Uses and Administration

Tizanidine hydrochloride is a centrally acting skeletal muscle relaxant. It is an α_2-adrenergic agonist structurally related to clonidine (p.1247) and acts mainly at spinal and supraspinal levels to inhibit excitatory interneurones. It is used for the symptomatic relief of spasticity associated with multiple sclerosis or with spinal cord injury or disease. It is also used in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions.

Tizanidine hydrochloride is given orally, usually in divided doses; doses are expressed in terms of the base. Tizanidine hydrochloride 1.14 mg is equivalent to about 1 mg of tizanidine. The usual initial daily dose in the UK in the management of spasticity is the equivalent of 2 mg of the base given as a single dose. The dose may be increased thereafter according to response in steps of 2 mg at intervals of at least 3 to 4 days, usually up to 24 mg daily given in 3 or 4 divided doses. A similar schedule, with an initial daily dose of 4 mg, increased as required in steps of 2 to 4 mg, is used in the USA. The maximum recommended dose is 36 mg daily. Maintenance doses have been given in some countries in the form of modified-release preparations. For dosage in renal impairment, see below.

In the treatment of painful muscle spasm tizanidine hydrochloride is given in doses equivalent to 2 to 4 mg of the base three times daily.

Administration in renal impairment. In the UK, licensed product information recommends that in patients with renal insufficiency, treatment with tizanidine hydrochloride should be started with the equivalent of 2 mg of the base once daily; thereafter it advises a slow increase in the once-daily dose before increasing the frequency of administration. Similar recommendations are made in the USA.

Headache. Results from an open-label study[1] and a later controlled study[2] suggested that tizanidine might be of value in the prophylaxis of chronic daily headache. However, an earlier controlled study[3] failed to show any significant advantage over placebo in the treatment of chronic tension-type headache. In another study[4] tizanidine was also effective when given with a long-acting NSAID as part of a detoxification regimen for patients with chronic daily headaches induced by analgesic overuse.

1. Saper JR, *et al.* An open-label dose-titration study of the efficacy and tolerability of tizanidine hydrochloride tablets in the prophylaxis of chronic daily headache. *Headache* 2001; **41:** 357–68.
2. Saper JR, *et al.* Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002; **42:** 470–82.
3. Murros K, *et al.* Modified-release formulation of tizanidine in chronic tension-type headache. *Headache* 2000; **40:** 633–7.
4. Smith TR. Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache* 2002; **42:** 175–7.

Premedication. The value of tizanidine as a premedicant is being studied.[1] A dose of tizanidine 12 mg appears to have sedative and sympatholytic effects comparable with clonidine 150 micrograms.

1. Meittinen TJ, *et al.* The sedative and sympatholytic effects of oral tizanidine in healthy volunteers. *Anesth Analg* 1996; **82:** 817–20.

Spasticity. The efficacy of tizanidine for spasticity (p.1887) associated with cerebral and spinal disorders[1,2] has been shown in several placebo-controlled studies and in comparative studies it has produced similar improvements in muscle tone to baclofen or diazepam. Carefully titrated doses of tizanidine and baclofen used together may have additive beneficial effects[1,2] but use with benzodiazepines is not recommended because of potential interactions.[1] It was considered that tizanidine might have the advantage of being better tolerated than baclofen.

1. Wagstaff AJ, Bryson HM. Tizanidine: a review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* 1997; **53:** 435–52.
2. Kamen L, *et al.* A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. *Curr Med Res Opin* 2008; **24:** 425–39.

Preparations

USP 31: Tizanidine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Sirdalud; **Austria:** Sirdalud; **Belg.:** Sirdalud; **Braz.:** Sirdalud; **Canad.:** Zanaflex; **Chile:** Sirdalud; **Cz.:** Sirdalud; **Denm.:** Sirdalud; **Fin.:** Sirdalud; **Ger.:** Sirdalud; **Gr.:** Sirdalud; **Hung.:** Sirdalud; **India:** Sirdalud; **Indon.:** Myores; Sirdalud; Zitanid; **Irl.:** Zanaflex; **Ital.:** Sirdalud; **Mex.:** Sirdalud; **Neth.:** Sirdalud; **Philipp.:** Sirdalud; Ternelax; **Pol.:** Sirdalud; **Port.:** Sirdalud; **Rus.:** Sirdalud (Сирдалуд); **Spain:** Sirdalud; **Switz.:** Sirdalud; **Thai.:** Sirdalud; Tizan; **Turk.:** Sirdalud; **UK:** Zanaflex; **USA:** Zanaflex; **Venez.:** Sirdalud.

Multi-ingredient: **India:** Kinectine-MR; Movon-MR; Niciflex-T; Nicip T; Nimulid MR; Valus-XT†; Vorth-XT†; Zerodol-MR.

Tolperisone Hydrochloride (BANM, rINNM)

Hidrocloruro de tolperisona; N-553; Tolpérisone, Chlorhydrate de; Tolperisoni Hydrochloridum. 2,4′-Dimethyl-3-piperidinopropiophenone hydrochloride.
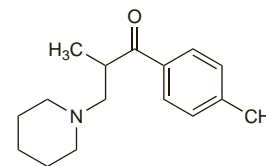
Тольперизона Гидрохлорид

$C_{16}H_{23}NO,HCl = 281.8$.

CAS — 728-88-1 (tolperisone); 3644-61-9 (tolperisone hydrochloride).
ATC — M03BX04.
ATC Vet — QM03BX04.

(tolperisone)

Pharmacopoeias. In *Jpn*.

Profile

Tolperisone hydrochloride is a centrally acting muscle relaxant that has been used for the symptomatic treatment of spasticity (p.1887) and muscle spasm (p.1887), in usual doses of 50 to 150 mg three times daily by mouth. It has also been given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Miodom; **Austria:** Mydocalm; **Cz.:** Mydocalm; **Ger.:** Mydocalm; **Hong Kong:** Mydocalm; **Hung.:** Myderison; Mydeton; **Jpn:** Muscalm; **Pol.:** Mydocalm; Tolperis; **Rus.:** Mydocalm (Мидокалм); **Switz.:** Mydocalm; **Thai.:** Biocalm; Musocalm; Mydocalm; Mydono; Mydosone; Myoxan; Risocalm; Shiwalax†; Soneriper; Spamus†; Tanderon.

Multi-ingredient: **Mex.:** Mydocalm-A.

27. Gin T, *et al*. Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at caesarean section. *Br J Anaesth* 1993; **70:** 311–116.

Intensive care

The use of neuromuscular blockers in patients requiring mechanical ventilation as part of intensive care has been discussed in a number of reviews[1-3] and guidelines.[4] Neuromuscular blockers are used to provide additional relaxation and facilitate ventilatory support in patients who fail to respond to sedation alone. It is important to ensure that such patients are adequately sedated and relatively pain free before these drugs are used. Patients who are considered most likely to benefit are those with spontaneous respiration that is counterproductive to mechanical ventilation. Patients with little inherent respiratory muscle activity are less likely to obtain an improvement in oxygenation. Neuromuscular blockers may also improve control of intracranial pressure in patients with intracranial hypertension, including prevention of rises in intracranial pressure associated with routine tracheobronchial suction.

Pancuronium has been widely used as a neuromuscular blocker in intensive care because of its tendency to increase arterial pressure and the majority of patients requiring a neuromuscular blocker can be adequately managed with pancuronium; however, its long duration of action may be a problem in some circumstances, and its vagolytic activity can also produce tachycardia. Vecuronium, atracurium, and cisatracurium have relatively few cardiovascular effects, but there has been some concern over the ability of the atracurium metabolite laudanosine to accumulate in the CNS (see Biotransformation, under Pharmacokinetics, p.1905). Atracurium and cisatracurium may also be more suitable in patients with hepatic or renal impairment as their metabolism does not lead to the accumulation of active metabolites. Other neuromuscular blockers that have been used in intensive care include doxacurium, pipecuronium, and rocuronium.

Close monitoring of neuromuscular blockade is recommended since the pharmacodynamics and pharmacokinetics of neuromuscular blockers may be altered in patients in intensive care;[1-4] this should also allow the lowest effective neuromuscular blocking dose to be used, and reduce adverse events. Prolonged neuromuscular blockade has been related to dosage.

Other factors that may potentiate neuromuscular blockade include drug interactions, electrolyte imbalance, hypothermia, or changes in acid–base balance.[1,3] Conversely, dosage requirements may be increased in patients with burns or in those receiving prolonged therapy. Tachyphylaxis has occurred with some neuromuscular blockers, but may resolve on switching to another blocker.

Prolonged neuromuscular blockade has been associated with adverse effects and should be avoided when possible. Recovery after withdrawal of prolonged treatment may be longer than pharmacologically predicted due to the accumulation of active metabolites; this is a particular problem for neuromuscular blockers with a long duration of action and for patients with hepatic or renal impairment. An acute myopathy has also followed prolonged use, most commonly with aminosteroid neuromuscular blockers (see Table 1, p.1900); there are case reports suggesting that use of corticosteroids might increase the risk.[4,5]

When rapid reversal of paralysis is necessary an anticholinesterase such as neostigmine may be used, but relatively little is known about the efficacy of anticholinesterases in reversing prolonged paralysis.[6]

Neonatal intensive care. Neuromuscular blockers such as pancuronium bromide are used in neonatal intensive care to obtain muscle relaxation during mechanical ventilation in infants with severe pulmonary disease, especially in those whose respiratory efforts are out of phase with the ventilator.[7] They are only used in infants at high risk of complications such as *pneumothorax* or *intraventricular haemorrhage*; their routine use in all ventilated neonates is not recommended.[8]

Abolition of spontaneous respiration during mechanical ventilation has had variable effects on the incidence of *pneumothorax* in infants with respiratory distress syndrome. Although a reduced incidence was found in one study[9] involving infants of less than 33 weeks' gestation, in another study[10] the incidence was reduced only in infants with a gestational age of 27 to 32 weeks; no reduction was obtained in those below 26 weeks' gestation. Paralysis also failed to reduce the incidence of pneumothorax or interstitial emphysema in a study[11] of infants with

hyaline membrane disease but did appear to speed recovery of lung function.

The aetiology of *intraventricular haemorrhage* remains obscure but there is a well recognised association with gestational age;[12] less mature neonates are more susceptible and the incidence decreases sharply after 30 weeks' gestation. There appears to be an association between fluctuating cerebral blood-flow velocity in the first day of life and subsequent development of intraventricular haemorrhage.[13] Respiratory paralysis from the first day of life until 72 hours of age has been reported[14] to stabilise both cerebral and arterial blood-flow velocity and to produce a decrease in the incidence and severity of intraventricular haemorrhage in infants with respiratory distress syndrome. However, respiratory paralysis has also been reported to have no effect on the development of intraventricular haemorrhage.[9,10]

The use of neuromuscular blockers in the newborn is not without complications. Multiple joint contractures, possibly potentiated by use of aminoglycosides or phenobarbital, have been reported[15,16] in infants given pancuronium, and regular passive limb movements should be performed during paralysis. Marked oedema, severe disturbances of fluid balance, renal failure and death have been reported in 2 neonates.[17] Hypoxaemia may develop after induction of paralysis unless a significant increase in ventilator support is made;[9,13,18] hypotension may also occur.[19] Drugs such as pancuronium which are metabolised in the liver and excreted in the urine have a prolonged action in premature infants.[7] As with adults (see above), continuous use of neuromuscular blockers in neonates has been associated with prolonged neuromuscular block on withdrawal.[20]

1. Coursin DB, *et al*. Muscle relaxants in critical care. *Curr Opin Anaesthesiol* 1993; **6:** 341–6.
2. Elliot JM, Bion JF. The use of neuromuscular blocking drugs in intensive care practice. *Acta Anaesthesiol Scand* 1995; **39** (suppl 10): 70–82.
3. Lewis KS, Rothenberg DM. Neuromuscular blockade in the intensive care unit. *Am J Health-Syst Pharm* 1999; **56:** 72–5.
4. Murray MJ, *et al*. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Am J Health-Syst Pharm* 2002; **59:** 179–95.
5. Fischer JR, Baer RK. Acute myopathy associated with combined use of corticosteroids and neuromuscular blocking agents. *Ann Pharmacother* 1996; **30:** 1437–45.
6. Watling SM, Dasta JF. Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: a review of the literature. *Crit Care Med* 1994; **22:** 884–93.
7. Levene MI, Quinn MW. Use of sedatives and muscle relaxants in newborn babies receiving mechanical ventilation. *Arch Dis Child* 1992; **67:** 870–3.
8. Cools F, Offringa M. Neuromuscular paralysis for newborn infants receiving mechanical ventilation. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 20/10/05).
9. Greenough A, *et al*. Pancuronium prevents pneumothoraces in ventilated premature babies who actively expire against positive pressure inflation. *Lancet* 1984; **i:** 1–3.
10. Cooke RWI, Rennie JM. Pancuronium and pneumothorax. *Lancet* 1984; **i:** 286–7.
11. Pollitzer MJ, *et al*. Pancuronium during mechanical ventilation speeds recovery of lungs of infants with hyaline membrane disease. *Lancet* 1981; **i:** 346–8.
12. Miall-Allen VM, *et al*. Blood pressure fluctuation and intraventricular hemorrhage in the preterm infant of less than 31 weeks' gestation. *Pediatrics* 1989; **83:** 657–61.
13. Perlman JM, *et al*. Fluctuating cerebral blood-flow velocity in respiratory distress syndrome. *N Engl J Med* 1983; **309:** 204–9.
14. Perlman JM, *et al*. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. *N Engl J Med* 1985; **312:** 1353–7.
15. Sinha SK, Levene MI. Pancuronium bromide induced joint contractures in the newborn. *Arch Dis Child* 1984; **59:** 73–5.
16. Fanconi S, *et al*. Effects of paralysis with pancuronium bromide on joint mobility in premature infants. *J Pediatr* 1995; **127:** 134–6.
17. Reynolds EOR, *et al*. Muscle relaxation and periventricular hemorrhage. *N Engl J Med* 1985; **313:** 955–6.
18. Philips JB, *et al*. Hypoxaemia in ventilated neonates after pancuronium paralysis. *Lancet* 1979; **i:** 877.
19. McIntosh N. Hypotension associated with pancuronium use in the newborn. *Lancet* 1985; **ii:** 279.
20. Björklund LJ. Use of sedatives and muscle relaxants in newborn babies receiving mechanical ventilation. *Arch Dis Child* 1993; **69:** 544.

Tetanus

The clinical manifestations of tetanus after infection with *Clostridium tetani* are caused by the highly potent neurotoxin tetanospasmin produced by its germinating spores.

The muscular symptoms of generalised tetanus include trismus (lockjaw), glottal spasm, generalised muscle spasm, opisthotonus (spasm of the back muscles resulting in backward arching of the body), respiratory spasm, and paralysis. Other complications include electrolyte disturbances and autonomic dysfunction leading to cardiovascular effects such as hypertension, tachycardia, and peripheral vasoconstriction. Patients may have a milder form in which the twitching and muscle spasms are limited to the

area near the site of the injury, but such localised tetanus is rare and can progress to the generalised form.

Treatment aims to destroy the causative organism and/or neutralise any unbound toxin in the body, to control rigidity and muscle spasms, and to control autonomic dysfunction. For the **antibacterial treatment and prevention** of tetanus and neutralisation of tetanospasmin, see p.196. After antibacterial therapy the mainstay of treatment of **rigidity and spasms** is sedation with *benzodiazepines* such as diazepam or midazolam; they may also reduce patient anxiety. *Opioid analgesics* can be added to treatment to provide analgesia and additional sedation; in addition, *fentanyl*, *morphine*, and *sufentanil* may control autonomic overactivity. *Antiepileptics*, particularly phenobarbital, may also provide additional sedation. *Chlorpromazine* is sometimes used with benzodiazepines to minimise rigidity and muscle spasms. Sedation with *propofol* may also control spasms and rigidity without the need for an additional relaxant; however, mechanical ventilation is required. Centrally acting muscle relaxants have also been tried to control muscle spasms. *Baclofen* has been given by the intrathecal route, but its therapeutic range in severe tetanus may be very narrow and deep coma and loss of spontaneous respiration has been reported. *Dantrolene* has also been reported to be effective. When muscle spasms are severe or interfere with respiration, *competitive neuromuscular blockers* have been used in addition to benzodiazepine sedation, to control spasms and to induce therapeutic paralysis so mechanical ventilation can be initiated.

Control of **autonomic overactivity** may be achieved with sedation; benzodiazepines, antiepileptics, and opioid analgesics have all been used (see above). *Beta blockers* such as propranolol have also been used; however, they are no longer recommended because of the potential for severe cardiovascular effects. Labetalol has both alpha- and beta-blocking activity but offers no advantage over propranolol. More recently, *esmolol*, a short-acting beta blocker, has been used. *Magnesium sulfate* has been found to minimise autonomic disturbance in ventilated patients and controls spasms in non-ventilated patients, but there is need for further investigation. **Electrolyte disturbance** is corrected with calcium and magnesium salts.
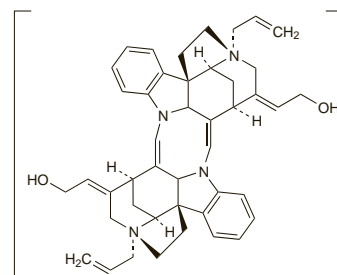
References.
1. Attygalle D, Karalliedde L. Unforgettable tetanus. *Eur J Anaesthesiol* 1997; **14:** 122–33.
2. Ernst ME, *et al*. Tetanus: pathophysiology and management. *Ann Pharmacother* 1997; **31:** 1507–13.
3. Farrar JJ, *et al*. Tetanus. *J Neurol Neurosurg Psychiatry* 2000; **69:** 292–301.
4. Cook TM, *et al*. Tetanus: a review of the literature. *Br J Anaesth* 2001; **87:** 477–87.
5. Edlich RF, *et al*. Management and prevention of tetanus. *J Long Term Eff Med Implants* 2003; **13:** 139–54.
6. Okoromah CN, Lesi FE. Diazepam for treating tetanus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 18/05/06).

Alcuronium Chloride (BAN, USAN, rINN)

Alcuronii chloridum; Alcuronium, chlorure d'; Alkuronio chloridas; Alkuronium-chlorid; Alkuroniumklorid; Alkurónium-klorid; Alkuroniumkloridi; Allnortoxiferin Chloride; Cloruro de alcuronio; Diallylnortoxiferin Dichloride; Diallyltoxiferine Chloride; Ro-4-3816. NN′-Diallylbisnortoxiferinium dichloride.

Алкурония Хлорид

$C_{44}H_{50}Cl_2N_4O_2 = 737.8$.

CAS — 23214-96-2 (alcuronium); 15180-03-7 (alcuronium chloride).
ATC — M03AA01.
ATC Vet — QM03AA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*
Ph. Eur. 6.2 (Alcuronium Chloride). A white or slightly greyish-white, crystalline powder. Freely soluble in water and in methyl