extra-ocular muscles as an alternative or adjunct to surgery in the correction of strabismus (p.1874). Not all patients respond to botulinum A toxin and many patients who do respond require more than one injection to maintain improvement. Botulinum A toxin does not appear to offer a better degree of correction than traditional surgery, and it has been suggested that it should be reserved for use in patients unresponsive to, or unsuitable for, surgery. In the USA botulinum A toxin as the preparation *Botox* (*Allergan, USA*) is indicated for the treatment of strabismus in patients 12 years of age or older. Depending on the direction and degree of deviation to be corrected the recommended initial dose of Botox to be injected into any one extra-ocular muscle ranges from 1.25 to 5 units. Paralysis is usually seen within the first 2 days and increases in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a further 2 to 6 weeks. It is recommended that patients are re-examined 7 to 14 days after injection to assess the effect of the dose given. If treatment is required for residual or recurrent strabismus, patients are either given treatment at the previous dosage if response was judged to have been adequate or up to twice the previous dose if paralysis had been incomplete; no more than 25 units should be injected into any one muscle. Repeat injections should not be given until the effects of the previous dose have dissipated. Injections should be diluted with unpreserved 0.9% sodium chloride solution so that the volume given per muscle is between 0.05 mL and 0.15 mL. Injections should also be made using an electromyographically guided needle to aid location of the target muscle.

References.

1. Biglan AW, *et al.* Management of strabismus with botulinum A toxin. *Ophthalmology* 1989; **96:** 935–43.
2. Carruthers JDA, *et al.* Botulinum vs adjustable suture surgery in the treatment of horizontal misalignment in adult patients lacking fusion. *Arch Ophthalmol* 1990; **108:** 1432–5.
3. Lyons CJ, *et al.* Botulinum toxin therapy in dysthyroid strabismus. *Eye* 1990; **4:** 538–42.
4. McNeer KW. An investigation of the clinical use of botulinum toxin A as a postoperative adjustment procedure in the therapy of strabismus. *J Pediatr Ophthalmol Strabismus* 1990; **27:** 3–9.
5. Scott AB, *et al.* Botulinum treatment of childhood strabismus. *Ophthalmology* 1990; **97:** 1434–8.
6. Petitto VB, Buckley EG. Use of botulinum toxin in strabismus after retinal detachment surgery. *Ophthalmology* 1991; **98:** 509–13.
7. Elston J. Is botulinum toxin helpful in squint management? *Br J Ophthalmol* 1998; **82:** 105.

8. Tejedor J, Rodríguez JM. Early retreatment of infantile esotropia: comparison of reoperation and botulinum toxin. *Br J Ophthalmol* 1999; **83:** 783–7.
9. Dawson EL, Lee JP. Does botulinum toxin have a role in the treatment of small-angle esotropia? *Strabismus* 2004; **12:** 257–60.
10. Dawson EL, *et al.* Does botulinum toxin have a role in the treatment of secondary strabismus? *Strabismus* 2005; **13:** 71–3.

Stuttering. Botulinum toxin may be of benefit in the treatment of stuttering (p.1001).[1,2]

1. Brin MF, *et al.* Laryngeal botulinum toxin injections for disabling stuttering in adults. *Neurology* 1994; **44:** 2262–6.
2. Cordivari C, *et al.* New therapeutic indications for botulinum toxins. *Mov Disord* 2004; **19** (suppl 8): S157–S161.

Tourette's syndrome. Improvement in tics was noted in patients with Tourette's syndrome (see Tics, p.954) treated with botulinum A toxin.[1,2]

1. Kwak CH, *et al.* Botulinum toxin in the treatment of tics. *Arch Neurol* 2000; **57:** 1190–3.
2. Marras C, *et al.* Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology* 2001; **56:** 605–10.

Tremor. Local injection of botulinum A toxin[1-4] has been tried in patients with essential tremor (p.1231) that fails to respond to conventional treatment. Botulinum A toxin injection has also been successfully used to treat essential palatal tremor[5-7] and associated symptoms such as uncomfortable ear clicking.

1. Henderson JM, *et al.* Botulinum toxin A in non-dystonic tremors. *Eur Neurol* 1996; **36:** 29–35.
2. Jankovic J, *et al.* A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord* 1996; **11:** 250–6.
3. Pacchetti C, *et al.* Botulinum toxin treatment for functional disability induced by essential tremor. *Neurol Sci* 2000; **21:** 349–53.
4. Brin MF, *et al.* A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology* 2001; **56:** 1523–8.
5. Deuschl G, *et al.* Ear click in palatal tremor: its origin and treatment with botulinum toxin. *Neurology* 1991; **41:** 1677–9.
6. Jamieson DRS, *et al.* Ear clicks in palatal tremor caused by activity of the levator veli palatini. *Neurology* 1996; **46:** 1168–9.
7. Cho JW, *et al.* Case of essential palatal tremor: atypical features and remarkable benefit from botulinum toxin injection. *Mov Disord* 2001; **16:** 779–82.

Vaginismus. Report[1] of one patient who had relief of vaginismus (painful involuntary spasm of the vaginal or perianal muscles severe enough to prevent intercourse) for more than 24 months after injection of botulinum toxin into the vaginal wall muscles.

1. Brin MF, Vapnek JM. Treatment of vaginismus with botulinum toxin injections. *Lancet* 1997; **349:** 252–3.

Preparations

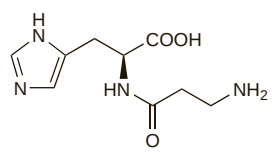
Ph. Eur.: Botulinum Toxin Type A for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Botox; Dysport; ***Austral.:*** Botox; Dysport; ***Austria:*** Botox; Dysport; NeuroBloc; ***Belg.:*** Botox; Dysport; ***Braz.:*** Botox; Dysport; Prosigne; ***Canad.:*** Botox; ***Chile:*** Dysl or; ***Cz.:*** Botox; Dysport; NeuroBloc; Vistabel; ***Denm.:*** Botox; Dysport; Vistabel; ***Fin.:*** Botox; Dysport; Vistabel; ***Fr.:*** Botox; Dysport; NeuroBloc; Vistabel; ***Ger.:*** Botox; Dysport; NeuroBloc†; Xeomin; ***Gr.:*** Botox; Dysport; Vistabel; ***Hong Kong:*** Botox; BTXA; Dysport; ***Hung.:*** Botox; Dysport; Vistabel; ***Indon.:*** Lanzox; ***Irl.:*** Botox; Dysport; NeuroBloc; ***Israel:*** Botox; Dysport; ***Ital.:*** Botox; Dysport; NeuroBloc; Vistabex; ***Jpn:*** Botox; ***Malaysia:*** Botox; Dysport; ***Mex.:*** Botox; ***Neth.:*** Botox; Dysport; NeuroBloc; ***Norw.:*** Botox; Dysport; Vistabel; ***NZ:*** Botox; Dysport; ***Philipp.:*** Botox; Dysport; ***Pol.:*** Botox; Dysport; ***Port.:*** Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Rus.:*** Botox (Ботокс); Dysport (Диспорт); ***S.Afr.:*** Botox; ***Singapore:*** Botox; Dysport; ***Spain:*** Botox; Dysport; NeuroBloc; Vistabel; ***Swed.:*** Botox; Dysport; Vistabel; ***Switz.:*** Botox; Dysport; Vistabel; ***Thai.:*** Botox; Dysport; ***Turk.:*** Botox; Dysport; ***UK:*** Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***USA:*** Botox; Myobloc; ***Venez.:*** Botox; Dysport.

Carisoprodol *(BAN, rINN)*

Carisoprodolum; Isopropylmeprobamate; Karisoprodol; Karisoprodoli; Karizoprodol; Karizoprodolis. 2-Methyl-2-propyltrimethylene carbamate isopropylcarbamate.

Каризопродол
$C_{12}H_{24}N_2O_4$ = 260.3.
CAS — 78-44-4.
ATC — M03BA02.
ATC Vet — QM03BA02.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Carisoprodol). A white or almost white fine powder. M.p. 92° to 95°. Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.
USP 31 (Carisoprodol). A white crystalline powder having a mild characteristic odour. M.p. 91° to 94°. Soluble 1 in 2083 of water, 1 in 2.5 of alcohol and of acetone, and 1 in 2.3 of chloroform. Store in airtight containers.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions

As for Meprobamate, p.1006.

The most common adverse effects reported with carisoprodol are drowsiness, dizziness, and headache. Sedation may affect the performance of skilled tasks and affected patients should not drive or operate machinery. Poor metabolisers, deficient in the cytochrome P450 isoenzyme CYP2C19, may be at greater risk of drowsiness.

Idiosyncratic reactions may occur within minutes of a dose in patients who have not previously received carisoprodol. Such reactions have been reported rarely and include anaphylactic shock, syncope, tachycardia, confusion, transient quadriplegia, and bronchospasm. Cross-reactivity can occur with its metabolite meprobamate.

Overdosage may result in seizures, stupor, coma, shock, respiratory depression, and rarely death.

Carisoprodol should be used with caution in patients with impaired hepatic or renal function.

Cases of dependence and abuse have been reported with the prolonged use of carisoprodol, particularly in patients with a history of addiction; withdrawal reactions have also occurred when treatment is suddenly stopped after prolonged use or the use of high doses. The increased risk of abuse and addiction with carisoprodol, as well as the risk of altered mental state and psychomotor impairment, has led the EMEA and some other authorities to recommend that it is suspended from the market; in the USA, however, it is recommended that use is limited to 2 to 3 weeks.

Abuse. Analysis[1] of data from the Norwegian Prescription Database found that carisoprodol was used in higher doses than recommended indicating its potential as a drug of abuse. Subsequently, the Norwegian Medicines Agency and the EMEA have recommended for suspension (see above).

1. Bramness JG, *et al.* Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol* 2007; **64:** 210–18.

Breast feeding. Carisoprodol is distributed into breast milk, achieving concentrations 2 to 4 times those in maternal plasma; UK licensed product information and the *BNF* recommend that it is best avoided in women who are breast feeding although US licensed product information states to use with caution.

Dependence. There are reports of carisoprodol dependence, probably due to its metabolism to meprobamate.[1,2] In one case the patient had symptoms of meprobamate withdrawal that resolved with a dose-reducing schedule of meprobamate.

Dependence may occur more often when carisoprodol is given in high doses and for prolonged periods, especially in patients with a history of alcohol or drug dependence or in those with marked personality disorders. One group[2] found that patients with a history of substance abuse were twice as likely to use carisoprodol in larger doses to those prescribed than those with no such history.

The risk of dependence with carisoprodol has led the EMEA and some other authorities to recommend its suspension from the market (see above).

1. Luehr JG, *et al.* Mail-order (veterinary) drug dependence. *JAMA* 1990; **263:** 657.
2. Reeves RR, *et al.* Carisoprodol (Soma): abuse potential and physician unawareness. *J Addict Dis* 1999; **18:** 51–6.

Porphyria. Carisoprodol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The CNS effects of carisoprodol may be potentiated by alcohol or other CNS depressants. Carisoprodol may cause hepatic enzyme induction and it may therefore affect the metabolism of a number of drugs. The metabolism of carisoprodol is mediated by the cytochrome P450 isoenzyme CYP2C19; use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of carisoprodol, however, there is a lack of data.

Pharmacokinetics

Carisoprodol is absorbed from the gastrointestinal tract and peak plasma concentrations are reached after 1.5 to 2 hours. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C19, which shows genetic polymorphism, and excreted in urine as metabolites, including meprobamate. The terminal elimination half-life of carisoprodol is about 2 hours. It is distributed in substantial amounts into breast milk.

◊ References.

1. Olsen H, *et al.* Carisoprodol elimination in humans. *Ther Drug Monit* 1994; **16:** 337–40.

Uses and Administration

Carisoprodol is a centrally acting skeletal muscle relaxant whose mechanism of action is not completely understood but may be related to its sedative actions. After oral doses its effects begin within about 30 minutes and last for 4 to 6 hours. It is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. A usual oral dose is 250 to 350 mg given three or four times daily for up to 2 to 3 weeks. Half the usual dose or less is recommended in elderly patients. It is also given with analgesics in compound preparations.

The EMEA and some other authorities have recommended for carisoprodol to be suspended from the market due to the increased risk of abuse and addiction, as well as the risk of altered mental state and psychomotor impairment.

Preparations

USP 31: Carisoprodol and Aspirin Tablets; Carisoprodol Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets.

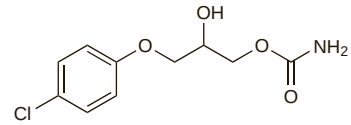
Proprietary Preparations (details are given in Part 3)
Arg.: Listaflex; ***Canad.:*** Soma†; ***Denm.:*** Somadril†; ***India:*** Carisoma; ***Mex.:*** Somacid; ***Norw.:*** Somadril†; ***Spain:*** Mio Relax†; ***Swed.:*** Somadril†; ***Thai.:*** Myolax†; ***UK:*** Carisoma†; ***USA:*** Soma.

Multi-ingredient: ***Arg.:*** Algiseda; Flexicamin; Flexicamin A; Flexicamin B12; Flogiatrin; Flogiatrin B12; Ketazon Flex†; Mefenix Relax†; Naprontag Flex; Rumisedan Fuerte†; Solocalm Plus; Solocalm-Flex; ***Braz.:*** Algi-Butazolon†; Algi-Tanderil†; Beserol; Cedrilax†; Diclofetamol; Dorilax; Flexalgin; Mio-Citalgan; Mioflex; Mioflex A; Mionevrix; Paceflex†; Sanilax; Sedilax; Tandene; Tanderalgin; Tandriflan; Tandrilax; Torsilax; Trilax†; ***Cz.:*** Scutamil C†; ***Fin.:*** Somadril Comp†; ***Gr.:*** Relacton-C†; ***Hung.:*** Scutamil C†; ***India:*** Carisoma Compound; Somaflam; ***Indon.:*** New Skelan; Somadril Compound; ***Ital.:*** Soma Complex†; ***Mex.:*** Blocacid; Contraxen; Dolaren; Dorsal; Duoflex; Empatil; Naxodol; Profenlax; Somalgesic; ***Spain:*** Flexagil†; Relaxibys†; ***Swed.:*** Somadril Comp†; ***Thai.:*** Alaxan; Asialax; Cariso-Co†; Carisoma Compound†; Caritasone; Cenpadol; Muscelax; Myophen; Polixan; ***USA:*** Sodol Compound; Soma Compound with Codeine†; Soma Compound†; ***Venez.:*** Cotar†; Flexidone†; Praxona.

Chlorphenesin Carbamate *(BANM, USAN, pINNM)*

Carbamato de clorfenesina; Chlorphénésine, Carbamate de; Chlorphenesini Carbamatum; U-19646. 3-(4-Chlorophenoxy)propane-1,2-diol 1-carbamate.

Хлорфенезина Карбамат
$C_{10}H_{12}ClNO_4$ = 245.7.
CAS — 104-29-0 (chlorphenesin); 886-74-8 (chlorphenesin carbamate).



Pharmacopoeias. In *Jpn*.

Adverse Effects and Precautions

Chlorphenesin carbamate produces drowsiness and dizziness. There may also be nausea, headache, weakness, confusion, agitation, and insomnia. Hypersensitivity reactions have been reported. There are rare reports of blood disorders.

It should be used with caution in patients with hepatic impairment. Patients affected by drowsiness should not drive or operate machinery.

Interactions

The CNS effects of chlorphenesin carbamate may be potentiated by alcohol or other CNS depressants.

Pharmacokinetics

Chlorphenesin carbamate is readily and completely absorbed from the gastrointestinal tract and partly metabolised in the liver. It is excreted in the urine, mainly as the glucuronide metabolite.

Uses and Administration

Chlorphenesin carbamate is a centrally acting skeletal muscle relaxant related to mephenesin (p.1897). Its mode of action may be related to general depressant effects on the CNS. It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual initial oral dose is 250 mg three times daily, adjusted according to response. It has been recommended that chlorphenesin carbamate should not be given for longer than 8 weeks.

Chlorphenesin base (p.529) is used as an antifungal.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Rinlaxer; ***USA:*** Maolate†.

Chlorzoxazone *(BAN, rINN)*

Chlorobenzoxazolinone; Chlorzoxazonum; Clorzoxazona; Klooritsoksatsoni; Klorzoksazon; Klorzoxazon. 5-Chlorobenzoxazol-2(3*H*)-one.

Хлорзоксазон
$C_7H_4ClNO_2$ = 169.6.
CAS — 95-25-0.
ATC — M03BB03.
ATC Vet — QM03BB03.