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.
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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 cloridas; Alkuronium-chlorid; Alkuroniumklorid; Alkurónium-klorid; Alkuroniumkloridi; Allnortoxiferin Chloride; Cloruro de alcuronio; Diallylnortoxiferine Dichloride; Diallyltoxiferine Chloride; Ro-4-3816. *NN*:Diallylbisnortoxiferinium dichloride.

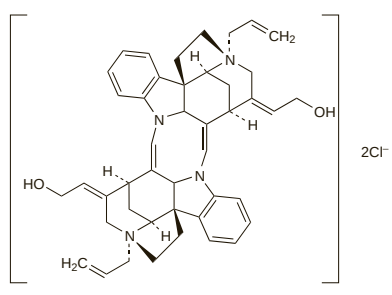
Аллкуроний Хлорид

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

alcohol; soluble in alcohol; practically insoluble in cyclohexane. Store under nitrogen in an airtight container. Protect from light.

Profile

Alcuronium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1905) that is used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900). It can induce histamine release to some degree. Anaphylactoid reactions have been associated with the use of alcuronium. It has some vagolytic action and may produce tachycardia; hypotension may also occur.

Doses of neuromuscular blockers need to be carefully titrated for individual patients according to response, and may vary with the procedure, the other drugs given, and the state of the patient; monitoring of the degree of block is recommended in order to reduce the risk of overdosage. An initial dose of 150 to 250 micrograms/kg has been given intravenously. Muscle relaxation occurs after about 2 minutes and the effect lasts for about 20 to 30 minutes. Supplementary doses of 30 micrograms/kg have been given to provide additional periods of muscle relaxation.

Porphyria. Alcuronium is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pregnancy. Alcuronium crosses the placenta. No evidence of neuromuscular block was seen in any of the neonates born to 12 women who received alcuronium 15 to 30 mg by intravenous injection, 5 to 10.5 minutes before delivery[1] but caution was advised if alcuronium was given in obstetrics in high doses or for a prolonged period.

1. Ho PC, *et al.* Caesarean section and placental transfer of alcuronium. *Anaesth Intensive Care* 1981; **9:** 113–18.

Renal impairment. Alcuronium is excreted mainly by the kidneys and accumulation, with prolonged paralysis, may therefore be expected in patients with renal impairment given large or repeated doses. A prolonged elimination half-life has been reported in anuria.[1] However, doses of 160 micrograms/kg have been used without any problems in patients with chronic renal failure undergoing renal transplantation.[2] The average duration of action of this dose was 37 minutes and any residual neuromuscular blockade at the end of surgery was successfully reversed using atropine and neostigmine.

1. Raaflaub J, Frey P. Zur Pharmakokinetik von Diallyl-nor-toxiferin beim Menschen. *Arzneimittelforschung* 1972; **22:** 73–8.
2. Kaushik S, *et al.* Use of alcuronium in patients undergoing renal transplantation. *Br J Anaesth* 1984; **56:** 1229–33.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Alloferin†; ***Braz.:*** Alloferine†; ***Ger.:*** Alloferin; ***Hong Kong:*** Alloferin†; ***Malaysia:*** Alloferin†; ***S.Afr.:*** Alloferin; ***Singapore:*** Alloferin†.

Atracurium Besilate *(BAN, rINN)*

33A74; Atracurii besilas; Atracurium, bésilate d'; Atracurium Besylate *(USAN)*; Atrakurio besilatas; Atrakuriumbesilaatti; Atrakuriumbesilat; Atrakurium-besylát; Atrakuryum Besilat; Besilato de atracurio; BW-33A. 2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) di(benzenesulphonate).

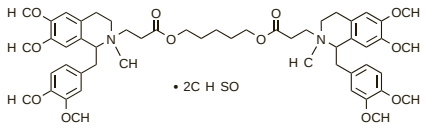
Атракурия Безилат

$C_{53}H_{72}N_2O_{12},2C_6H_5O_3S$ = 1243.5.

CAS — 64228-81-5.

ATC — M03AC04.

ATC Vet — QM03AC04.



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

Ph. Eur. 6.2 (Atracurium Besilate). A white to yellowish-white, slightly hygroscopic powder. It contains 55.0 to 60.0% of the *cis-cis* isomer, 34.5 to 38.5% of the *cis-trans* isomer, and 5.0 to 6.5% of the *trans-trans* isomer. Soluble in water; very soluble in alcohol, in acetonitrile, and in dichloromethane. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Atracurium Besylate). A white to off-white solid. It contains not less than 5.0% and not more than 6.5% of the *trans-trans* isomer, not less than 34.5% and not more than 38.5% of the *cis-trans* isomer, and not less than 55.0% and not more than 60.0% of the *cis-cis* isomer. It is unstable at room temperature. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Cisatracurium Besilate *(BAN, rINN)*

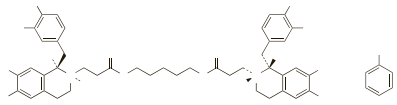
Bésilate de Cisatracurium; Besilato de cisatracurio; BW-51W (cisatracurium); BW-51W89 (cisatracurium); Cisatracurii Besilas; Cisatracurium, Bésilate de; Cisatracurium Besylate; Sisatrakuryum Bezilat; 51W89 (cisatracurium). (1*R*,1′*R*,2*R*,2′*R*)-2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.

Цисатракурия Безилат

CAS — 96946-42-8.

ATC — M03AC11.

ATC Vet — QM03AC11.



Incompatibility. Neuromuscular blockers are generally incompatible with alkaline solutions, for example barbiturates such as thiopental sodium. It is good practice not to give neuromuscular blockers in the same syringe, or simultaneously through the same needle, as other drugs.

The manufacturers state that cisatracurium is incompatible with ketorolac trometamol or propofol emulsion; in addition, lactated Ringer's injection with glucose 5% or lactated Ringer's solution should not be used as a diluent when preparing solutions of cisatracurium for infusion.

Stability. In a stability study,[1] solutions of cisatracurium (as the besilate) in concentrations of 2 or 10 mg/mL were stable for at least 90 days when stored in the original vials at 4° either exposed to or protected from light; similar solutions stored at 23° were stable for at least 45 days. Solutions of 2 mg/mL stored in plastic syringes at 4° or 23° were stable for at least 30 days. Solutions of 0.1, 2, or 5 mg/mL in 5% glucose injection or 0.9% sodium chloride injection in PVC minibags were stable for at least 30 days stored at 4°; the 5 mg/mL solution was also stable for at least 30 days stored at 23°.

1. Xu QA, *et al.* Stability of cisatracurium besylate in vials, syringes, and infusion admixtures. *Am J Health-Syst Pharm* 1998; **55:** 1037–41.

Adverse Effects

The adverse effects of competitive neuromuscular blockers are generally similar although they differ in their propensity to cause histamine release and associated cardiovascular effects. The latter appear to be rare with the aminosteroidal blockers and the benzylisoquinolinium blocker cisatracurium (see below). Competitive neuromuscular blockers with vagolytic activity may produce tachycardia and a rise in blood pressure. The use of blockers that lack an effect on the vagus will not counteract the bradycardia produced during anaesthesia by the other drugs employed or by vagal stimulation. Reduction in blood pressure with compensatory tachycardia may occur with some competitive neuromuscular blockers, in part because of sympathetic ganglion blockade or the release of histamine. Reduction in gastrointestinal motility and tone may occur as a result of ganglionic blockade.

Histamine release may also lead to wheal-and-flare effects at the site of injection, flushing, occasionally bronchospasm, and rarely anaphylactoid reactions.

Malignant hyperthermia has been associated rarely with competitive neuromuscular blockers.

Some competitive neuromuscular blockers such as pancuronium, tubocurarine, and vecuronium can cause a decrease in the partial thromboplastin time and prothrombin time.

In overdosage there is prolonged apnoea due to paralysis of the intercostal muscles and diaphragm, with cardiovascular collapse and the effects of histamine release.

Atracurium and its isomer cisatracurium have no significant vagal or ganglionic blocking activity at recommended doses. Unlike atracurium, cisatracurium does not induce histamine release and is therefore associated with greater cardiovascular stability.

For possible risks from their major metabolite laudanosine, see Biotransformation, under Pharmacokinetics, below.

Effects on body temperature. Competitive neuromuscular blockers are not considered to be a trigger factor for malignant hyperthermia; however, there have been rare case reports of apparent association. Two cases of mild malignant hyperthermia have been reported[1] where tubocurarine was probably the triggering drug. Each episode developed in a member of a family known to be susceptible to malignant hyperthermia, despite preventive measures such as prophylactic cooling, and avoidance of potent inhalation anaesthetics and depolarising neuromuscular blockers. Another case[2] was associated with the use of pancuronium.

1. Britt BA, *et al.* Malignant hyperthermia induced by curare. *Can Anaesth Soc J* 1974; **21:** 371–5.
2. Waterman PM, *et al.* Malignant hyperthermia: a case report. *Anesth Analg* 1980; **59:** 220–1.

Effects on the muscles. For reference to acute myopathy and prolonged muscle weakness after withdrawal of long-term continuous infusions of competitive neuromuscular blockers, see Intensive Care, p.1901.

Hypersensitivity. There have been reports of severe anaphylactoid reactions after use of atracurium[1,2] or cisatracurium.[3-5] For a discussion of hypersensitivity reactions associated with neuromuscular blockers, see under Suxamethonium Chloride, p.1910.

1. Stirton-Hopkins C. Life-threatening reaction to atracurium. *Br J Anaesth* 1988; **60:** 597–8.
2. Oh TE, Horton JM. Adverse reactions to atracurium. *Br J Anaesth* 1989; **62:** 467–8.
3. Briassoulis G, *et al.* Persistent anaphylactic reaction after induction with thiopentone and cisatracurium. *Paediatr Anaesth* 2000; **10:** 429–34.
4. Legros CB, *et al.* Severe anaphylactic reaction to cisatracurium in a child. *Anesth Analg* 2001; **92:** 648–9.
5. Fraser BA, Smart JA. Anaphylaxis to cisatracurium following negative skin testing. *Anaesth Intensive Care* 2005; **33:** 816–19.

Treatment of Adverse Effects

It is essential to maintain assisted respiration in patients who have received a competitive neuromuscular blocker until spontaneous breathing is fully restored; in addition a cholinesterase inhibitor such as neostigmine is usually given intravenously, with atropine or glycopyrronium, to hasten reversal of the neuromuscular block. Patients need to be closely monitored after reversal of block to ensure that muscle relaxation does not return.

Severe hypotension may require intravenous fluid replacement and cautious use of a pressor agent; the patient should be positioned to facilitate venous return from the muscles.

Giving an antihistamine before induction of neuromuscular blockade may help to prevent histamine-induced adverse effects in patients with asthma or those susceptible to bronchospasm.

Reversal of neuromuscular blockade. For a discussion of the use of anticholinesterases for reversal of residual neuromuscular block produced by intermediate- or short-acting blockers after surgical or similar procedures, see under Neostigmine, p.633.

Precautions

Patients who have received a neuromuscular blocker should always have their respiration assisted or controlled until the drug has been inactivated or antagonised.

Atracurium and other competitive neuromuscular blockers should be used with great care, if at all, in respiratory insufficiency or pulmonary disease and in the dehydrated or severely ill patient. The response to neuromuscular blockers is often unpredictable in patients with neuromuscular disorders and they should be used with great care in these patients (see below). Caution is also needed in patients with a history of conditions such as asthma where release of histamine would be a hazard. Care is also required in patients with a history of hypersensitivity to any neuromuscular blocker because high rates of cross-sensitivity have been reported. For a discussion of hypersensitivity reactions associated with neuromuscular blockers, see under Adverse Effects of Suxamethonium Chloride, p.1910.

Resistance to the effects of competitive neuromuscular blockers may occur in patients with burns (see below). The effect of competitive neuromuscular blockers may vary in patients with hepatic impairment: resistance appears to occur to some, such as doxacurium, metocurine, pancuronium, and tubocurarine, while dosage of others, including mivacurium and rocuronium, may need to be reduced because of a prolonged action.

Competitive neuromuscular blockers excreted mainly in the urine should be used with caution in renal impairment; a reduction in dosage may be necessary. Doses may need to be reduced in infants and neonates because of increased sensitivity to competitive muscle relaxants. Doses in obese patients should usually be based upon the patient's ideal body-weight rather than actual body-weight.

The effects of competitive neuromuscular blockers are increased by metabolic or respiratory acidosis and hypokalaemia, hypermagnesaemia, hypocalcaemia, and