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