Baclofen *(BAN, USAN, rINN)*

Aminomethyl Chlorohydrocinnamic Acid; Ba-34647; Baclofène; Baclofeno; Baclofenum; Baklofeeni; Baklofén; Baklofen; Baklofenas. β-Aminomethyl-*p*-chlorohydrocinnamic acid; (*RS*)-Amino-3-(4-chlorophenyl)butyric acid.

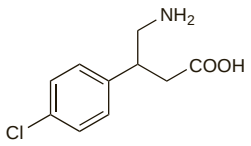
Баклофен

$C_{10}H_{12}ClNO_2$ = 213.7.

CAS — 1134-47-0.

ATC — M03BX01.

ATC Vet — QM03BX01.



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

Ph. Eur. 6.2 (Baclofen). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

USP 31 (Baclofen). A white to off-white, odourless or practically odourless, crystalline powder. Slightly soluble in water; very slightly soluble in methyl alcohol; insoluble in chloroform. Store in airtight containers.

Adverse Effects

Adverse effects associated with baclofen are often transient and dose-related. They may be minimised by increasing doses gradually or controlled by a reduction in dosage.

The most common adverse effects include drowsiness, nausea, dizziness, lassitude, lightheadedness, confusion, fatigue, muscular pain and weakness, and hypotension. Other adverse effects include euphoria, hallucinations, depression, headache, tinnitus, convulsions, paraesthesias, slurred speech, dry mouth, taste alterations, vomiting, diarrhoea or constipation, ataxia, nystagmus, tremors, insomnia, visual disturbances, skin rashes, pruritus, increased sweating, urinary disturbances, respiratory or cardiovascular depression, blood sugar changes, alterations in liver function values, and a paradoxical increase in spasticity. Problems with erection and ejaculation have also been reported with intrathecal baclofen; these are usually reversible on withdrawal of therapy.

Overdosage may lead to muscular hypotonia, hypothermia, drowsiness, respiratory depression, coma, and convulsions (see also below).

Stopping baclofen abruptly may result in a withdrawal syndrome (see under Precautions, below).

Effects on the nervous system. Epilepsy, progressing to status epilepticus, has been associated with the use of baclofen in a patient who had had no history of seizures.[1] Baclofen had been given in a dose of 80 mg daily and symptoms had resolved after gradual withdrawal and the use of antiepileptics.

1. Rush JM, Gibberd FB. Baclofen-induced epilepsy. *J R Soc Med* 1990; **83:** 115–16.

Treatment of Adverse Effects

Treatment of baclofen overdosage is symptomatic. Consideration should be given to the use of activated charcoal in adults who have ingested more than 100 mg, and children who have taken more than 5 mg/kg, within an hour of presentation. Alternatively, gastric lavage may be considered in adults within an hour of ingesting a life-threatening overdose. Haemodialysis should be considered in severe cases. Observation should continue for at least 6 hours after ingestion. For the use of physostigmine salicylate in the treatment of intrathecal baclofen overdosage, see below.

Overdosage. Atropine sulfate 600 micrograms intravenously[1] was used to treat a patient who had ingested 420 mg of baclofen and had failed to improve after gastric lavage and induced diuresis. Bradycardia, hypotension, hypothermia, and respiratory depression all improved and no further treatment was needed. The clinical course and management of acute intoxication in 8 adolescents, who ingested estimated amounts of baclofen ranging from 60 to more than 600 mg, has also been described.[2]

Accidental *intrathecal* overdosage has caused respiratory depression, decreased alertness, coma, muscle weakness, and vomiting.[3] Mild intrathecal bolus overdoses of baclofen in patients without cardiac compromise have been treated using physostigmine although the use of physostigmine in poisoning is now generally considered hazardous (see Antimuscarinic Poisoning, p.1884). Physostigmine salicylate was given intravenously in a dose of 1 to 2 mg over 5 minutes and repeated if necessary at intervals of 30 to 60 minutes.[3,4] Physostigmine was ineffective in a patient who accidentally received 10 mg of baclofen intrathecally;[5] in such severe overdosage, respiratory support and time to recover is needed.[4] A lumbar tap to remove about 30 to 50 mL of CSF may help to reduce the intrathecal concentration of baclofen if implemented soon after the overdose.

1. Ferner RE. Atropine treatment for baclofen overdose. *Postgrad Med J* 1981; **57:** 580–1.
2. Perry HE, *et al.* Baclofen overdose: drug experimentation in a group of adolescents. *Pediatrics* 1998; **101:** 1045–8.
3. Müller-Schwefe G, Penn RD. Physostigmine in the treatment of intrathecal baclofen overdose. *J Neurosurg* 1989; **71:** 273–5.
4. Penn RD, Kroin JS. Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; **322:** 1533–4.
5. Saltuari L, *et al.* Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; **322:** 1533.

Precautions

Baclofen stimulates gastric acid secretion and should be used with caution in patients with a history of peptic ulcer and avoided in those with active peptic ulcer disease. It should also be used with caution in patients with severe psychiatric disorders or epilepsy or convulsive disorders since these disorders may be exacerbated by baclofen. Liver function should be monitored in patients with liver disease; patients with renal impairment need a reduced dose. Baclofen should be used with caution in patients with respiratory impairment. Observations of increased blood sugar concentrations suggest caution in patients with diabetes mellitus. Care is also required in the elderly, in whom adverse effects may be more common, and in patients with cerebrovascular disease (who tolerate baclofen poorly). It should be used with caution in patients who use their spasticity to maintain posture or to increase function. Urine retention may be exacerbated in patients with hypertonic bladder sphincters. Baclofen may cause drowsiness; patients affected should not drive or operate machinery.

Abrupt withdrawal of baclofen may result in a withdrawal syndrome and exacerbation of spasticity; dosage should be reduced gradually over at least 1 to 2 weeks, or longer if symptoms occur.

Anaesthesia. Acute bradycardia and hypotension occurred after rib retraction in 3 patients given baclofen 30 mg orally 90 minutes before thoracic surgery under general anaesthesia, but not in a further 3 patients given placebo.[1] Giving atropine and ephedrine relieved bradycardia and hypotension in 2 patients, but a brief cardiac arrest occurred in 1. Baclofen may disturb autonomic control of the circulation during general anaesthesia and surgery.

1. Sill JC, *et al.* Bradycardia and hypotension associated with baclofen used during general anaesthesia. *Anesthesiology* 1986; **64:** 255–8.

Breast feeding. The concentrations of baclofen found in breast milk are small[1] and UK licensed product information states that no undesirable effects are to be expected in breast-fed infants. The American Academy of Pediatrics also considers that baclofen is usually compatible with breast feeding; no adverse effects have been seen in breast-feeding infants whose mothers were receiving baclofen.[2]

1. Eriksson G, Swahn C-G. Concentrations of baclofen in serum and breast milk from a lactating woman. *Scand J Clin Lab Invest* 1981; **41:** 185–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 23/06/04)

Peptic ulcer. Results of a study of baclofen-stimulated gastric acid secretion in 10 healthy subjects given 600 micrograms/kg intravenously suggested that patients on baclofen might be at risk from baclofen-induced hyperacidity.[1]

1. Pugh S, *et al.* Clinical and experimental significance of the newly discovered activity of baclofen (PCP-GABA) as a stimulant of gastric acid secretion. *Gut* 1985; **26:** A545.

Porphyria. Baclofen is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Pregnancy and the neonate. Two successful pregnancies have been reported[1] in a woman receiving intrathecal baclofen; there was no evidence of teratogenicity, and neurodevelopmental outcome in the children seemed normal. However, convulsions were seen in a week-old infant whose mother had taken oral baclofen during pregnancy.[2] The convulsions, which were refractory to antiepileptics, lidocaine, and pyridoxine, ceased within 30 minutes of giving baclofen to the infant.

1. Calderón Muñoz F, *et al.* Pregnancy outcome in a woman exposed to continuous intrathecal baclofen infusion. *Ann Pharmacother* 2000; **34:** 956.
2. Ratnayaka BDM, *et al.* Neonatal convulsions after withdrawal of baclofen. *BMJ* 2001; **323:** 85.

Renal impairment. Reports of baclofen toxicity in patients with severe renal impairment.[1] Most patients had received 15 mg or more of baclofen daily although one patient who had received the manufacturer's suggested dose of 5 mg daily still developed toxic symptoms after only 4 days of treatment.

1. Chen K-S, *et al.* Baclofen toxicity in patients with severely impaired renal function. *Ann Pharmacother* 1997; **31:** 1315–20.

Respiratory disorders. Baclofen might precipitate bronchoconstriction in susceptible individuals. A patient with asthma developed symptomatic bronchoconstriction after taking baclofen on two separate occasions.[1] Another patient who had a history of exercise-induced dyspnoea and wheezing was found to have bronchial hyperresponsiveness to methacholine only after taking baclofen.

1. Dicpinigaitis PV, *et al.* Baclofen-induced bronchoconstriction. *Ann Pharmacother* 1993; **27:** 883–4.

Withdrawal. Psychiatric reactions including hallucinations, paranoia, delusions, psychosis, anxiety, confusion, and agitation have been reported[1-4] on abrupt withdrawal of oral baclofen; symptoms generally resolved on restarting. Convulsions have also been reported.[5] The abrupt withdrawal of intrathecal baclofen may also result in high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity which in rare cases has advanced to rhabdomyolysis, multiple organ failure, and death.[6-8]

Except for serious adverse reactions, the dose of oral baclofen should be gradually reduced: the UK CSM recommends reduction over at least 1 to 2 weeks or longer if symptoms occur. Similarly, the FDA has advised against the abrupt withdrawal of intrathecal baclofen.[8]

1. Lees AJ, *et al.* Hallucinations after withdrawal of baclofen. *Lancet* 1977; **i:** 858.
2. Stein R. Hallucinations after sudden withdrawal of baclofen. *Lancet* 1977; **ii:** 44–5.
3. Harrison SA, Wood CA. Hallucinations after preoperative baclofen discontinuation in spinal cord injury patients. *Drug Intell Clin Pharm* 1985; **19:** 747–9.
4. Committee on Safety of Medicines/Medicines Control Agency. Severe withdrawal reactions with baclofen. *Current Problems* 1997; **23:** 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015623&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
5. Barker I, Grant IS. Convulsions after abrupt withdrawal of baclofen. *Lancet* 1982; **ii:** 556–7.
6. Grenier B, *et al.* Hyperthermie grave liée à un sevrage brutal de baclofène administré de façon continue par voie intrathécale. *Ann Fr Anesth Reanim* 1996; **15:** 659–62.
7. Green LB, Nelson VS. Death after acute withdrawal of intrathecal baclofen: case report and literature review. *Arch Phys Med Rehabil* 1999; **80:** 1600–4.
8. Coffey RJ [Medtronic]. Important drug warning (issued April 2002). Available at: http://www.fda.gov/medwatch/SAFETY/2002/baclofen.pdf (accessed 23/06/04)

Interactions

Alcohol and other CNS depressants may exacerbate the CNS effects of baclofen and should be avoided; severe aggravation of hyperkinetic symptoms may possibly occur in patients taking lithium. There may be increased weakness if baclofen is given to patients taking a tricyclic antidepressant and there may be an increased hypotensive effect if it is given to patients receiving antihypertensive therapy. Ibuprofen (see below) and other drugs that produce renal insufficiency may reduce baclofen excretion leading to toxicity.

Dopaminergics. For reports of patients with Parkinson's disease taking *levodopa* who have had adverse effects when given baclofen, see under Levodopa, on p.808.

NSAIDs. There has been a report of an elderly patient who developed baclofen toxicity after *ibuprofen* therapy was also started.[1] It appeared that acute renal insufficiency caused by ibuprofen had impaired baclofen excretion.

1. Dahlin PA, George J. Baclofen toxicity associated with declining renal clearance after ibuprofen. *Drug Intell Clin Pharm* 1984; **18:** 805–8.

Pharmacokinetics

Baclofen is rapidly and almost completely absorbed from the gastrointestinal tract after an oral dose. Peak plasma concentrations occur about 0.5 to 3 hours after ingestion, but the rate and extent of absorption vary between patients, and may vary inversely with the dose. After oral doses some baclofen crosses the blood-brain

barrier, with concentrations in CSF about 12% of those in the plasma. About 30% of baclofen is bound to plasma proteins. About 70 to 80% of a dose is excreted in the urine mainly as unchanged drug; about 15% is metabolised in the liver. The elimination half-life of baclofen is about 3 to 4 hours in plasma and about 1 to 5 hours in the CSF. Baclofen crosses the placenta and is distributed into breast milk.

Absorption. A crossover study in 5 healthy subjects given baclofen 20 mg orally after an overnight fast or a standardised breakfast showed that baclofen was rapidly absorbed in both cases, and the rate and extent of absorption were not significantly altered by the presence of food.[1] There is no need to modify the current practice of giving baclofen with food to minimise gastrointestinal adverse effects.

1. Peterson GM, *et al*. Food does not affect the bioavailability of baclofen. *Med J Aust* 1985; **142:** 689–90.

Uses and Administration

Baclofen, an analogue of gamma-aminobutyric acid (p.2308), is a centrally acting skeletal muscle relaxant. It interferes with the release of excitatory neurotransmitters and inhibits monosynaptic and polysynaptic transmission at the spinal cord level. It may also act at supraspinal sites producing CNS depression. Baclofen is one of the drugs commonly used for the symptomatic relief of severe chronic spasticity associated with a variety of conditions.

Baclofen is given *orally* in divided doses, preferably with or after food or milk. The initial dose of baclofen is 5 mg three times daily for 3 days, increased to 10 mg three times daily for 3 days, then in similar increments and intervals until either a dose of 20 mg three times daily is reached or until the desired therapeutic effect is obtained. Higher doses have been used. Doses of more than 80 to 100 mg daily are not generally recommended although doses of up to 150 mg daily have been given to carefully supervised patients.

In the UK a dosage range of 0.75 to 2 mg/kg daily has been used for children; in children over 10 years a maximum daily dosage of 2.5 mg/kg may be given. It is usual to start with a low dose of 2.5 mg given four times daily, increased cautiously about every 3 days until the desired therapeutic effect is obtained. The recommended daily maintenance doses are: 12 months to 2 years, 10 to 20 mg; 2 to 6 years, 20 to 30 mg; 6 to 10 years, 30 to 60 mg.

Elderly patients should receive lower initial doses, although final maintenance doses may be in the same range as younger adults. For dosage in renal impairment, see below.

If no benefit is apparent within 6 weeks of achieving the maximum dosage, therapy should probably be gradually withdrawn.

Baclofen is also given *by continuous intrathecal infusion* in the treatment of spasticity in patients intolerant of, or unresponsive to, oral baclofen. Before beginning the intrathecal regimen any existing antispastic therapy should be gradually withdrawn to avoid overdosage or drug interactions. Intrathecal test doses are given initially to determine if there is going to be any benefit before implanting a controlled infusion pump. It is important that patients are monitored closely in experienced centres during screening and immediately after implantation of the infusion pump and that resuscitation equipment is available for immediate use.

Test doses start at 25 or 50 micrograms given over at least 1 minute and are increased by 25 micrograms every 24 hours until a dose of 100 micrograms is reached or a positive response of about 4 to 8 hours is obtained. Patients who fail to respond to a test dose of up to 100 micrograms are considered to be unsuitable for intrathecal treatment. For children aged 4 to 18 years with spasticity of cerebral origin an initial test dose of 25 micrograms is recommended. However, the manufacturers do not recommend the use of intrathecal baclofen in patients in this age group with spasticity of spinal origin.

For patients showing a positive response lasting for longer than 8 to 12 hours, the test dose that was required to produce the response can then be given as a 24-hour infusion; if the response to the test dose lasted 8 to 12 hours or less, then a dose equivalent to twice the test dose is given. Daily dosage can then be adjusted as required. Maintenance doses range from about 10 micrograms to 2 mg daily, depending on the cause of spasticity, with most patients being adequately maintained with 300 to 800 micrograms daily.

Administration in renal impairment. Doses of baclofen should be reduced in renal impairment or in patients undergoing chronic haemodialysis; 5 mg daily by mouth has been suggested (but see also under Precautions, above).

Dystonias. There have been reports of improvement in patients with various forms of dystonia (p.809) treated with baclofen[1-5] although there has also been a report[6] of a patient whose condition deteriorated during baclofen therapy.

1. Narayan RK, *et al*. Intrathecal baclofen for intractable axial dystonia. *Neurology* 1991; **41:** 1141–2.
2. Greene PE, Fahn S. Baclofen in the treatment of idiopathic dystonia in children. *Mov Disord* 1992; **7:** 48–52.
3. van Hilten BJ, *et al*. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N Engl J Med* 2000; **343:** 625–30.
4. Albright AL, *et al*. Intrathecal baclofen for generalized dystonia. *Dev Med Child Neurol* 2001; **43:** 652–7.
5. Jaffe MS, Nienstedt LJ. Intrathecal baclofen for generalized dystonia: a case report. *Arch Phys Med Rehabil* 2001; **82:** 853–5.
6. Silbert PL, Stewart-Wynne EG. Increased dystonia after intrathecal baclofen. *Neurology* 1992; **42:** 1639–40.

Gastro-oesophageal reflux disease. Baclofen has been tried[1,2] in the treatment of gastro-oesophageal reflux disease (p.1696). It may control gastro-oesophageal reflux by inhibiting transient sphincter relaxation. Although both studies reported a reduction in the number of reflux episodes there was no effect on acid reflux symptoms. However, a subsequent study[3] has shown a positive effect on the symptoms of acid reflux. It has been suggested that although baclofen may be of benefit, its adverse CNS effects mean that new oral selective GABA-B agonists should be developed for this indication.[4]

1. Van Herwaarden MA, *et al*. The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. *Aliment Pharmacol Ther* 2002; **16:** 1655–62.
2. Zhang Q, *et al*. Control of transient lower oesophageal sphincter relaxations and reflux by the GABA agonist baclofen in patients with gastro-oesophageal reflux disease. *Gut* 2002; **50:** 19–24.
3. Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the GABA agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. *Gut* 2003; **52:** 464–70.
4. Tonini M, *et al*. Progress with novel pharmacological strategies for gastro-oesophageal reflux disease. *Drugs* 2004; **64:** 347–61.

Hiccup. Baclofen has been given orally in daily divided doses ranging from 10 to 80 mg for the management of intractable hiccup (p.976) poorly controlled by other drugs. It has also been combined with gabapentin.

References.

1. Burke AM, *et al*. Baclofen for intractable hiccups. *N Engl J Med* 1988; **319:** 1354.
2. Lance JW, Bassil GT. Familial intractable hiccup relieved by baclofen. *Lancet* 1989; **ii:** 276–7.
3. Yaqoob M, *et al*. Baclofen for intractable hiccups. *Lancet* 1989; **ii:** 562–3.
4. Ramirez FC, Graham DY. Treatment of intractable hiccup with baclofen: results of a double-blind randomized, controlled, cross-over study. *Am J Gastroenterol* 1992; **87:** 1789–91.
5. Ramirez FC, Graham DY. Hiccups, compulsive water drinking, and hyponatremia. *Ann Intern Med* 1993; **118:** 649.
6. Walker P, *et al*. Baclofen, a treatment for chronic hiccup. *J Pain Symptom Manage* 1998; **16:** 125–32.
7. Hernández JL, *et al*. Gabapentin for intractable hiccup. *Am J Med* 2004; **117:** 279–81.

Migraine and cluster headache. The efficacy of baclofen in conditions such as trigeminal neuralgia or various types of neuropathic pain suggested that it may be useful in migraine or cluster headache. Pilot studies confirmed these hypotheses with baclofen proving useful for prophylaxis[1] in migraine (p.616) and for treatment[2] in cluster headache (p.616).

1. Hering-Hanit R. Baclofen for prevention of migraine. *Cephalalgia* 1999; **19:** 589–91.
2. Hering-Hanit R, Gadoth N. The use of baclofen in cluster headache. *Curr Pain Headache Rep* 2001; **5:** 79–82.

Pain. Like some other muscle relaxants baclofen is used in the management of painful conditions associated with muscle spasm or spasticity (see below). The use of muscle relaxants for conditions such as acute low back pain is referred to on p.7. Baclofen does not appear to possess conventional analgesic activity[1] but may potentiate the analgesia produced by opioid analgesics,[2] and has been used as an adjuvant in neuropathic pain,[3,4] notably trigeminal neuralgia[5] (p.9).

1. Terrence CF, *et al*. Is baclofen an analgesic? *Clin Neuropharmacol* 1983; **6:** 241–5.
2. Panerai AE, *et al*. Baclofen prolongs the analgesic effect of fentanyl in man. *Br J Anaesth* 1985; **57:** 954–5.
3. Fromm GH. Baclofen as an adjuvant analgesic. *J Pain Symptom Manage* 1994; **9:** 500–9.
4. Slonimski M, *et al*. Intrathecal baclofen in pain management. *Reg Anesth Pain Med* 2004; **29:** 269–76.
5. Fromm GH, *et al*. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. *Ann Neurol* 1984; **15:** 240–4.

Spasticity. Baclofen is one of the main drugs used in the management of spasticity (see p.1887). It is used to reduce muscle spasm and pain especially in spinal cord lesions in conditions such as multiple sclerosis or paraplegia. Baclofen is also used for spasticity of cerebral origin.

Oral doses of 30 to 80 mg daily are usually quite well tolerated,[1] but patients with severe spasticity often require high doses of baclofen before a response occurs and, consequently, some may fail to respond because adverse effects limit increases in dosage. Intrathecal baclofen is therefore sometimes tried as this produces much higher concentrations in the CNS than oral doses.[1-3] It may be given intrathecally by bolus injection or by continuous infusion; infusion is probably preferred[4] to minimise the risk of overdosage. Because patients are screened for response before beginning continuous infusion, results have generally been good.[1]

There is a large interindividual variation in the dose required to produce improvement in spasticity:

- in patients with spasticity of spinal origin, maintenance doses have ranged from 12 micrograms to about 2 mg daily, with most adequately managed on 300 to 800 micrograms daily
- in patients with spasticity of cerebral origin, maintenance doses have ranged from 22 micrograms to 1.4 mg daily, with an average daily dose of 276 micrograms after 12 months and 307 micrograms after 24 months
- for children under the age of 12 years with spasticity of cerebral origin, maintenance doses have ranged from 24 micrograms to about 1.2 mg daily, with an average daily dose of 274 micrograms

An increased dose of baclofen may be given at night to prevent spasms that interfere with sleep.

Although reports of tolerance to the effect of intrathecal baclofen have raised doubt[5] over whether long-term benefit can be maintained, a number of workers have achieved long-term efficacy.[6-9] It has been reported[10] that some patients receiving long-term intrathecal baclofen treatment have been able to stop their therapy without symptoms of spasticity re-appearing and others have been able to reduce the dosage required.

1. Dario A, Tomei G. A benefit-risk assessment of baclofen in severe spinal spasticity. *Drug Safety* 2004; **27:** 799–818.
2. McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med* 1993; **49:** 262–7.
3. Anonymous. Intrathecal baclofen for spasticity. *Med Lett Drugs Ther* 1994; **36:** 21–2.
4. Penn RD, Kroin JS. Intrathecal baclofen. *N Engl J Med* 1989; **321:** 1414–15.
5. Lewis KS, Mueller WM. Intrathecal baclofen for severe spasticity secondary to spinal cord injury. *Ann Pharmacother* 1993; **27:** 767–74.
6. Penn RD, *et al*. Intrathecal baclofen for severe spinal spasticity. *N Engl J Med* 1989; **320:** 1517–21.
7. Azouvi P, *et al*. Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. *Arch Phys Med Rehabil* 1996; **77:** 35–9.
8. Dario A, *et al*. Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood. *Acta Neurol Scand* 2002; **105:** 83–7.
9. Campbell WM, *et al*. Long-term safety and efficacy of continuous intrathecal baclofen. *Dev Med Child Neurol* 2002; **44:** 660–5.
10. Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; **60:** 168–73.

Stiff-man syndrome. There have been anecdotal case reports[1] of benefit with intrathecal baclofen in a patient with stiff-man syndrome (see under Muscle Spasm, p.993) inadequately controlled with other drugs or oral baclofen. However, in a double-blind placebo-controlled study[2] clinical improvement was evident in only 1 of 3 patients given intrathecal baclofen.

1. Stayer C, *et al*. Intrathecal baclofen therapy for stiff-man syndrome and progressive encephalomyelopathy with rigidity and myoclonus. *Neurology* 1997; **49:** 1591–7.
2. Silbert PL, *et al*. Intrathecal baclofen therapy in stiff-man syndrome: a double-blind, placebo-controlled trial. *Neurology* 1995; **45:** 1893–7.

Tardive dyskinesia. Baclofen is one of many drugs that have been tried in antipsychotic-induced tardive dyskinesia (see Extrapyramidal Disorders, p.971) but its efficacy is unclear. A systematic review[1] found the effects of baclofen, and other gamma-aminobutyric acid agonists to be inconclusive and unconvincing in the management of antipsychotic-induced tardive dyskinesia. The review also pointed out that the adverse effects caused by use of these drugs might outweigh any benefits.

1. Soares KVS, *et al*. Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 20/10/05).

Tetanus. The management of tetanus is described on p.1901 and p.196. Beneficial responses have been seen with baclofen by continuous intrathecal infusion,[1-5] usually in doses of 1 to 2 mg daily.[1,5] However, the therapeutic range of intrathecal baclofen in severe tetanus may be very narrow and deep coma with loss of spontaneous respiration and reflexes has been reported[6] after an increase in dosage from 1.2 mg to 2 mg daily. This adverse effect

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