Muscle Relaxants

The muscle relaxants included in this chapter are used in the management of musculoskeletal and neuromuscular disorders. There are 2 main types:

- **centrally acting relaxants**—these generally have a selective action on the CNS and are principally used for relieving painful muscle spasms or spasticity occurring in musculoskeletal and neuromuscular disorders. Their mechanism of action may be due to their CNS-depressant activity. Baclofen and tizanidine are two examples.
- **directly acting relaxants**—dantrolene is a drug that has a direct action on skeletal muscle and is used for the relief of spasticity associated with a variety of conditions.

Also included in this chapter are **botulinum toxins A and B**, which inhibit the release of acetylcholine at the motor nerve terminals.

Some benzodiazepines are also used in the treatment of muscle spasms; further details may be found under Diazepam, p.986.

Other drugs that block transmission at the neuromuscular junction and are used as adjuncts to general anaesthesia are discussed in the chapter on Neuromuscular Blockers, p.1900.

Drugs used to relax *smooth muscle* include the various antispasmodics (p.1692) used for their antimuscarinic or direct smooth-muscle relaxant effects in the management of gastrointestinal disorders, as well as some other drugs such as papaverine (p.2191).

Muscle spasm

Spasm is a painful involuntary contraction of muscle that can cause involuntary movement, interfere with function, and cause distortion. It is a symptom of many muscular and other types of disorders and treatment should primarily be aimed at the underlying cause. Centrally acting muscle relaxants and benzodiazepines are used to treat muscle spasms such as *splinting* that occur in response to local trauma or musculoskeletal and joint disorders. Splinting is a reflex muscular spasm that produces muscular rigidity and acts as a protective mechanism to prevent movement and further damage of the affected part. Short courses of muscle relaxants may be considered in the management of acute low back pain (p.7).

Cramps are muscle spasms of abrupt onset that occur at rest and usually last for a few seconds or minutes. They are often precipitated by dehydration and hyponatraemia produced by vigorous exercise, excessive sweating, diarrhoea, and vomiting, or may be associated with drug therapy or haemodialysis (see Haemodialysis-induced Cramp, p.1671). Pregnant women, the elderly, and those with peripheral vascular disease, appear to be particularly susceptible to night cramps of the feet or legs, the cause of which is not well understood.

The management of muscle cramps has been reviewed.[1,2] Quinine has traditionally been used for *nocturnal cramps* but there has been concern over its efficacy and potential for adverse effects, especially in the elderly. Meta-analyses[3,4] have indicated that although quinine was modestly effective in the treatment of nocturnal cramps in ambulatory patients the risk of serious adverse effects should be borne in mind; patients should be closely monitored over a period of at least 4 weeks while the efficacy of quinine was assessed. In the UK, it is recommended that treatment should be stopped every 3 months to see whether it is still needed.[5] In the USA, the FDA has ruled that quinine products should no longer be used for the management of nocturnal cramps.[6,7] There is little convincing evidence to support the use of other drugs.[1,2,6]

A systematic review[8] concluded that magnesium (as the lactate and citrate) is modestly effective in the treatment of *leg cramps in pregnancy*; calcium salts were ineffective, and although early evidence suggested benefit with sodium chloride, high doses were required with their attendant cardiovascular risks.

1. McGee SR. Muscle cramps. *Arch Intern Med* 1990; **150:** 511–18.
2. Butler JV, *et al.* Nocturnal leg cramps in older people. *Postgrad Med J* 2002; **78:** 596–8.
3. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; **310:** 13–17.
4. Man-Son-Hing M, *et al.* Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; **13:** 600–606.
5. Anonymous. Quinine for nocturnal leg cramps? *Drug Ther Bull* 1996; **34:** 7–8.
6. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
7. Nightingale SL. Quinine for nocturnal leg cramps. *ACP J Club* 1995; **123:** 86.
8. Young GL, Jewell D. Interventions for leg cramps in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 16/06/05).

Spasticity

The term spasticity has been loosely applied to various disorders of motor control resulting from CNS disease and marked by effects such as increased muscle tone, exaggerated stretch reflexes, impaired voluntary movement, weakness, loss of dexterity, abnormal posture, and often disturbed gait. In some patients muscle spasm and pain may be more distressing than impaired movement. Other complications may include contractures, pressure sores, and infection. Spasticity is a feature of neurological conditions such as multiple sclerosis, cerebral palsy, head injury, and stroke, particularly if there are spinal lesions.

Spasticity is disabling and difficult to treat when severe, but mild or moderate forms may be effectively managed by conservative treatment. Some patients may even use spasticity to provide a means of posture control and care should be taken that treatment does not lead to increased disability.

Various discussions on the management of spasticity have been published.[1-10] The mainstay of management is physiotherapy with antispastic drugs, although the evidence for the latter is rather scanty.[9,11,12] Baclofen, dantrolene, diazepam, and tizanidine are the drugs most often used. These 4 drugs act via different mechanisms, which are not fully understood.

Baclofen is thought to act at the spinal cord level but may also have supraspinal sites of action. It is a powerful neuronal depressant and may exert its inhibitory effects by acting as an agonist at GABA (gamma aminobutyric acid) receptors. *Diazepam* is also thought to act centrally by enhancing the response to GABA. In contrast, *dantrolene* acts directly on muscles, possibly by interfering with the release of calcium from muscular sarcoplasmic reticulum needed for contraction. *Tizanidine* is a centrally acting relaxant and α-adrenergic agonist; it is thought to act at spinal and supraspinal levels by inhibiting the presynaptic activity of excitatory interneurones.[7] It can produce additive effects with baclofen, allowing a reduction in the dosage of both drugs; use with benzodiazepines is not recommended because of the potential for interactions. All these are usually given by mouth but baclofen may also be given intrathecally in severe chronic spasticity.[10,13,14] Injection directly into the spinal subarachnoid space allows immediate delivery to the site of action in the spinal cord and the use of considerably lower doses than those given orally. It has been reported[15] that some patients receiving long-term intrathecal baclofen treatment have been able to stop their therapy without symptoms of spasticity re-appearing, and that others have been able to reduce the dosage required.

Other drugs that may produce some benefit or are being studied in spasticity include *other benzodiazepines*, *clonidine*, *gabapentin*, and *memantine*.

Alternative approaches to treatment include nerve blocks using *local anaesthetics*; they should generally only be used when further muscle relaxation would not increase disability. *Chemical neurolysis* using alcohol or phenol is only considered when there is intractable continuous pain. Local injections of *botulinum A toxin* have produced some encouraging results in the management of limb spasticity in post-stroke or spinal injury patients and in children with cerebral palsy;[16-18] its temporary effect may be an advantage over chemical neurolysis but the need for regular injections may limit acceptability in children.[16] Systematic reviews[19,20] have found insufficient evidence to support or refute such use in children with cerebral palsy.

Nondrug treatments have included electrical stimulation techniques such as transcutaneous nerve stimulation and dorsal column stimulation; vibration applied to agonist spastic muscles to improve voluntary movement; cooling to decrease afferent inputs from peripheral receptors; and orthopaedic surgery or neurosurgery.

1. Young RR. Spasticity: a review. *Neurology* 1994; **44** (suppl 9): S12–S20.
2. Ko CK, Ward AB. Management of spasticity. *Br J Hosp Med* 1997; **58:** 400–5.
3. Kita M, Goodkin DE. Drugs used to treat spasticity. *Drugs* 2000; **59:** 487–95.
4. Anonymous. The management of spasticity. *Drug Ther Bull* 2000; **38:** 44–6.
5. Bhakta BB. Management of spasticity in stroke. *Br Med Bull* 2000; **56:** 476–85.
6. Burchiel KJ, Hsu FPK. Pain and spasticity after spinal cord injury: mechanisms and treatment. *Spine* 2001; **26** (suppl): S146–S160.
7. Ward AB. A summary of spasticity management – a treatment algorithm. *Eur J Neurol* 2002; **9** (suppl 1): 48–52.
8. Abbruzzese G. The medical management of spasticity. *Eur J Neurol* 2002; **9** (suppl 1): 30–4.
9. Montané E, *et al.* Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. *Neurology* 2004; **63:** 1357–63.
10. Verrotti A, *et al.* Pharmacotherapy of spasticity in children with cerebral palsy. *Pediatr Neurol* 2006; **34:** 1–6.
11. Taricco M, *et al.* Pharmacological interventions for spasticity following spinal cord injury. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/06/05).
12. Shakespeare DT, *et al.* Anti-spasticity agents for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 16/06/05).
13. McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med* 1993; **49:** 262–7.
14. Anonymous. Intrathecal baclofen for spasticity. *Med Lett Drugs Ther* 1994; **36:** 21–2.
15. Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; **60:** 168–73.
16. Neville B. Botulinum toxin in the cerebral palsies. *BMJ* 1994; **309:** 1526–7.
17. Fried GW, Fried KM. Spinal cord injury and use of botulinum toxin in reducing spasticity. *Phys Med Rehabil Clin N Am* 2003; **14:** 901–10.
18. Preiss RA, *et al.* The effects of botulinum toxin (BTX-A) on spasticity of the lower limb and on gait in cerebral palsy. *J Bone Joint Surg Br* 2003; **85:** 943–8.
19. 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).
20. 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).

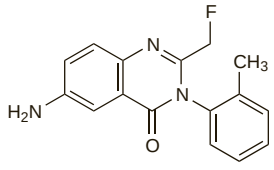
Afloqualone *(rINN)*

Aflocualona; Afloqualonum; HQ-495. 6-Amino-2-fluoromethyl-3-*o*-tolylquinazolin-4(3*H*)-one.

Афлоквалон

$C_{16}H_{14}FN_3O$ = 283.3.

CAS — 56287-74-2.



Pharmacopoeias. In *Jpn.*

Profile

Afloqualone is a centrally acting skeletal muscle relaxant that has been given orally for the treatment of muscle spasm associated with musculoskeletal conditions. Photosensitivity reactions have been reported.

◊ References.

1. Ishikawa T, *et al.* Photoleukomelanodermatitis (Kobori) induced by afloqualone. *J Dermatol* 1994; **21:** 430–3.

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.

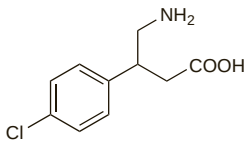
Баклофен

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