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).

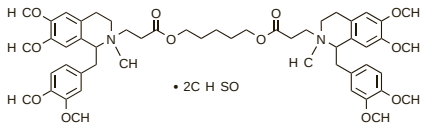
Атракурия Безилат

$C_{53}H_{72}N_2O_{12},2C_6H_5O_3S$ = 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)*

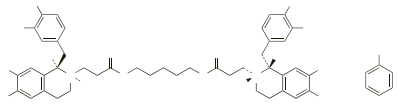
Bésilate de Cisatracurium; Besilato de cisatracurio; BW-51W (cisatracurium); BW-51W89 (cisatracurium); Cisatracurii Besilas; Cisatracurium, Bésilate de; Cisatracurium Besylate; Sisatrakuryum Bezilat; 51W89 (cisatracurium). (1*R*,1′*R*,2*R*,2′*R*)-2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium)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

hypophosphataemia and dehydration. Competitive neuromuscular blockade may also be enhanced by raised body temperature and reduced in hypothermia.

In contrast to other competitive neuromuscular blockers, reduction in body temperature may necessitate a dosage reduction for *atracurium and its isomer cisatracurium* since cooling reduces the rate of inactivation of atracurium and cisatracurium, but physiological variations in body temperature and pH will not significantly affect their action.

Burns. The dose requirements of competitive neuromuscular blockers are increased in patients with burns,[1-3] the dose correlating with both the extent of the burn and time after injury. This resistance is usually not seen in patients with less than 10% body-surface burns but if more than 40% of the body-surface is affected the dose of competitive blocker may need to be up to five times higher than in patients without burns. Resistance peaks about 2 weeks after injury, persists for many months in patients with major burns, and decreases gradually with healing of the burn. The mechanism of resistance is multifactorial but may be partly explained by increased protein binding, increased volume of distribution, and increased numbers of acetylcholine receptors at the motor end-plate requiring more muscle relaxant to produce a given effect. Despite the high doses of competitive relaxants that are required, recovery from neuromuscular blockade is not seriously impaired and their effects can be reversed with usual doses of an anticholinesterase.

1. Martyn J, *et al.* Clinical pharmacology of muscle relaxants in patients with burns. *J Clin Pharmacol* 1986; **26:** 680–5.
2. Anonymous. Neuromuscular blockers in patients with burns. *Lancet* 1988; **ii:** 1003–4.
3. Tschida SJ, *et al.* Resistance to nondepolarizing neuromuscular blocking agents. *Pharmacotherapy* 1996; **16:** 409–18.

Cardiopulmonary bypass. The effect of cardiopulmonary bypass on the pharmacokinetics and pharmacodynamics of competitive neuromuscular blockers can be complex but generally their dosage may need to be reduced. Although the intensity of neuromuscular blockade of most competitive neuromuscular blockers is reduced by hypothermia[1] used during cardiopulmonary bypass, their use during this procedure is associated with rises in plasma concentrations, reduced clearance, and prolongation of the elimination half-life.[2-6] Various mechanisms, including reduced distribution to highly perfused tissues such as the lungs, have been proposed to explain this effect.[2] For atracurium, it appears that it is a reduction in the temperature-dependent inactivation by Hofmann elimination during hypothermia that enables lower doses to be used.[7]

1. Buzello W, *et al.* Unequal effects of cardiopulmonary bypass-induced hypothermia on neuromuscular blockade from constant infusion of alcuronium, d-tubocurarine, pancuronium, and vecuronium. *Anesthesiology* 1987; **66:** 842–6.
2. Walker JS, *et al.* Alcuronium kinetics in patients undergoing cardiopulmonary bypass surgery. *Br J Clin Pharmacol* 1983; **15:** 237–44.
3. Walker JS, *et al.* Altered d-tubocurarine disposition during cardiopulmonary bypass surgery. *Clin Pharmacol Ther* 1984; **35:** 686–94.
4. Wierda JMKH, Agoston S. Pharmacokinetics of vecuronium during hypothermic bypass. *Br J Anaesth* 1989; **63:** 627P–628P.
5. Smeulers NJ, *et al.* Hypothermic cardiopulmonary bypass influences the concentration-response relationship and the biodisposition of rocuronium. *Eur J Anaesthesiol* 1995; **12** (suppl 11): 91–4.
6. Asokumar B, *et al.* Pharmacokinetics of doxacurium during normothermic and hypothermic cardiopulmonary bypass surgery. *Can J Anaesth* 1998; **45:** 515–20.
7. Flynn PJ, *et al.* Use of atracurium in cardiac surgery involving cardiopulmonary bypass with induced hypothermia. *Br J Anaesth* 1984; **56:** 967–72.

Hepatic impairment. The effect of competitive neuromuscular blockers may vary in patients with hepatic impairment (see Precautions, above) but alterations in the pharmacokinetics of atracurium and cisatracurium in patients with hepatic impairment (see Biotransformation, under Pharmacokinetics, below) do not appear to be clinically significant and a reduction in dosage is not generally recommended.

Neuromuscular disorders. Caution is needed if competitive neuromuscular blockers are given to patients with neuromuscular disease since severe complications have been reported.[1] Increased response may be seen in patients with paraplegia or quadriplegia, but resistance has been reported in patients with hemiplegia. Increased response also may occur in patients with amyotrophic lateral sclerosis, neurofibromatosis, and poliomyelitis; this is of little concern unless the respiratory muscles are involved when prolonged apnoea may occur. Patients with myasthenia gravis usually show increased sensitivity to competitive neuromuscular blockers although small doses have been given without complications. During remission of myasthenia gravis a normal response is usual but since remission is often incomplete, small intermittent doses are advised. A significantly greater exaggeration of response is seen in patients with the myasthenic syndrome. Both normal and increased responses have been reported in patients with myotonias or muscular dystrophies but exquisite sensitivity occurs in patients with ocular muscular dystrophy. A normal response to competitive relaxants may be expected in patients with multiple sclerosis, muscular denervation, Parkinson's disease, and tetanus.

1. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; **61:** 173–87.

Pregnancy. A review[1] of the pharmacokinetics of neuromuscular blockers in pregnancy concluded that atracurium and mivacurium are the best choice in pregnancy since their actions are predictable; their duration of action is either unchanged or only slightly prolonged. Atracurium also has a low umbilical to maternal vein concentration (uv/mv) ratio. In general, it is advisable[1] to choose a neuromuscular blocker with a low uv/mv ratio and a short duration of action, and to inject the lowest dose required to produce adequate surgical conditions.

Atracurium 300 micrograms/kg given to 26 women undergoing caesarean section, with subsequent incremental doses of 100 or 200 micrograms/kg if necessary, produced good surgical relaxation in all patients without any complications.[2] Of the 26 neonates delivered, respiration was established within 90 seconds in 21, with an Apgar score of 10 at 5 minutes. The remaining 5 neonates were delivered by caesarean section because of fetal distress and were slower to start breathing.

A study[3] of 22 women in the immediate postpartum period found the onset and duration of cisatracurium to be significantly shorter when compared with nonpregnant patients.

1. Guay J, *et al.* Clinical pharmacokinetics of neuromuscular relaxants in pregnancy. *Clin Pharmacokinet* 1998; **34:** 483–96.
2. Frank M, *et al.* Atracurium in obstetric anaesthesia: a preliminary report. *Br J Anaesth* 1983; **55:** 113S-114S.
3. Pan PH, Moore C. Comparison of cisatracurium-induced neuromuscular blockade between immediate postpartum and nonpregnant patients. *J Clin Anesth* 2001; **13:** 112–17.

Renal impairment. Although some differences in the pharmacokinetics of atracurium and cisatracurium have been reported in patients with renal impairment (see Biotransformation, under Pharmacokinetics, below), duration of their neuromuscular blocking action is not significantly dependent on renal function and usual doses may be given to such patients.[1,2] Atracurium has been given by infusion to patients with end-stage renal failure[3] when the initial dose required for induction of neuromuscular block was 37% higher than that required by patients without renal impairment. The increase could be explained by the larger extracellular fluid volume in patients with chronic renal failure.

Although the pharmacokinetics of atracurium and cisatracurium are not appreciably different in renal impairment, those of their metabolites may be (see Biotransformation, under Pharmacokinetics, below) and therefore it has been suggested that neuromuscular function should be monitored during use of atracurium.[4]

1. Hunter JM, *et al.* Use of the muscle relaxant atracurium in anephric patients: preliminary communication. *J R Soc Med* 1982; **75:** 336–340.
2. Boyd AH, *et al.* Pharmacodynamics of the 1R cis-1′R cis isomer of atracurium (51W89) in health and chronic renal failure. *Br J Anaesth* 1995; **74:** 400–404.
3. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interactions with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.
4. Vandenbrom RHG, *et al.* Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clin Pharmacokinet* 1990; **19:** 230–40.

Resistance. The aetiology of resistance to competitive blockers is not clear but might be due to pharmacodynamic or pharmacokinetic alterations associated with disease states such as burn injuries (see above) or hepatic impairment (see above) or therapy with other drugs (see Interactions, below). One review[1] noted that there had been numerous case reports of resistance to competitive neuromuscular blockers; most had been associated with use of single doses or short-term intermittent therapy, but more recent reports had documented resistance during continuous infusions in 9 patients of whom 7 had received atracurium and 2 rocuronium. Resistance to atracurium had followed 2 different patterns. Patients had required either usual or raised doses for initial control but both groups had subsequently required progressive increases. Most patients with resistance to atracurium were successfully managed by transfer to pancuronium or doxacurium.

1. Tschida SJ, *et al.* Resistance to nondepolarizing neuromuscular blocking agents. *Pharmacotherapy* 1996; **16:** 409–18.

Tourniquets. Atracurium might be unsuitable for neuromuscular blockade of a limb that has been isolated with a tourniquet in order to provide a bloodless field for surgery.[1] Atracurium undergoes non-enzymatic degradation in plasma and would therefore continue to degrade locally leading to a loss of blockade in the limb, which could not be corrected by further doses unless the tourniquet was deflated.

1. Shannon PF. Neuromuscular block and tourniquets. *Br J Anaesth* 1994; **73:** 726.

Interactions

A number of drugs may influence neuromuscular transmission and thus interfere with the action of both competitive and depolarising neuromuscular blockers, resulting in potentiation or antagonism of neuromuscular block. Some interactions may be advantageous, such as the reversal of competitive neuromuscular block by anticholinesterases. In general, adverse interactions are potentially more serious in patients with impaired neuromuscular function (see Neuromuscular Disorders, above, and under Suxamethonium Chloride, p.1911).

Drug interactions affecting neuromuscular blockers of either type (competitive and depolarising) as well as those specific for competitive neuromuscular blockers are discussed below. For drug interactions specific to depolarising neuromuscular blockers see under Interactions of Suxamethonium Chloride, p.1911.

◊ Reviews.

1. Feldman S, Karalliedde L. Drug interactions with neuromuscular blockers. *Drug Safety* 1996; **15:** 261–73.
2. Cammu G. Interactions of neuromuscular blocking drugs. *Acta Anaesthesiol Belg* 2001; **52:** 357–63.

Antiarrhythmics. *Lidocaine, procainamide, quinidine,* and *verapamil* all have some neuromuscular blocking activity and may enhance the block produced by neuromuscular blockers. Large doses of lidocaine may reduce the release of acetylcholine and act directly on the muscle membrane. Quinidine has a curare-like action at the neuromuscular junction and depresses the muscle action potential. If given during recovery from neuromuscular block it can result in muscle weakness and apnoea and it should be avoided, if possible, in the immediate postoperative period. For details regarding interactions with calcium-channel blockers, see below.

Antibacterials. Some antibacterials in very high concentration can produce a muscle paralysis that may be additive to or synergistic with that produced by neuromuscular blockers. The neuromuscular block produced by antibacterials may be enhanced in patients with intracellular potassium deficiency, low plasma-calcium concentration, neuromuscular disease, or a tendency to a high plasma-antibacterial concentration, for example after large doses or in renal impairment. The interaction appears to be more important for competitive neuromuscular blockers. The antibacterials most commonly implicated are aminoglycosides, lincosamides, polymyxins, and, more rarely, tetracyclines.

The *aminoglycosides* reduce release of, and sensitivity to, acetylcholine and their effect can be reversed, at least in part, by calcium, fampridine, or an anticholinesterase. The interaction can occur with aminoglycosides given by most routes. There are reports of potentiation of neuromuscular blockade occurring with many different aminoglycoside-neuromuscular blocker combinations[1-6] and all aminoglycosides should be used with extreme caution during surgery and in the postoperative period.

The *lincosamides* (*clindamycin* and *lincomycin*) can prolong the action of muscle relaxants producing a neuromuscular block that may be difficult to reverse with calcium or anticholinesterases.[7-9] Patients should be monitored for prolonged paralysis.

There have been reports of prolonged apnoea[2,5,8] after use of *polymyxins* (*colistin, polymyxin B*) with a neuromuscular blocker. The block is difficult to reverse; calcium may be partially successful, but neostigmine may increase the block.

Tetracyclines have weak neuromuscular blocking properties; potentiation of neuromuscular block has been reported in patients with myasthenia gravis.[2] Reversal of the block may be partly achieved with calcium, but the value of anticholinesterases is questionable.

The *ureidopenicillins* (*azlocillin* and *mezlocillin*), and the closely related *piperacillin,* are reported to prolong the block produced by vecuronium.[10,11]

Vancomycin has been reported to increase neuromuscular blockade by vecuronium.[12] Prolonged paralysis and apnoea has occurred in a patient recovering from suxamethonium-induced blockade after being given vancomycin.[13]

1. Hall DR, *et al.* Gentamicin, tubocurarine, lignocaine and neuromuscular blockade. *Br J Anaesth* 1972; **44:** 1329–32.
2. Pittinger CB, *et al.* Antibiotic-induced paralysis. *Anesth Analg Curr Res* 1970; **49:** 487–501.
3. Waterman PM, Smith RB. Tobramycin-curare interaction. *Anesth Analg Curr Res* 1977; **56:** 587–8.
4. Regan AG, Perumbetti PPV. Pancuronium and gentamicin interaction in patients with renal failure. *Anesth Analg* 1980; **59:** 393.
5. Giala MM, Paradelis AG. Two cases of prolonged respiratory depression due to interaction of pancuronium with colistin and streptomycin. *J Antimicrob Chemother* 1979; **5:** 234–5.
6. Jedeikin R, *et al.* Prolongation of neuromuscular blocking effect of vecuronium by antibiotics. *Anaesthesia* 1987; **42:** 858–60.
7. Booij LHD, *et al.* Neostigmine and 4-aminopyridine antagonism of lincomycin-pancuronium neuromuscular blockade in man. *Anesth Analg* 1978; **57:** 316–21.
8. de Gouw NE, *et al.* Interaction of antibiotics on pipecuronium-induced neuromuscular blockade. *J Clin Anesth* 1993; **5:** 212–15.
9. Sloan PA, Rasul M. Prolongation of rapacuronium neuromuscular blockade by clindamycin and magnesium. *Anesth Analg* 2002; **94:** 123–4.
10. Tryba M. Wirkungsverstäkung nicht-depolarisierender Muskelrelaxantien durch Acylaminopenicilline: Untersuchungen am Beispiel von Vecuronium. *Anaesthesist* 1985; **34:** 651–5.
11. Tryba M, Klemm D. Wechselwirkungen zwischen Acylaminopenicillinen und nicht depolarisierenden Muskelrelaxantien. *Fortschr Antimikrob Antineoplast Chemother* 1985; **4–7:** 1827–33.
12. Huang KC, *et al.* Vancomycin enhances the neuromuscular blockade of vecuronium. *Anesth Analg* 1990; **70:** 194–6.
13. Albrecht RF, Lanier WL. Potentiation of succinylcholine-induced phase II block by vancomycin. *Anesth Analg* 1993; **77:** 1300–2.

Anticholinesterases. Anticholinesterases, including *ecothiopate, edrophonium, galantamine, neostigmine, pyridostigmine, rivastigmine,* and possibly *donepezil*, antagonise the effect of competitive neuromuscular blockers. Some anticholinesterases such as neostigmine inhibit both acetylcholinesterase and plasma cholinesterase, and are used clinically to antagonise competitive neuromuscular blockade. Conversely, anticholinesterases enhance the action of depolarising muscle relaxants such as suxamethonium thus prolonging neuromuscular block, although sux-

amethonium-induced phase II block can be reversed with an anticholinesterase. See also Interactions in Suxamethonium Chloride, p.1911.

Antiepileptics. Resistance to competitive neuromuscular blockers has been reported in patients receiving chronic treatment with *carbamazepine*[1,2] or *phenytoin*[3,4] and rapid recovery from neuromuscular block may occur. In addition, children on chronic antiepileptic drugs (carbamazepine and/or phenytoin) were found to recover quicker from rocuronium-induced paralysis than those not on antiepileptics[5]. In a study[6] with cisatracurium, faster recovery rates were also recorded in patients receiving acute or chronic treatment with unspecified antiepileptics. However, atracurium[1] and mivacurium[7] appear to be unaffected by chronic carbamazepine therapy and the effect of chronic phenytoin treatment on atracurium has usually been minimal.[3] Although one study[8] did report that epileptic patients receiving one or more antiepileptics had significantly shorter times to recovery from atracurium, the authors pointed out that the patient populations were different from those in the previous studies.[1,3]

A report of sensitivity to vecuronium[9] has suggested that acute dosage of phenytoin may increase rather than decrease the effect of competitive neuromuscular blockers.

1. Ebrahim Z, *et al.* Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg* 1988; **67:** S55.
2. Whalley DG, Ebrahim Z. Influence of carbamazepine on the dose-response relationship of vecuronium. *Br J Anaesth* 1994; **72:** 125–6.
3. Ornstein E, *et al.* The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. *Anesthesiology* 1987; **67:** 191–6.
4. Hernández-Palazón J, *et al.* Rocuronium-induced neuromuscular blockade is affected by chronic phenytoin therapy. *J Neurosurg Anesthesiol* 2001; **13:** 79–81.
5. Soriano SG, *et al.* Onset and duration of action of rocuronium in children receiving chronic anticonvulsant therapy. *Paediatr Anaesth* 2000; **10:** 133–6.
6. Koenig HM, Edwards TL. Cisatracurium-induced neuromuscular blockade in anticonvulsant treated neurosurgical patients. *J Neurosurg Anesthesiol* 2000; **12:** 314–18.
7. Spacek A, *et al.* Chronic carbamazepine therapy does not influence mivacurium-induced neuromuscular block. *Br J Anaesth* 1996; **77:** 500–502.
8. Tempelhoff R, *et al.* Resistance to atracurium-induced neuromuscular blockade in patients with intractable seizure disorders treated with anticonvulsants. *Anesth Analg* 1990; **71:** 665–9.
9. Baumgardner JE, Bagshaw R. Acute versus chronic phenytoin therapy and neuromuscular blockade. *Anaesthesia* 1990; **45:** 493–4.

Antineoplastics. It has been recommended that atracurium should be used with care in patients receiving anti-oestrogenic drugs,[1] after a case of prolonged neuromuscular blockade with atracurium in a patient receiving *tamoxifen*. See also under Interactions of Suxamethonium Chloride, p.1911.

1. Naguib M, Gyasi HK. Antiestrogenic drugs and atracurium—a possible interaction? *Can Anaesth Soc J* 1986; **33:** 682–3.

Aprotinin. After reports of apnoea, caution has been advised when aprotinin is used with neuromuscular blockers.[1,2]

1. Chasapakis G, Dimas C. Possible interaction between muscle relaxants and the kallikrein-trypsin inactivator "Trasylol". *Br J Anaesth* 1966; **38:** 838–9.
2. Marcello B, Porati U. Trasylol e blocco neuromuscolare: nota preventiva. *Minerva Anestesiol* 1967; **33:** 814–15.

Benzodiazepines. There are conflicting reports of the effect of *diazepam* on neuromuscular blockers; potentiation,[1,2] or antagonism[1] of neuromuscular block, and a lack of interaction[3-5] have all been reported.

1. Feldman SA, Crawley BE. Interaction of diazepam with the muscle-relaxant drugs. *BMJ* 1970; **2:** 336–8.
2. Yuan H-B, *et al.* The interaction of diazepam with vecuronium: a clinical study. *Chin Med J* 1994; **54:** 259–64.
3. Bradshaw EG, Maddison S. Effect of diazepam at the neuromuscular junction. *Br J Anaesth* 1979; **51:** 955–60.
4. Asbury AJ, *et al.* Effect of diazepam on pancuronium-induced neuromuscular blockade maintained by a feedback system. *Br J Anaesth* 1981; **53:** 859–63.
5. Driessen JJ, *et al.* Benzodiazepines and neuromuscular blocking drugs in patients. *Acta Anaesthesiol Scand* 1986; **30:** 642–6.

Beta blockers. There is conflicting evidence for the effect of beta blockers on the activity of neuromuscular blockers. Lack of effect on depolarising neuromuscular block[1] and antagonism[2,3] or enhancement[4,5] of both competitive and depolarising block have been reported. The exact mechanism of interaction is not clear. There have also been reports of some neuromuscular blockers such as atracurium[6,7] and alcuronium[8] increasing the hypotension and bradycardia associated with the use of anaesthesia in patients receiving beta blockers; these include reports in patients using beta blockers in eye drops for glaucoma.

1. McCammon RL, *et al.* The effect of esmolol on the onset and duration of succinylcholine-induced neuromuscular blockade. *Anesthesiology* 1985; **63:** A317.
2. Varma YS, *et al.* Effect of propranolol hydrochloride on the neuromuscular blocking action of d-tubocurarine and succinylcholine in man. *Indian J Med Res* 1972; **60:** 266–72.
3. Varma YS, *et al.* Comparative effect of propranolol, oxprenolol and pindolol on neuromuscular blocking action of d-tubocurarine in man. *Indian J Med Res* 1973; **61:** 1382–6.
4. Rozen MS, Whan FM. Prolonged curarization associated with propranolol. *Med J Aust* 1972; **1:** 467–8.
5. Murthy VS, *et al.* Cardiovascular and neuromuscular effects of esmolol during induction of anesthesia. *J Clin Pharmacol* 1986; **26:** 351–7.
6. Glynne GL. Drug Interaction? *Anaesthesia* 1984; **39:** 293.
7. Rowlands DE. Drug Interaction? *Anaesthesia* 1984; **39:** 1252.
8. Yate B, Mostafa SM. Drug Interaction? *Anaesthesia* 1984; **39:** 728.

Botulinum A toxin. The neuromuscular block induced by botulinum toxins is enhanced by competitive neuromuscular blockers.

Calcium-channel blockers. Calcium-channel blockers such as diltiazem, nicardipine, nifedipine, and verapamil enhance the effect of competitive neuromuscular blockers.[1-6] *Verapamil* may interfere with the release of acetylcholine and prolonged use may lead to a reduction in intracellular calcium concentration. Potentiation of neuromuscular blockade has been reported[1,6] and the block may be resistant to reversal with neostigmine; edrophonium may be required. The dose requirement for vecuronium was reduced by as much as 50% in surgical patients receiving *diltiazem*.[2,3] A similar effect was seen with *nicardipine*,[4] which reduced the requirement for vecuronium in a dose-dependent fashion. The interaction of vecuronium with diltiazem appeared to be due to a pharmacodynamic mechanism[2] but nicardipine also reduced the plasma clearance of vecuronium, indicating a partial pharmacokinetic mechanism as well.[4] *Nifedipine* also caused an increase in the intensity and duration of action of atracurium and vecuronium when given during anaesthesia.[5]

1. van Poorten JF, *et al.* Verapamil and reversal of vecuronium neuromuscular blockade. *Anesth Analg* 1984; **63:** 155–7.
2. Sumikawa K, *et al.* Reduction in vecuronium infusion dose requirements by diltiazem in humans. *Anesthesiology* 1992; **77:** A939.
3. Takasaki Y, *et al.* Diltiazem potentiates the neuromuscular blockade by vecuronium in humans. *Jpn J Anesthesiol* 1995; **44:** 503–7.
4. Kawabata K, *et al.* Decrease in vecuronium infusion dose requirements by nicardipine in humans. *Anesth Analg* 1994; **79:** 1159–64.
5. Jelen-Esselborn S, Blobner M. Wirkungsverstärkung von nichtdepolarisierenden Muskelrelaxanzien durch Nifedipin i.v. in Inhalationsanaesthesie. *Anaesthesist* 1990; **39:** 173–8.
6. Jones RM, *et al.* Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium. *Anesth Analg* 1985; **64:** 1021–5.

Cardiac inotropes. Pancuronium or suxamethonium may interact with *cardiac glycosides*[1] resulting in an increased incidence of arrhythmias; the interaction is more likely with pancuronium.

1. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* 1983; **58:** 567–9.

Corticosteroids. Antagonism of the neuromuscular blocking effects of pancuronium[1] and vecuronium[2] has been reported in patients taking corticosteroids. This interaction may occur only with long-term corticosteroid treatment and may be expected with all competitive neuromuscular blockers.

For reference to a suggestion that use of corticosteroids might increase the risk of acute myopathy associated with prolonged use of neuromuscular blockers, see Intensive Care, p.1901.

1. Azar I, *et al.* Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. *Can Anaesth Soc J* 1982; **29:** 280–2.
2. Parr SM, *et al.* Betamethasone-induced resistance to vecuronium: a potential problem in neurosurgery? *Anaesth Intensive Care* 1991; **19:** 103–5.

Diuretics. *Furosemide*, and possibly *mannitol*, have been reported to enhance tubocurarine neuromuscular block in patients with renal failure,[1] but antagonism of tubocurarine by furosemide has also occurred.[2] Small doses of furosemide (less than 100 micrograms/kg) may inhibit protein kinase, which inhibits muscle contraction and potentiates neuromuscular blockade, whereas high doses inhibit phosphodiesterase, increasing cAMP activity and resulting in antagonism of neuromuscular blockade. The potassium-depleting effect of diuretics may enhance the effect of competitive neuromuscular blockers.

1. Miller RD, *et al.* Enhancement of d-tubocurarine neuromuscular blockade by diuretics in man. *Anesthesiology* 1976; **45:** 442–5.
2. Azar I, *et al.* Furosemide facilitates recovery of evoked twitch response after pancuronium. *Anesth Analg* 1980; **59:** 55–7.

Ganglion blockers. Prolonged neuromuscular blockade has been reported[1,2] in patients given neuromuscular blockers and *trimetaphan*. Trimetaphan may have direct neuromuscular blocking activity and some activity against plasma cholinesterase.

1. Wilson SL, *et al.* Prolonged neuromuscular blockade associated with trimethaphan: a case report. *Anesth Analg Curr Res* 1976; **55:** 353–6.
2. Poulton TH, *et al.* Prolonged apnea following trimethaphan and succinylcholine. *Anesthesiology* 1979; **50:** 54–6.

General anaesthetics. Neuromuscular blockers are potentiated in a dose-dependent manner by inhalation anaesthetics.[1-5] The dose of neuromuscular blocker may need to be reduced by up to 70%[1] depending on the anaesthetic used and its concentration, and on the choice of blocker; the interaction is of greater clinical importance with competitive blockers. *Isoflurane, enflurane, desflurane*, and *sevoflurane* produce the greater potentiation, followed by *halothane* and *cyclopropane.* Reversal of competitive block with an anticholinesterase has been reported to be reduced.[6,7] See also under Interactions of Suxamethonium Chloride, p.1911.

Potentiation of the neuromuscular blocking effects of tubocurarine[8] and atracurium[9] has been reported after the intravenous use of *ketamine*. Results from studies *in vitro* suggest that ketamine decreases sensitivity to acetylcholine and it would therefore be expected to potentiate all neuromuscular blockers, but no interaction was reported for pancuronium.[8] Early data[10] suggesting that ketamine potentiates suxamethonium-induced blockade have not been confirmed by later studies.[8,11]

For incompatibility between neuromuscular blockers and alkaline solutions such as thiopental sodium, see under Incompatibility, above.

1. Cannon JE, *et al.* Continuous infusion of vecuronium: the effect of anesthetic agents. *Anesthesiology* 1987; **67:** 503–6.
2. Swen J, *et al.* Interaction between nondepolarizing neuromuscular blocking agents and inhalation anesthetics. *Anesth Analg* 1989; **69:** 752–5.
3. Ghourin AF, White PF. Comparative effects of desflurane and isoflurane on vecuronium-induced neuromuscular blockade. *J Clin Anesth* 1992; **4:** 34–8.
4. Vanlinthout LEM, *et al.* Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium. *Br J Anaesth* 1996; **76:** 389–95.
5. Wulf H, *et al.* Augmentation of the neuromuscular blocking effects of cisatracurium during desflurane, sevoflurane, isoflurane or total i.v. anaesthesia. *Br J Anaesth* 1998; **80:** 308–12.
6. Delisle S, Bevan DR. Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. *Br J Anaesth* 1982; **54:** 441–5.
7. Gill SS, *et al.* Edrophonium antagonism of atracurium during enflurane anaesthesia. *Br J Anaesth* 1990; **64:** 300–5.
8. Johnston RR, *et al.* The interaction of ketamine with d-tubocurarine, pancuronium, and succinylcholine in man. *Anesth Analg Curr Res* 1974; **53:** 496–501.
9. Toft P, Helbo-Hansen S. Interaction of ketamine with atracurium. *Br J Anaesth* 1989; **62:** 319–20.
10. Bovill JG, *et al.* Current status of ketamine anaesthesia. *Lancet* 1971; **i:** 1285–8.
11. Helbo-Hansen HS, *et al.* Ketamine does not affect suxamethonium-induced neuromuscular blockade in man. *Eur J Anaesthesiol* 1989; **6:** 419–23.

Histamine H_2-antagonists. There are conflicting reports of the effects of histamine H_2-antagonists on neuromuscular blockade. *Cimetidine* has been variously reported to prolong suxamethonium-induced paralysis[1] or to have no effect.[2] *Famotidine* and *ranitidine* have been reported[2] not to interact with suxamethonium. Cimetidine, but not ranitidine, has been reported[3] to delay recovery from vecuronium-induced neuromuscular block. Neither drug appeared to affect recovery after the use of atracurium.

1. Kambam JR, *et al.* Effect of cimetidine on duration of action of succinylcholine. *Anesth Analg* 1987; **66:** 191–2.
2. Turner DR, *et al.* Neuromuscular block by suxamethonium following treatment with histamine type 2 antagonists or metoclopramide. *Br J Anaesth* 1989; **63:** 348–50.
3. McCarthy G, *et al.* Effect of H2-receptor antagonist pretreatment on vecuronium- and atracurium-induced neuromuscular blockade. *Br J Anaesth* 1991; **66:** 713–15.

Immunosuppressants. Antagonism of the neuromuscular blocking effects of competitive neuromuscular blockers has been reported with *azathioprine*,[1] although the effect may not be clinically important. Azathioprine probably inhibits phosphodiesterase activity at the motor nerve terminal resulting in increased release of acetylcholine. There have been reports of prolonged neuromuscular blockade with atracurium, pancuronium, and vecuronium in some patients receiving *ciclosporin* intravenously.[2,3] This effect has been attributed to an interaction with polyethoxylated castor oil used as the solvent for intravenous ciclosporin but a similar reaction has been reported in a patient receiving ciclosporin orally.[4]

1. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure: dose-response properties and interaction with azathioprine. *Br J Anaesth* 1987; **59:** 995–1003.
2. Crosby E, Robblee JA. Cyclosporine-pancuronium interaction in a patient with a renal allograft. *Can J Anaesth* 1988; **35:** 300–302.
3. Sidi A, *et al.* Prolonged neuromuscular blockade and ventilatory failure after renal transplantation and cyclosporine. *Can J Anaesth* 1990; **37:** 543–8.
4. Ganjoo P, Tewari P. Oral cyclosporine-vecuronium interaction. *Can J Anaesth* 1994; **41:** 1017.

Lithium. There have been isolated reports of prolonged neuromuscular blockade after the use of neuromuscular blockers in patients receiving lithium.[1,2]

1. Borden H, *et al.* The use of pancuronium bromide in patients receiving lithium carbonate. *Can Anaesth Soc J* 1974; **21:** 79–82.
2. Hill GE, *et al.* Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. *Anesthesiology* 1976; **44:** 439–42.

Local anaesthetics. Healthy subjects who had undergone regional anaesthesia of the forearm experienced symptoms suggestive of local anaesthetic toxicity on deflation of the tourniquet cuff when mivacurium and *prilocaine* had been used together for anaesthesia;[1] giving prilocaine or mivacurium alone did not produce such an effect. The suggestion that mivacurium may alter vascular permeability, allowing a more rapid diffusion of prilocaine back into the blood from the tissues, should be investigated.[2]

The interaction between neuromuscular blockers and *lidocaine* is discussed in Antiarrhythmics above.

1. Torrance JM, *et al.* Low-dose mivacurium supplementation of prilocaine i.v. regional anaesthesia. *Br J Anaesth* 1997; **78:** 222–3.
2. Torrance JM, *et al.* Interactions between mivacurium and prilocaine. *Br J Anaesth* 1997; **78:** 262.

Magnesium salts. Parenteral magnesium salts may potentiate the effects of competitive and depolarising neuromuscular blockers;[1] the neuromuscular block is deepened and prolonged and a reduction in the dose of the blocker may be needed. Magnesium salts should be used with caution in the postoperative period, as use shortly after recovery from neuromuscular block can lead to

recurarisation.[2] Magnesium salts reduce release of and sensitivity to acetylcholine, thus contributing to neuromuscular blockade.

1. Ghoneim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. *Anesthesiology* 1970; **32:** 23–7.
2. Fuchs-Buder T, Tassonyi E. Magnesium sulphate enhances residual neuromuscular block induced by vecuronium. *Br J Anaesth* 1996; **76:** 565–6.

MAOIs. There appears to be a theoretical hazard with pancuronium in patients receiving MAOIs since it releases stored adrenaline;[1] alcuronium, atracurium, or vecuronium would appear to be suitable alternatives.

1. Stack CG, *et al.* Monoamine oxidase inhibitors and anaesthesia: a review. *Br J Anaesth* 1988; **60:** 222–7.

Neuromuscular blockers. A competitive neuromuscular blocker given shortly before a depolarising blocker such as suxamethonium antagonises the depolarising neuromuscular block. This interaction has been used clinically to reduce muscle fasciculations caused by suxamethonium (see Effects on the Muscles, p.1910) and tried for other adverse effects associated with suxamethonium (see Effects on Plasma-potassium Concentration, p.1910). To achieve this antagonism a small non-paralysing dose of a competitive blocker is given before suxamethonium. If a paralysing dose of a competitive blocker is followed some time later with a dose of suxamethonium, for example to facilitate abdominal closure, the resulting neuromuscular block is influenced by the competitive blocker used, the depth of residual block, the dose of suxamethonium, and whether an anticholinesterase is given; antagonism, enhancement, and a combination of the two have been seen.[1,2]

A competitive blocker is often given after the short-acting suxamethonium to maintain neuromuscular blockade during long procedures. The action of the competitive blocker has been reported to be considerably potentiated and prolonged in these circumstances,[3,4] and reduction in the dose of the competitive blocker may be appropriate.

Combination of competitive blockers may have additive or synergistic effects and the interaction may differ depending on which blocker is given first. Caution is needed if a small dose of a shorter-acting blocker is given near the end of an operation in which a long-acting blocker has been given previously, since the resulting block may be greater than expected and much longer than desired.[5-8]

1. Scott RPF, Norman J. Effect of suxamethonium given during recovery from atracurium. *Br J Anaesth* 1988; **61:** 292–6.
2. Black AMS. Effect of suxamethonium given during recovery from atracurium. *Br J Anaesth* 1989; **62:** 348–9.
3. d'Hollander AA, *et al.* Clinical and pharmacological actions of a bolus injection of suxamethonium: two phenomena of distinct duration. *Br J Anaesth* 1983; **55:** 131–4.
4. Ono K, *et al.* Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium. *Br J Anaesth* 1989; **62:** 324–6.
5. Rashkovsky OM, *et al.* Interaction between pancuronium bromide and vecuronium bromide. *Br J Anaesth* 1985; **57:** 1063–6.
6. Middleton CM, *et al.* Use of atracurium or vecuronium to prolong the action of tubocurarine. *Br J Anaesth* 1989; **62:** 659–63.
7. Kim KS, *et al.*Interactions between mivacurium and pancuronium. *Br J Anaesth* 1997; **79:** 19–23.
8. Motamed C, *et al.* Interaction between mivacurium and pancuronium: impact of the order of administration. *Eur J Clin Pharmacol* 2005; **61:** 175–7.

Sex hormones. Resistance to the neuromuscular blocking effects of suxamethonium and vecuronium in a patient was attributed to previous long-term therapy with *testosterone*,[1] although the exact mechanism could not be explained. See also under Interactions of Suxamethonium Chloride, p.1912.

1. Reddy P, *et al.* Resistance to muscle relaxants in a patient receiving prolonged testosterone therapy. *Anesthesiology* 1989; **70:** 871–3.

Smoking. Smoking may affect the dose requirements for neuromuscular blockers. One study[1] found that smokers needed more vecuronium than non-smokers; it was considered that the effect might be explained at the receptor level, although increased metabolism of vecuronium could not be excluded. In contrast, an earlier study[2] found the amount of atracurium required was reduced in smokers.

1. Teiriä H, *et al.* Effect of smoking on dose requirements for vecuronium. *Br J Anaesth* 1996; **76:** 154–5.
2. Kroeker KA, *et al.* Neuromuscular blockade in the setting of chronic nicotine exposure. *Anesthesiology* 1994; **81:** A1120.

Sympathomimetics. Intravenous *salbutamol* has been reported to enhance the blockade obtained with pancuronium and vecuronium.[1] See also under Interactions of Suxamethonium Chloride, p.1912.

1. Salib Y, Donati F. Potentiation of pancuronium and vecuronium neuromuscular blockade by intravenous salbutamol. *Can J Anaesth* 1993; **40:** 50–3.

Xanthines. Resistance to neuromuscular block with pancuronium, requiring an increase in dosage or transfer to vecuronium, has been reported in patients receiving *aminophylline* with[1] or without[2] corticosteroid therapy. It was suggested that this effect might be due to inhibition of phosphodiesterase by aminophylline resulting in increased release of acetylcholine at the nerve terminal.

1. Azar I, *et al.* Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. *Can Anaesth Soc J* 1982; **29:** 280–2.
2. Daller JA, *et al.* Aminophylline antagonizes the neuromuscular blockade of pancuronium but not vecuronium. *Crit Care Med* 1991; **19:** 983–5.

Pharmacokinetics

On intravenous injection both atracurium besilate and cisatracurium besilate undergo spontaneous degradation via Hofmann elimination (a non-enzymatic breakdown process occurring at physiological pH and temperature) to produce laudanosine and other metabolites. There is also ester hydrolysis by non-specific plasma esterases. The metabolites have no neuromuscular blocking activity.

About 80% of atracurium besilate is bound to plasma proteins. Atracurium besilate and its metabolites cross the placenta in clinically insignificant amounts. Excretion of atracurium and cisatracurium is in urine and bile, mostly as metabolites. The elimination half-life has been reported to be about 20 minutes for atracurium and 22 to 29 minutes for cisatracurium but laudanosine has an elimination half-life of about 3 to 6 hours.

◊ Reviews.

1. Kisor DF, Schmith VD. Clinical pharmacokinetics of cisatracurium besilate. *Clin Pharmacokinet* 1999; **36:** 27–40.
2. Atherton DPL, Hunter JM. Clinical pharmacokinetics of the newer neuromuscular blocking drugs. *Clin Pharmacokinet* 1999; **36:** 169–89.
3. Booij LHDJ, Vree TB. Skeletal muscle relaxants: pharmacodynamics and pharmacokinetics in different patient groups. *Int J Clin Pract* 2000; **54:** 526–34.

Biotransformation. Atracurium and cisatracurium are degraded by Hofmann elimination and metabolised by non-specific plasma esterases. Hofmann elimination is generally believed to be the main route of degradation but *in-vitro* work suggests ester hydrolysis is more important.[1] Both routes are independent of renal and hepatic function and no dosage reduction is recommended for elderly patients or those with impaired renal or hepatic function. However, the elimination half-life of atracurium has been found to be slightly longer in elderly patients[2] and in those with hepatic cirrhosis[3] compared with young and healthy patients, although others[4] have found no change in the pharmacokinetics of atracurium in the elderly. Renal and hepatic involvement in the metabolism of atracurium[2] may help to explain any tendency to reduced elimination but this does not appear to be clinically significant. Although clearance of cisatracurium has been reported to be reduced in patients with renal failure[5] this appears to have little significant effect on its pharmacodynamics.[6] Differences in the pharmacokinetics of cisatracurium in patients with hepatic impairment have been reported to be minor.[7]

The major biotransformation product of atracurium and cisatracurium is *laudanosine*; it has no clinical neuromuscular blocking activity but has been associated with CNS stimulation in *animal* studies. It is more lipid soluble than atracurium and cisatracurium and has a half-life of around 3 hours compared with one of approximately 20 minutes for atracurium. Higher plasma-laudanosine concentrations have been reported in patients with renal failure[5,8,9] than in patients with normal renal function. The elimination half-life of laudanosine was found to be significantly greater in patients with hepatic cirrhosis[3] and in elderly patients[2] compared with healthy and young patients respectively. High plasma-laudanosine concentrations were also seen in 10 critically ill patients with acute respiratory distress syndrome;[10] no adverse effects were noted.

Laudanosine crosses the blood-brain barrier in man. The concentration of laudanosine in the CSF increases during an infusion of atracurium and the CSF-to-plasma ratio gradually increases. A ratio of 0.14 was found at 125 to 140 minutes[11] during an infusion of atracurium at a mean rate of 510 micrograms/kg per hour. No evidence of CNS stimulation has been reported in man although patients given atracurium[12] had a 20% higher mean arterial-thiopental concentration at awakening compared with patients given vecuronium, suggesting that laudanosine may have had a minor stimulatory effect on the CNS. The blood-brain barrier appears to be effective in preventing a very high concentration of laudanosine from reaching the CNS and it is considered unlikely[13] that concentrations great enough to provoke seizures will be reached. Cisatracurium may be associated with the production of less laudanosine than atracurium.[14]

1. Stiller RL, *et al.* In vitro degradation of atracurium in human plasma. *Br J Anaesth* 1985; **57:** 1085–8.
2. Kent AP, *et al.* Pharmacokinetics of atracurium and laudanosine in the elderly. *Br J Anaesth* 1989; **63:** 661–6.
3. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. *Br J Anaesth* 1989; **62:** 177–83.
4. d'Hollander AA, *et al.* Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology* 1983; **59:** 237–40.
5. Eastwood NB, *et al.* Pharmacokinetics of 1R-cis 1′R-cis atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. *Br J Anaesth* 1995; **75:** 431–5.
6. Boyd AH, *et al.* Pharmacodynamics of the 1R cis-1′R cis isomer of atracurium (51W89) in health and chronic renal failure. *Br J Anaesth* 1995; **74:** 400–404.
7. De Wolf AM, *et al.* Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. *Br J Anaesth* 1996; **76:** 624–8.
8. Fahey MR, *et al.* Effect of renal failure on laudanosine excretion in man. *Br J Anaesth* 1985; **57:** 1049–51.
9. Vandenbrom RHG, *et al.* Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clin Pharmacokinet* 1990; **19:** 230–40.
10. Farenc C, *et al.* Pharmacokinetic-pharmacodynamic modeling of atracurium in intensive care patients. *J Clin Pharmacol* 2001; **41:** 44–50.
11. Eddleston JM, *et al.* Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma during intracranial surgery. *Br J Anaesth* 1989; **63:** 525–30.
12. Beemer GH, *et al.* Production of laudanosine following infusion of atracurium in man and its effects on awakening. *Br J Anaesth* 1989; **63:** 76–80.
13. Yate PM, *et al.* Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. *Br J Anaesth* 1987; **59:** 211–17.
14. Boyd AH, *et al.* Comparison of the pharmacokinetics and pharmacodynamics of an infusion of cis-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit. *Br J Anaesth* 1996; **76:** 382–8.

Uses and Administration

Competitive neuromuscular blockers act by competing with acetylcholine for receptors on the motor end-plate of the neuromuscular junction to produce blockade. The muscles that produce fine rapid movements such as those of the face are the first to be affected, followed by those of the limbs and torso; the last to be affected are those of the diaphragm. The paralysis is reversible with recovery occurring in reverse order. Restoration of normal neuromuscular function can be hastened by increasing the concentration of acetylcholine at the motor end-plate by giving an anticholinesterase such as neostigmine.

Atracurium and cisatracurium are competitive benzylisoquinolinium neuromuscular blockers. The commercial preparation of atracurium is a mixture of 10 stereoisomers of which cisatracurium constitutes about 15%. Cisatracurium, the *R-cis,1′R-cis*-isomer of atracurium, is about 3 times more potent than the mixture of isomers of atracurium. After an intravenous dose of atracurium, muscle relaxation begins in about 2 minutes and lasts for 15 to 35 minutes; onset may be slightly slower for cisatracurium.

Atracurium besilate and cisatracurium besilate are used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

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.

For **atracurium besilate**, the usual initial dose for adults and children over 1 month of age is 300 to 600 micrograms/kg by intravenous injection. Subsequent doses of 100 to 200 micrograms/kg may be given as necessary, typically every 15 to 25 minutes for maintenance in prolonged procedures. It is recommended that in patients with cardiovascular disease the initial dose should be given over a period of 60 seconds.

Atracurium besilate may also be given by continuous intravenous infusion at a rate of 5 to 10 micrograms/kg per minute to maintain neuromuscular block during prolonged procedures. Somewhat higher infusion rates may be used in patients undergoing controlled ventilation in intensive care.

Cisatracurium is given as the besilate but doses are expressed as the base. Cisatracurium 1 mg is equivalent to about 1.34 mg of cisatracurium besilate. The usual initial dose for adults is 150 micrograms/kg by intravenous injection. The neuromuscular block may be extended with a maintenance dose of 30 micrograms/kg about every 20 minutes. The usual initial dose for children aged 1 month and over is 150 micrograms/kg. The neuromuscular block may be extended in children aged 2 years and over with a maintenance dose of 20 micrograms/kg about every 9 minutes. The *BNFC* suggests that a maintenance dose of 30 micrograms/kg, repeated about every 20 minutes, may be given to younger children aged 1 month and over; however, such use is unlicensed in the UK.

Cisatracurium besilate may also be given by continuous intravenous infusion to adults and children over 2

years of age at an initial rate equivalent to cisatracurium 3 micrograms/kg per minute followed by a rate of 1 to 2 micrograms/kg per minute after stabilisation.

◊ Reviews.

1. Bryson HM, Faulds D. Cisatracurium besilate: a review of its pharmacology and clinical potential in anaesthetic practice. *Drugs* 1997; **53:** 848–66.

Administration in infants and children. Children generally require larger doses of competitive neuromuscular blockers on a weight basis than adolescents or adults to achieve similar degrees of neuromuscular blockade and may recover more quickly. In contrast, neonates and infants under 1 year of age are more sensitive and usual doses may produce prolonged neuromuscular blockade (see also above for some suggested doses).

References.

1. Brandom BW, Fine GF. Neuromuscular blocking drugs in pediatric anesthesia. *Anesthesiol Clin North America* 2002; **20:** 45–58.

ECT. Competitive neuromuscular blockers have been used to reduce the intensity of muscle contractions and minimise trauma in patients receiving ECT, but suxamethonium (p.1912) is generally preferred because of its short duration of action.

Intravenous regional anaesthesia. Competitive neuromuscular blockers and/or opioid analgesics have been added to the local anaesthetic used in intravenous regional anaesthesia (p.1853) to improve the quality of anaesthesia. However atracurium (see Tourniquets under Precautions, above) and mivacurium (see Tourniquets, p.1907) might be unsuitable for such use.

Shivering. Various drugs have been tried in the treatment of postoperative shivering (p.1779). There are reports of neuromuscular blockers being used to treat shivering after cardiac surgery in order to reduce cardiovascular stress;[1] one study[2] has suggested that vecuronium might be preferable to pancuronium as it does not increase myocardial work and may be associated with fewer complications.

1. Cruise C, *et al.* Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; **39:** 563–8.
2. Dupuis J-Y, *et al.* Pancuronium or vecuronium for the treatment of shivering after cardiac surgery. *Anesth Analg* 1994; **79:** 472–81.

Tetanus. For a comment on the role of competitive neuromuscular blockers in the management of muscle spasms caused by tetanus, see p.1901.

Preparations

USP 31: Atracurium Besylate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Gelolagar; Nimbex†; Nimbium; Tracrium; Tracurix; Tracuron; ***Austral.:*** Nimbex; Tracrium; ***Austria:*** Nimbex; Tracrium; ***Belg.:*** Nimbex; Tracrium; ***Braz.:*** Abbottracurium; Nimbium; Sitrac†; Tracrium; Tracur; ***Canad.:*** Nimbex; ***Chile:*** Nimbex; Tracrium; ***Cz.:*** Nimbex; Tracrium; ***Denm.:*** Nimbex; Tracrium†; ***Fin.:*** Nimbex; ***Fr.:*** Nimbex; Tracrium; ***Ger.:*** Nimbex; Tracrium; ***Gr.:*** Nimbex; Tracrium; ***Hong Kong:*** Nimbex; Tracrium; ***Hung.:*** Nimbex; Tracrium; ***India:*** Tracrium; ***Indon.:*** Notrixum; Tracrium; Tramus; ***Irl.:*** Nimbex; Tracrium; ***Israel:*** Mycurium; Tracrium; ***Ital.:*** Acurmil; Nimbex; Tracrium; ***Malaysia:*** Nimbex; Tracrium; ***Mex.:*** Ifacur†; Nimbex; Relatrac; Trablok; Tracrium; ***Neth.:*** Nimbex; Tracrium; ***Norw.:*** Nimbex; ***NZ:*** Tracrium; ***Philipp.:*** Tracrium; ***Pol.:*** Abbocurium; Nimbex; Tracrium; ***Port.:*** Faulcurium; Nimbex; Tracrium; ***Rus.:*** Nimbex (Нимбекс); Tracrium (Тракриум); ***S.Afr.:*** Nimbex; Tracrium; ***Singapore:*** Nimbex†; Tracrium; ***Spain:*** Laurak; Nimbex; Tracrium; ***Swed.:*** Nimbex; Tracrium; ***Switz.:*** Nimbex; Tracrium; ***Thai.:*** Nimbex; Tracrium; ***Turk.:*** Dematrac; Nimbex; Tracrium; ***UK:*** Nimbex; Tracrium; ***USA:*** Nimbex; Tracrium.

Doxacurium Chloride *(BAN, USAN, rINN)*

BW-A938U; Cloruro de doxacurio; Doksakuriumkloridi; Doxacurii Chloridum; Doxacurium, Chlorure de; Doxakuriumklorid. A mixture of the (*1R,1′S,2S,2′R*), (*1R,1′R,2S,2′S*), and (*1S,1′S,2R,2′R*) stereoisomers (a *meso* isomer and two enantiomers respectively) of 1,1′,2,2′,3,3′,4,4′-octahydro-6,6′,7,7′,8,8′-hexamethoxy-2,2′-dimethyl-1,1′-bis(3,4,5-trimethoxybenzyl)-2,2′-[butanedioylbis(oxytrimethylene)]di-isoquinolinium dichloride, all of which are in a *trans* configuration at the 1 and 2 positions of the isoquinolinium rings.

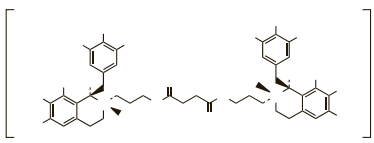
Доксакурия Хлорид

$C_{56}H_{78}Cl_2N_2O_{16}$ = 1106.1.

CAS — 133814-18-3 (doxacurium); 106819-53-8 (doxacurium chloride, meso isomer); 83348-52-1 (doxacurium chloride, total racemate).

ATC — M03AC07.

ATC Vet — QM03AC07.



Profile

Doxacurium chloride is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1902). It has been used for endotracheal intubation and to provide muscle relaxation in general anaesthesia for surgical procedures and to aid controlled ventilation. Doxacurium has little histamine-releasing activity and causes negligible vagal or sympathetic blockade so that significant cardiovascular adverse effects are not a problem.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Nuromax†; ***USA:*** Nuromax†.

Gallamine Triethiodide *(BANM, rINN)*

Benzcurine Iodide; Galamin Trietiyodür; Galamino trietjodidas; Gallamiinitrietjodidi; Gallamine, triéthiodure de; Gallamini triethiodidum; Gallamin-triethojodid; Gallamintrietjodid; Gallamin-trietjodid; Gallamone Triethiodide; Trietioduro de galamina. 2,2′,2″-(Benzene-1,2,3-triyltrioxy)tris(tetraethylammonium) tri-iodide.

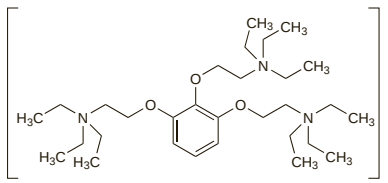
Галламина Триэтйодид

$C_{30}H_{60}I_3N_3O_3$ = 891.5.

CAS — 153-76-4 (gallamine); 65-29-2 (gallamine triethiodide).

ATC — M03AC02.

ATC Vet — QM03AC02.



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

Ph. Eur. 6.2 (Gallamine Triethiodide). A white, or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Gallamine Triethiodide). A white, hygroscopic, odourless, amorphous powder. Very soluble in water; sparingly soluble in alcohol; very slightly soluble in chloroform. pH of a 2% solution in water is between 5.3 and 7.0. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902). Tachycardia often develops due to the vagolytic action of gallamine triethiodide and blood pressure may be raised. It has a small histamine-releasing effect; occasional anaphylactoid reactions have been reported. It should be avoided in patients hypersensitive to iodine and in severe renal impairment. Although competitive muscle relaxants have been given with great care to patients with myasthenia gravis (see Neuromuscular Disorders, p.1903), UK licensed product information for gallamine triethiodide recommended that it should not be used in such patients.

Cardiopulmonary bypass. Alterations in the pharmacokinetics of competitive neuromuscular blockers in patients undergoing surgery involving cardiopulmonary bypass usually necessitate the use of reduced doses (see p.1903). However, the pharmacokinetics of gallamine in patients undergoing cardiopulmonary bypass appear not to differ significantly from those in control patients.[1]

1. Shanks CA, *et al.* Gallamine disposition in open-heart surgery involving cardiopulmonary bypass. *Clin Pharmacol Ther* 1983; **33:** 792–9.

Renal impairment. Gallamine triethiodide is excreted unchanged in the urine and UK licensed product information considered that it should be avoided in severe renal impairment since prolonged paralysis may occur. Significantly prolonged elimination half-life and reduced clearance have been reported[1] in patients with chronic renal failure given gallamine triethiodide in initial doses of 2 mg/kg intravenously.

1. Ramzan MI, *et al.* Gallamine disposition in surgical patients with chronic renal failure. *Br J Clin Pharmacol* 1981; **12:** 141–7.

Interactions

For interactions associated with competitive neuromuscular blockers, see Atracurium, p.1903.

Pharmacokinetics

After intravenous use gallamine triethiodide is distributed throughout body tissues. It is not metabolised, and is excreted in the urine as unchanged drug.

Uses and Administration

Gallamine triethiodide is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1905). Muscle relaxation occurs within about 1 to 2 minutes after intravenous injection and lasts for about 20 to 30 minutes. It has been used to provide muscle relaxation in general anaesthesia for surgical procedures (see Anaesthesia, p.1900) and to aid controlled ventilation (see Intensive Care, p.1901).

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 test dose of 20 mg may be given intravenously to the patient before anaesthesia to determine undue sensitivity. In the UK, initial doses of 80 to 120 mg by intravenous injection have been recommended, with further doses of 20 to 40 mg as required. In children, a dose of 1.5 mg/kg has been recommended, reduced to 600 micrograms/kg for neonates.

In some other countries lower doses have generally been used; an initial dose of 1 mg/kg intravenously, up to a maximum of 80 mg, with additional doses of 0.5 to 1 mg/kg after about 50 to 60 minutes if required.

Gallamine triethiodide has also been given intramuscularly, with or without hyaluronidase.

Preparations

BP 2008: Gallamine Injection;
USP 31: Gallamine Triethiodide Injection.

Proprietary Preparations (details are given in Part 3)
UK: Flaxedil†.

Metocurine Iodide *(USAN)*

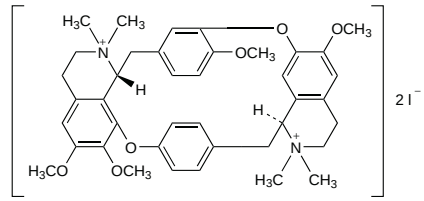
Dimethyl Tubocurarine Iodide; (+)-*O,O′*-Dimethylchondrocurarine Di-iodide; Dimethyltubocurarine Iodide; Dimetiltubocurarinio, ioduro de; Metocurini Iodidum; Metokuriinijodidi; Metokurinjodid; Trimethyltubocurarine Iodide. (+)-6,6′,7′,12′-Tetramethoxy-2,2,2′,2′-tetramethyltubocuraranium di-iodide.

$C_{40}H_{48}I_2N_2O_6$ = 906.6.

CAS — 5152-30-7 (metocurine); 7601-55-0 (metocurine iodide).

ATC — M03AA04.

ATC Vet — QM03AA04.



Profile

Metocurine iodide is a benzylisoquinolinium competitive neuromuscular blocker (see Atracurium, p.1905) that has been used to provide muscle relaxation in surgical and other procedures.

Metocurine iodide has a moderate risk of inducing histamine release; it also has some ganglion blocking activity.

Mivacurium Chloride *(BAN, USAN, rINN)*

BW-B1090U; Cloruro de mivacurio; Mivacurii Chloridum; Mivacurium, Chlorure de; Mivakuriumklorid; Mivakuriumkloridi; Mivakuryum Klorür. A mixture of the stereoisomers of (*E*)-1,1′,2,2′,3,3′,4,4′-octahydro-6,6′,7,7′-tetramethoxy-2,2′-dimethyl-1,1′-bis(3,4,5-trimethoxybenzyl)-2,2′-[oct-4-enedioylbis(oxytrimethylene)]di-isoquinolinium dichloride.

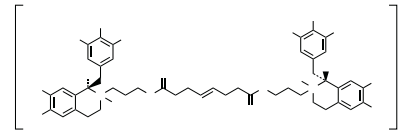
Мивакурия Хлорид

$C_{58}H_{80}Cl_2N_2O_{14}$ = 1100.2.

CAS — 106861-44-3 (mivacurium chloride, total racemate).

ATC — M03AC10.

ATC Vet — QM03AC10.



Incompatibility. See under Atracurium, p.1902 for details regarding the incompatibility of neuromuscular blockers.

Adverse Effects, Treatment, and Precautions

As for competitive neuromuscular blockers in general (see Atracurium, p.1902). Mivacurium chloride has no significant vagal or ganglion blocking activity at recommended doses. It may induce histamine release especially when given in large doses rapidly.

Mivacurium should be used with caution, if at all, in patients with plasma cholinesterase deficiency, since its duration of action will be prolonged in such patients.

Burns. In common with other competitive muscle relaxants patients with burns may develop resistance to mivacurium and require increased doses (see under Atracurium, p.1903). However, as these patients may also have reduced plasma cholinesterase activity dosage requirements could also be reduced. Licensed