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Adverse Effects of Neuromuscular Blockers and Their Antagonists

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Summary

Among all the drugs used for general anaesthesia, neuromuscular blockers appear to play a prominent role in the incidence of severe adverse reactions. It now seems likely that most serious adverse drug reactions occurring during anaesthesia are immunological in type. The frequency of life-threatening anaphylactic or anaphylactoid reactions occurring during anaesthesia has been estimated to be between 1 in 1000 and 1 in 25 000 anaesthetic procedures, with the neuromuscular blockers being involved in 80% of cases. The mortality from such serious reactions is reported to be in the range of 3.4 to 6%. The highly immunogenic drug, suxamethonium chloride (succinylcholine), was found to be the most hazardous agent. Drug-specific immunoglobulin E antibodies to suxamethonium chloride and other neuromuscular blockers have been demonstrated. This sensitivity to neuromuscular blockers seems to be a long-lasting phenomenon.

During anaesthesia, the clinical features of an allergic reaction are often masked. Tachycardia and circulatory collapse may be the only signs of an allergic reaction, and they are easily misdiagnosed. Bronchospasm is reported to be present in about 40% of cases. Successful management of these patients includes stabilisation during the acute reaction and avoidance of future reactions. The latter

is based on the identification of the causative drug and potentially cross-reacting compounds.

The use of suxamethonium chloride is associated with many other adverse effects, such as fasciculations, myalgia, potassium release, changes in the heart rate, increases in intragastric and intraocular pressures, and malignant hyperthermia. Because of the dangers of hyperkalaemic cardiac arrest after suxamethonium chloride administration in children with unrecognised muscular dystrophy, there have now been moves to limit the use of this drug in children.

Although neuromuscular blockers are designed to specifically block nicotinic cholinergic receptors at the neuromuscular junction, many bind to muscarinic cholinergic receptors on ganglia and smooth muscle, and alter parasympathetically mediated heart rate and airway calibre. Most benzylisoquinolinium muscle relaxants can induce histamine release, especially when they are administered rapidly, which can lead to disturbances of cardiovascular function. In addition, nondepolarising neuromuscular blockers have been implicated in causing generalised weakness following their long term administration to patients on an intensive care unit.

The problem with these adverse drug reactions is their unpredictable nature. Therefore, prompt recognition with appropriate therapy can help to improve the outcome.

Neuromuscular blockers are frequently implicated in systemic adverse reactions during general anaesthesia; the Committee on the Safety of Medicines in the UK reported that 10.8% of adverse drug reactions (218 out of 2014) of and 7.3% deaths (21 out of 286) during general anaesthesia were attributable to neuromuscular blockers.[1] The incidence for 3 of the currently used drugs is shown in table I.

The highest mortality rate among neuromuscular blockers has been noted with suxamethonium chloride (succinylcholine), which is responsible for 81% of deaths associated with neuromuscular blockers.[1] Similarly, the National Adverse Anaesthetic Reactions Advisory Service in the UK noted that suxamethonium chloride was the most hazardous neuromuscular blocker, while pancuronium bromide was the best tolerated (table II).[2]

Table I. Adverse reactions to neuromuscular blocking reported to the Committee on Safety of Medicines in the UK between 1964 and 1985[1]

Neuromuscular blocker	Number of adverse reactions[a]	Number of deaths
Atracurium besilate	72	1
Suxamethonium chloride (succinylcholine)	63	17
Vecuronium bromide	14	0

a Such as syncope, palpitations, apnoea, cardiac arrest, seizures and application-site reaction.

It now seems likely that most serious adverse drug reactions occurring during anaesthesia are immunological in nature.[4] The Boston Collaborative Drug Surveillance Program in the US estimated the incidence of severe allergic reactions to be 3 per 10 000 hospital patients, with a mortality in affected patients between 3 and 9%.[5] The frequency of life-threatening anaphylactic or anaphylactoid reactions occurring during anaesthesia has been estimated to be between 1 in 1000 and 1 in 25 000 anaesthetic procedures, with the neuromuscular blockers involved in 80% of cases.[6-8] The mortality from such serious reactions is reported to be in the range of 3.4 to 6%.[7,9] Minor systemic reactions attributable to histamine release probably occur in >1% of all anaesthetic procedures.[10] Neuromuscular blockers are the triggering agents in 50% or more of these reactions.[11]

This review focuses on the adverse effects of suxamethonium chloride and the currently available nondepolarising neuromuscular blockers, and their antagonists. Adverse effects of older drugs such as gallamine triethiodide, alcuronium chlor-

Table II. Incidence of reports of serious anaphylactoid reactions during inductions of anaesthesia with various neuromuscular blockers (after Watkins,[2,3] with permission)

Neuromuscular blocker	1985	1986	1987	1988	1989	1990	1991	1992
Suxamethonium chloride	28	45	48	52	61	73	44	47
Tubocurarine	4	5	4	7	3	5	1	1
Vecuronium bromide	1	9	10	15	12	14	15	12
Atracurium besilate	8	5	11	10	23	25	22	22
Pancuronium bromide	1	2	3	2			3	2

ide and fazadinium are not discussed. Drug interactions between neuromuscular blocking agents and other drugs, and the effects of pH, temperature, electrolytes, age or disease states are outside the scope of this review.

1. Mechanisms

Four mechanisms of allergic reactions have been postulated: type I immune-mediated hypersensitivity, classical pathway activation of the complement system, alternative complement activation and a direct pharmacological effect (fig. 1).[12]

2. General Management

Clinical features of allergic reactions are easily overlooked and/or misdiagnosed during anaesthesia. Cardiovascular collapse accompanied by tachycardia are the presenting features in about 80% of cases.[7]

The goals of treatment are to correct arterial hypoxaemia, inhibit further release of chemical mediators, and restore intravascular volume.[9,12] 100% oxygen and intravenous epinephrine (adrenaline) 10 to 20 μg/kg should be administered immediately. Early tracheal intubation with a cuffed tracheal tube should be considered in patients with rapidly developing angioedema. Fluids (crystalloid and/or colloid solutions) must be administered concurrently. Norepinephrine (noradrenaline) or a sympathomimetic drug (metaraminol, phenylephrine) delivered intravenously may also be necessary to maintain perfusion pressure until intravascular fluid volume can be restored. Dysrhythmias should be treated and the use of a cardiac assist device, e.g. an intra-aortic balloon pump, may be considered in a patient with profound myocardial depression.[13] The use of antihistamines and/or corticosteroids is controversial.

The investigation of a reaction during anaesthesia requires serial blood samples during the first 24 to 72 hours and further laboratory tests, such as intradermal allergen testing, leucocyte histamine-release testing and antigen-specific immunoglobulin E (IgE) antibody testing (radioallergo-sorbent test; RAST).[4,12,14,15] The possibility of cross-reactivity with other neuromuscular blockers should also be investigated, and the patient issued with an appropriate 'warning-card'.

3. Specific Adverse Effects

3.1 Haematological Effects

Approximately 20% of children receiving intravenous suxamethonium chloride, and 40% receiving suxamethonium chloride plus halothane, will develop myoglobinaemia.[16,17] This adverse effect is seen less frequently in adults.[16,17]

In children, the susceptibility of muscle to release myoglobin following depolarisation with suxamethonium chloride cannot yet be explained. Among the theories on the aetiology of suxamethonium chloride–induced muscle damage, it has been suggested that shearing forces associated with the fasciculations at the onset of blockade produce muscle fibre damage.[18] However, the development of myoglobinaemia is not dose-related, and can occur with or without fasciculations.[19,20] The prophylactic administration of defasciculating doses of nondepolarising neuromuscular blocking agents significantly reduces the degree of myoglobinaemia/myoglobinuria observed in children, including those as young as 2 years old.[20,21]

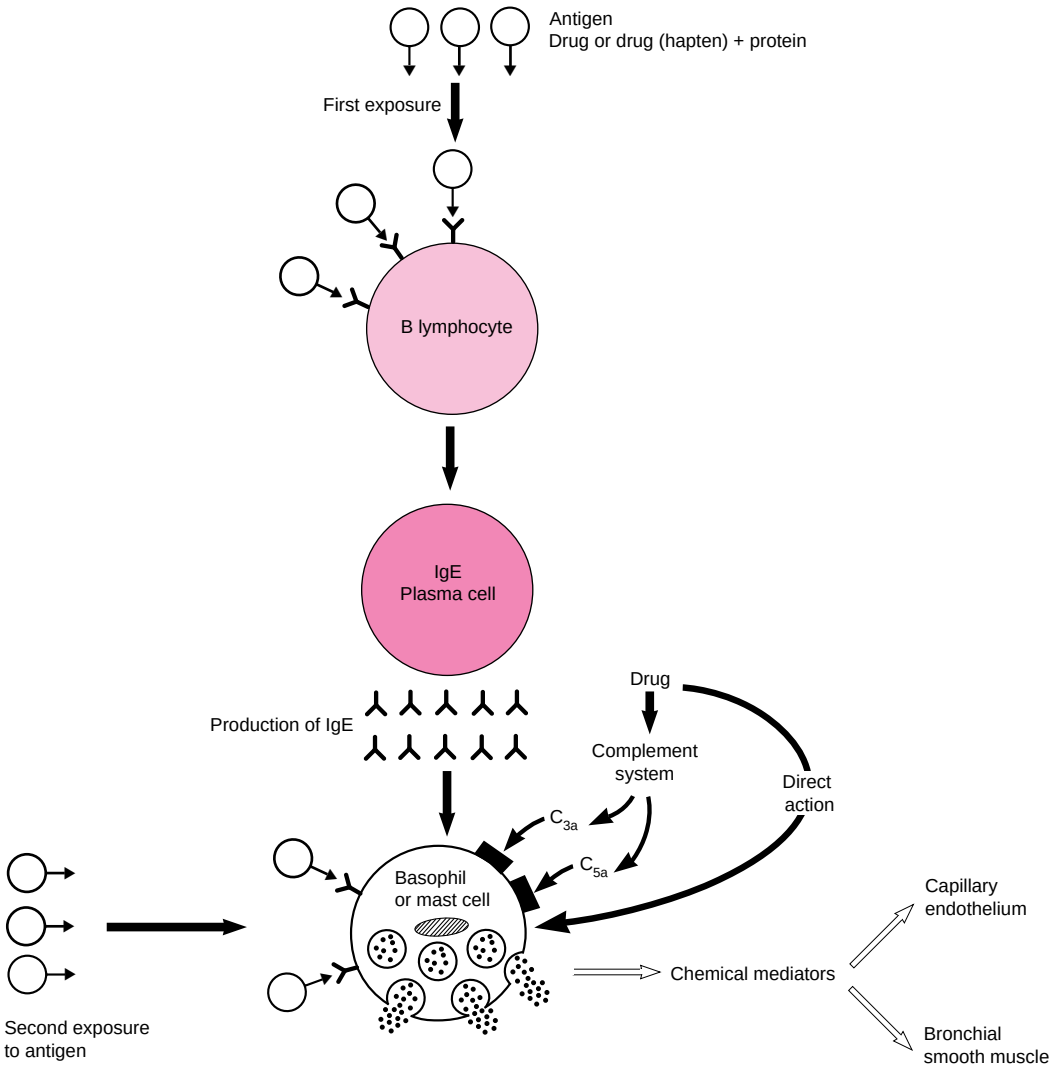

Fig. 1. Illustration of the possible mechanisms of allergic reactions induced by anaesthetic drugs (including neuromuscular blocking agents). The *in vivo* administration of a drug or a drug hapten combining with a large carrier molecule can induce the synthesis of specific immunoglobulin E (IgE) antibody against drug (sensitisation). IgE antibodies bind to the high affinity receptor for the Fc_ε fragment of IgE ($Fc_\varepsilon RI$) present on the surface of basophils and mast cells. On subsequent exposure, the drug combines with IgE antibody on basophil/mast cell surface, leading to release of chemical mediators (such as histamine, prostaglandins, platelet aggregating factor, serotonin and tryptase) resulting in anaphylaxis (type I hypersensitivity). There is also the possibility that some drugs are able to activate the classical or alternative pathways of complement. In this case, anaphylatoxins (C3a and C5a) can induce the release of chemical mediators through an interaction with specific membrane-bound receptors. Finally, histamine can be released because of a direct effect of the drug on basophil/mast cells. In contrast to anaphylaxis, an allergic reaction caused by activation of the complement system (direct or indirect) or because of the direct effect on basophil/mast cells does not require prior sensitisation and can occur with the first exposure to the drug.

Although myoglobinaemia does not usually cause clinical problems, in some cases, it can induce acute renal failure.[22] The glomerular tubules excrete myoglobin, which dissociates into ferrihaemate at pH values <5.6. Ferrihaemate is toxic to the proximal tubular cells.[23] Urine alkalinisation prevents dissociation, and the use of loop or osmotic diuretics is beneficial.

3.2 Cardiovascular Effects

Cardiac arrest and death caused by acute hyperkalaemic rhabdomyolysis have been reported following suxamethonium chloride 1 to 2 mg/kg in children with Duchenne muscular dystrophy.[24-26] This resulted in the US Food and Drug Administration recently mandating changes in the suxamethonium chloride package insert.[27,28] Because of the dangers of hyperkalaemic cardiac arrest after suxamethonium chloride in children with unrecognised muscular dystrophy, there have now been moves to limit the use of suxamethonium chloride in children.[28-31]

The administration of suxamethonium chloride in healthy humans results in a small increase in serum potassium level.[32] Depolarising muscle relaxants act at the motor end-plate of normal muscle cells, and open a ligand-gated ion channel, allowing sodium and calcium ion influx and potassium ion efflux. This initiates depolarisation of the muscle cell.[33]

Administration of suxamethonium chloride to patients with a variety of other clinical conditions can produce an exaggerated hyperkalaemic response, resulting in ventricular dysrhythmias and cardiac arrest. This exaggerated release of potassium ions after administration of suxamethonium chloride has been reported in patients after massive trauma,[34] burns,[35] neuromuscular disease,[36,37] intra-abdominal infections[38] and closed head injury.[39]

Sinus bradycardia, junctional rhythms and ventricular dysrhythmias, ranging from unifocal premature ventricular contractions to ventricular fibrillation, have been reported with suxamethonium chloride.[40,41] The risk of dysrhythmias is increased in children, with repeated doses, and in the presence of hypoxia and/or electrolyte abnormalities (e.g. hyperkalaemia). The risk is also increased in patients with digitalis toxicity.[42,43]

Since it comprises 2 molecules of acetylcholine linked together, suxamethonium chloride may reproduce all of the effects of acetylcholine at both nicotinic and muscarinic receptors.[44] Nevertheless, stimulation of sympathetic ganglia has been invoked as being a probable cause of the tachycardia and increase in blood pressure, which sometimes transiently occur after the administration of this drug.[44] Likewise, stimulation of parasympathetic ganglia, or direct stimulation of cardiac muscarinic receptors, may be responsible for the more commonly occurring bradycardia. Differences in resting sympathetic and vagal tone are believed to account for the more frequent occurrence of tachycardia in 'vagotonic' adults and bradycardia in 'sympathotonic' children.

The transient mild increase in blood pressure is possibly the result of the initial fasciculations inducing an increase in venous return, which may also result in bradycardia. Stimulation of afferent receptors in the carotid sinus has also been claimed to cause reflex bradycardia. The vagal type of effect with intravenous suxamethonium chloride is not observed after intramuscular administration. The negative inotropic and chronotropic responses can be attenuated by prior administration of atropine, ganglion-blocking agents (e.g. trimetaphan camsilate) or small doses of nondepolarising neuromuscular blockers.[17,45]

When benzylisoquinolinium muscle relaxants (e.g. mivacurium chloride, atracurium besilate, metocurine or tubocurarine) are rapidly administered, significant increases in plasma histamine levels may occur (fig. 2).[46-50] This is frequently associated with facial erythema, reductions in arterial pressure and increases in heart rate (figs 3 and 4).[48,49] Naguib et al.[48] noted average peak increases in plasma levels of histamine of 370, 234 and 252% of the control values 1 minute after the administration of mivacurium chloride, atracurium besilate and tubocurarine, respectively. This ad-

verse effect is absent with doxacurium chloride and cisatracurium besilate,[51,52] and may be reduced considerably by a slower rate of injection. It is also prevented by prophylactic use of combinations of histamine H_1 and H_2 antagonists.[53] Ganglionic blockade secondary to the administration of tubocurarine has been shown to occur in various species.[54] Steroidal compounds (e.g. rocuronium bromide, vecuronium bromide, pancuronium bromide or pipecuronium bromide) do not induce histamine release (figs 2 to 4).[48,49]

Although neuromuscular blockers are designed to specifically block nicotinic cholinergic receptors at the neuromuscular junction, many bind to

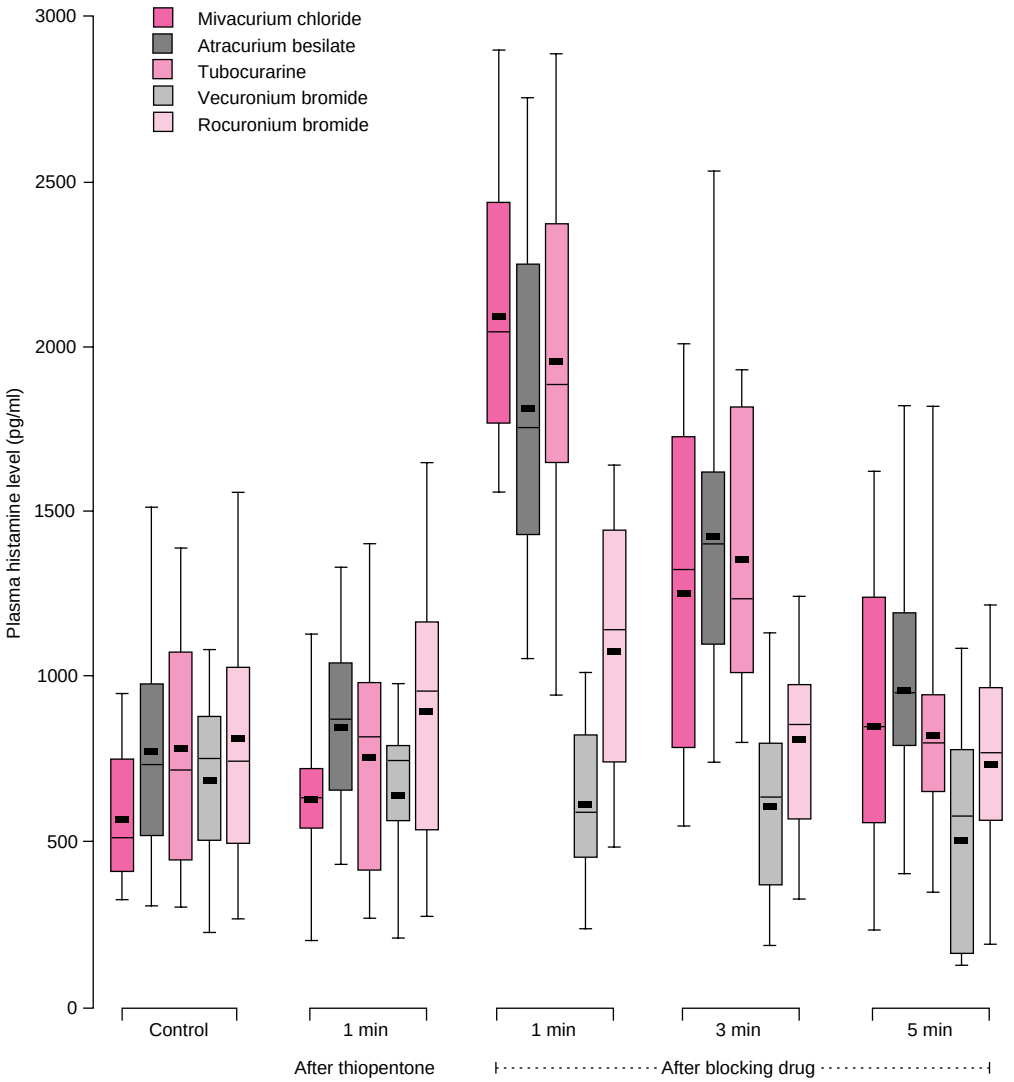

Fig. 2. Plasma histamine levels after administration of mivacurium chloride, atracurium besilate, tubocurarine, vecuronium bromide or rocuronium bromide. The horizontal lines within each box indicate the median, the rectangular symbols within each box indicate the mean, the lower and upper borders of the box indicate the 25th to 75th percentiles, and the extended bars indicate the overall ranges of values (from Naguib et al.,[48] with permission). *Symbol:* * = $p < 0.01$ *vs* control values.

muscarinic cholinergic receptors on ganglia, nerve endings and smooth muscle, and alter the parasympathetically mediated heart rate.[55]

Pharmacologically, muscarinic acetylcholine receptors have been classified into 3 main subtypes, termed neuronal-M_1, cardiac-M_2 and functional smooth muscle or glandular-M_3.[56,57] Five muscarinic receptors have been cloned from rat and human tissues.[58-60] Cloned m1, m2, m3 and m4 muscarinic receptors correspond to the pharmacologically defined M_1, M_2, M_3 and M_4 receptor subtypes, respectively.[59-62]

In contrast to benzylisoquinolinium compounds, steroidal compounds generally exhibit a vagolytic property. An interaction with cardiac M_2 muscarinic receptors has been demonstrated, with a rank order of potency of: pancuronium bromide > vecuronium bromide > pipecuronium bromide > rocuronium bromide.[63] The vagolytic effect of pancuronium bromide increases heart rate, and hence blood pressure and cardiac output.[64] Pancuronium bromide probably increases heart rate via both a vagolytic effect and sympathetic stimulation.[65] This adverse effect is moderate after pancuronium bromide, slight to moderate after rocuronium bromide, and absent with pipecuronium bromide and vecuronium bromide. All steroidal neuromuscular blocking compounds contain an acetylcholine-like fragment in the D-ring, and possess a potent neuromuscular action, whereas only pancuronium bromide, with an acetylcholine-like fragment in the A-ring, is a potent blocker of muscarinic receptors.[63,64] The lack of an acetylcholine moiety in the A-ring of the steroid nucleus of pipecuronium bromide, vecuronium bromide and rocuronium bromide may be responsible for their reduced potency in blocking cardiac M_2 muscarinic receptors.[66]

Atropine and glycopyrronium bromide are used to antagonise the cholinergic effects of anticholinesterases during the reversal of nondepolarising neuromuscular blockers. Supraventricular tachycardia and dysrhythmias, including Wenckebach phenomena, premature atrial contractions, atrioventricular dissociation, premature ventricular

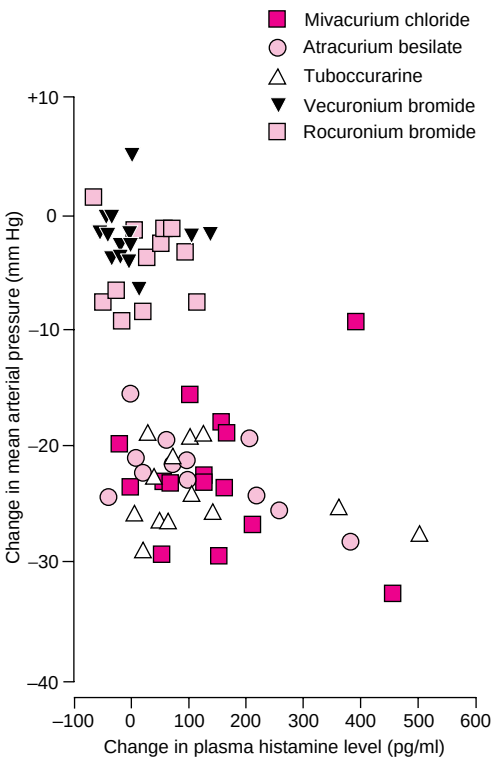

Fig. 3. Correlation of changes from control values between plasma histamine levels and mean arterial pressure 3 minutes after administration of mivacurium chloride 0.2 mg/kg, atracurium besilate 0.6 mg/kg, tubocurarine 0.5 mg/kg, vecuronium bromide 0.1 mg/kg or rocuronium bromide 0.6 mg/kg ($n = 75$; $r = –0.38$; $p < 0.001$) [reproduced from Naguib et al.,[48] with permission].

contractions and bigeminy, have been reported after combinations of edrophonium or neostigmine with atropine.[67-69] However, these combinations are generally useful and they are used in routine clinical practice. However, these adverse effects are sometimes seen and are usually self-limiting.

3.3 CNS Effects

Perioperative dreaming has been reported in children after the intermittent suxamethonium chloride technique (repeated administration of the agent) has been used during light general anaesthesia. This has been attributed to the increased afferent 'traffic' from muscle spindles.[70] In addition,

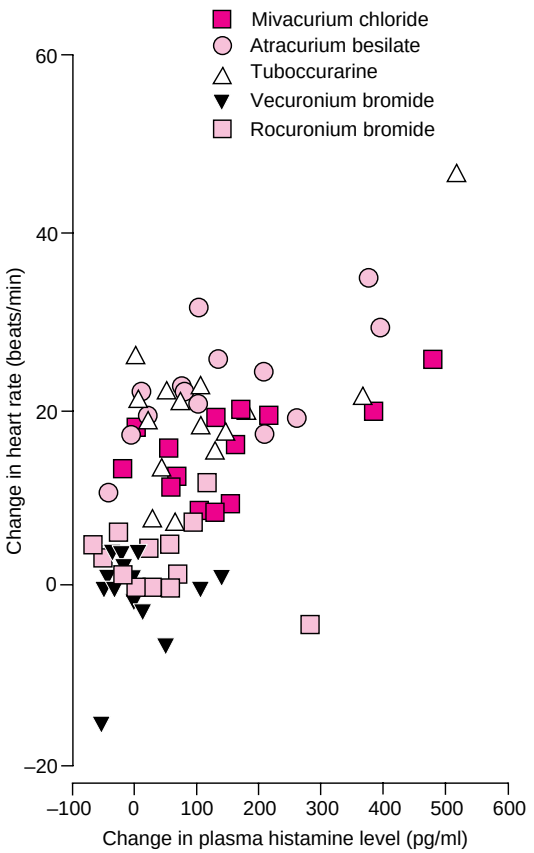

Fig. 4. Correlation of changes from control values for plasma levels of histamine and heart rate in patients, 3 minutes after administration of mivacurium chloride 0.2 mg/kg, atracurium besilate 0.6 mg/kg, tubocurarine 0.5 mg/kg, vecuronium bromide 0.1 mg/kg or rocuronium bromide 0.6 mg/kg (n = 75; r = –0.37; p < 0.01) [reproduced from Naguib et al.,[48] with permission].

suxamethonium chloride can cause a transient increase in intracranial pressure, probably as a result of an increase in cerebral blood volume;[71] the mean rise is approximately 6 to 9mm Hg. Therefore, the use of suxamethonium chloride could be catastrophic in patients who have reduced intracranial compliance, e.g. patients with brain tumours.

Laudanosine is one of the major breakdown products of atracurium besilate, and has been shown to have a potent convulsive action in dogs[72] and rats.[73] In addition, laudanosine was also found to increase the minimum alveolar concentration (MAC) of anaesthetics, antagonising the anaesthetic action of volatile anaesthetics, and to affect heart rate and arterial blood pressure.[74,75] CSF : plasma ratios of laudanosine in humans have been reported to be between 0.01 and 0.14 after atracurium besilate 0.5 mg/kg.[76]

Under normal circumstances plasma concentrations of laudanosine in humans will be far below those required for significant CNS stimulation. In fact, convulsant activity attributed to laudanosine has not been reported in humans. Laudanosine is cleared partly by the kidneys,[77] and probably also by the liver.[78] Therefore, higher plasma concentrations of laudanosine are likely to be found in patients with severe hepatic dysfunction, particularly if it is associated with renal failure after prolonged administration of atracurium besilate. In contrast, plasma concentrations of laudanosine observed after administration of cisatracurium besilate (an isomer of atracurium) were found to be approximately one-third of those observed after an equipotent dose of atracurium besilate.[79]

Neuromuscular blockers are highly ionised, have relatively low lipophilicity and ordinarily do not cross the blood-brain barrier. Nevertheless, detectable CSF concentrations of tubocurarine were found in humans after administration of relatively small intravenous doses of tubocurarine.[80] Although the pharmacological effects of neuromuscular blockers in the CSF are unknown in humans, several observations suggest that such drugs are not inert when they appear in the CSF. It has been shown that intrathecal administration of neuromuscular blockers can cause dose-dependent CNS excitation and seizures in rats.[81] The clinical significance of the results of this study is not clear.

Many of the drugs used in anaesthesia may cause blockade of central cholinergic neurotransmission. Central anticholinergic syndrome (CAS) is known to occur with the administration of a variety of drugs, most notably the anticholinergic agents, atropine and scopolamine (hyoscine).[82-84] The incidence of this syndrome in the perioperative

period has been estimated to be between 1 and 40%, and is believed to occur more often in patients who have received several drugs with central anticholinergic activity. CAS is manifested by seizures, restlessness, hallucinations, disorientation, signs of CNS depression (such as stupor and coma), and/or respiratory depression. Post-anaesthetic CAS can be treated by administration of physostigmine. Fever of a relatively mild degree has been reported in association with CAS with clinical doses of anticholinergics in approximately 25% of patients.[82-84]

3.4 Endocrine and Metabolic Effects

Suxamethonium chloride (among other drugs such as volatile anaesthetics, ketamine, vasopressors, digoxin, quinidine and calcium) can cause malignant hyperthermia (MH). MH is a heterogeneous disorder that may be triggered by suxamethonium chloride in genetically susceptible patients, and the severity of signs and symptoms differ among patients. Tubocurarine has also been identified as a probable cause of MH.[85] In MH, skeletal muscle acutely and unexpectedly increases its oxygen consumption and lactate production, resulting in greater heat production, respiratory and metabolic acidosis, muscle rigidity, sympathetic stimulation and increased cellular permeability.[86]

The aetiology of MH is unknown, but it is thought to be associated with an increase in free ionised myoplasmic calcium, possibly caused by a failure of the sarcoplasmic reticulum to bind calcium. As a result, aerobic and anaerobic metabolism are increased, resulting in the typical features of the syndrome, which are tachycardia, muscle stiffness, hypercarbia, tachypnoea, cardiac dysrhythmias, respiratory and metabolic acidosis, fever, unstable/rising blood pressure, cyanosis/mottling and myoglobinuria. MH acts as an autosomal dominant genetic condition, with reduced penetrance, giving a 50% likelihood of being MH-susceptible.[85] In North America and Europe, the overall incidence is 1 in 15 000 anaesthetic procedures. However, in adults, it may be as low as 1 in 50 000 anaesthetic procedures. The mortality rate is higher than 60% in untreated patients.

To date, most of the cases of MH described in the literature have occurred during anaesthesia or in the recovery room.[87] When all of the precautions for MH are combined (identification of MH susceptibility from family medical history or previous positive testing using the halothane-caffeine test, use of 'clean' or 'volatile agent–free' anaesthetic equipment and the avoidance of trigger agents), the incidence of MH reactions in the perioperative period is markedly reduced.

Some anaesthetic agents are more often associated with MH than others and these agents are known as triggering agents (see table III). It is usually, but not always, the combination of 2 triggering agents in a susceptible patient that brings about the condition.

Dantrolene sodium is a lipid soluble hydantoin analogue that has proved invaluable in the treatment of MH crises, presumably by preventing calcium release from the sarcoplasmic reticulum.[88] If MH occurs, dantrolene sodium 2 to 3 mg/kg should be rapidly administered, with increments up to 10 mg/kg can be given over a period of 15 minutes. Occasionally, a total dose above than 10 mg/kg may be needed. Sodium bicarbonate should be administered to correct metabolic acidosis, as

Table III. Trigger agents for malignant hyperthermia[a]

Muscle relaxants
Suxamethonium chloride (succinylcholine), decamethonium, gallamine, tubocurarine
Inhalational agents
Halothane, isoflurane, enflurane, sevoflurane and desflurane
Intravenous anaesthetics
Ketamine
Sympathomimetics
Vasopressors and isoprenaline (isoproterenol)
Cardiac drugs
Digoxin, quinidine and calcium
Stress
Both immediately preceding anaesthesia or after surgery

a This is by no means a definitive list and it is constantly amended.

guided by blood gas analysis. The hyperthermic patient should be cooled with intravenous iced saline (not Ringer's lactate). Dysrhythmias should be treated with lidocaine (lignocaine) 1 mg/kg and urine output should be maintained above 2 ml/kg/h. Hyperkalaemia is common, and should be treated with hyperventilation, bicarbonate, intravenous glucose and insulin (10 units regular insulin in 50ml 50% glucose titrated against the serum potassium level). Life-threatening hyperkalaemia may also be treated with calcium chloride 2 to 5 mg/kg administered over approximately 5 to 10 minutes.

Atropine has been shown to inhibit the normal exercise-induced increase in plasma growth hormone levels. The significance of this finding in relation to anaesthetic practice is not known.[89]

3.5 Gastrointestinal and Hepatic Effects

The increase in intragastric pressure (IGP) after suxamethonium chloride administration is quite variable between patients and appears to be related to the intensity of fasciculations.[42] Increased IGP can be prevented by pretreatment with nondepolarising neuromuscular blockers.[90] However, the likelihood of regurgitation of the stomach contents is small in most patients, since an increase in IGP coincides with an increase in the high pressure zone of the lower oesophageal sphincter.[90-92] The risk is increased if the normal angle of the entry of the oesophagus into the stomach is changed because of pregnancy, bowel distension, or hiatus hernia. Anticholinergic drugs also adversely affect barrier pressure by decreasing lower oesophageal sphincter pressure.[93]

Administration of anticholinesterases is associated with increased salivation, which can be blocked by atropine or another antisialagogue. It has been noted that intraluminal pressure, and colonic and rectal motor activity, are increased,[94] and mesenteric blood flow is reduced by up to 50%, after clinical doses of neostigmine.[95] This reduction is associated with the increased gastrointestinal motility and partly antagonised by atropine.[95] The muscarinic effects of anticholinesterases increase gastrointestinal motility, which may contribute to an increased incidence of postoperative nausea and vomiting (PONV). King et al.[96] showed a significant relationship between PONV and the presence of antagonism of neuromuscular blockade by neostigmine and atropine.[96] However, the results of a recent study have shown that when neostigmine was given to antagonise neuromuscular block, it did not increase the incidence or severity of PONV.[97] It has also been noted that neostigmine might cause excessive traction on anastomotic suture lines, resulting in leakage.[98,99] Neostigmine is used to antagonise the residual effects of nondepolarising neuromuscular blocking drugs. However, if adequate recovery of neuromuscular function (as monitored by a neural stimulator) has occurred, there is no need to use anticholinesterase drugs.

It has been observed in one study[100] that newborns exposed to pancuronium bromide had a 1.2-fold increase in relative risk of hyperbilirubinaemia. The risk was greatest in exposed infants during the first 4 days after administration of pancuronium bromide.

3.6 Respiratory Effects

The administration of benzylisoquinolinium neuromuscular blockers (with the exception of cisatracurium besilate and doxacurium chloride) is associated with histamine release, which may result in increased airway resistance and bronchospasm in patients with hyper-reactive airway disease.[101] Additionally, histamine potentiates the effects of leukotrienes and prostaglandins,[4] which are involved in the pathophysiology of bronchospasm.

The affinity of neuromuscular blockers for muscarinic receptors seems to have some influence on the neural control of airway calibre. Pancuronium bromide and atracurium besilate (but not vecuronium bromide) were found to enhance the increases in pulmonary resistance induced by vagus nerve stimulation, probably by blocking prejunctional muscarinic receptors (M_2), which physiologically inhibit vagally mediated increases in pulmonary resistance.[102] Mivacurium chloride is a more po-

tent antagonist at M_3 than M_2 receptors, and should not potentiate irritant-induced bronchoconstriction in the clinical range.[103] Blockade of M_3 muscarinic receptors in airway smooth muscle inhibits vagally induced bronchoconstriction. It has been shown that vecuronium bromide–induced partial neuromuscular block reduces the ventilatory response to isocapnic hypoxia without altering the response to hypercapnia.[104]

Anticholinesterases may increase airway secretions and can also precipitate bronchospasm. These effects can be prevented by glycopyrronium bromide or atropine.

3.7 Ocular Effects

Suxamethonium chloride can increase intraocular pressure (IOP) by an average of 8mm Hg.[105] The peak rise in IOP is observed during the fasciculatory phase and dissipates within 4 to 10 minutes.[106] This increase is poorly antagonised by nondepolarising neuromuscular blockers.[107]

The mechanism of action of this change in ocular dynamics remains unknown, but presumably involves contraction of tonic myofibrils or transient dilation of choroidal blood vessels.[108] Recent evidence indicates that changes in extraocular muscle tone do not significantly contribute to the increase in intraocular pressure noted after suxamethonium chloride administration.[108]

The use of suxamethonium chloride in open-globe injuries is controversial. Nevertheless, administration of suxamethonium chloride is best avoided in patients with an open eye injury or a recent ocular incision.[107]

Mydriasis and cycloplegia from anticholinergic drugs could be undesirable in patients with glaucoma because of the resulting increase in IOP. Blindness was reported in a patient following intravenous administration of atropine.[109] However, doses of atropine used for premedication ar+e probably inadequate to elevate IOP, even in susceptible patients, assuming that medications being used to treat glaucoma are continued. Atropine and glycopyrronium chloride may be less likely to increase IOP than scopolamine.[110] Reversal doses of atropine, when given in conjunction with neostigmine, do not significantly alter IOP and, even in patients with glaucoma, this combination may be safely used.[111]

3.8 Musculoskeletal Effects

In most adult patients, administration of suxamethonium chloride causes transient muscle fasciculations during the onset of the neuromuscular blockade. It has been shown that fasciculations are caused by antidromically conducted axonal depolarisations initiated by the agonist action of suxamethonium chloride on presynaptic nicotinic receptors at the neuromuscular junction; this leads to the simultaneous contraction of all muscle fibres of individual motor units.[112] The incidence and duration of fasciculations can be significantly reduced by pretreatment with nondepolarising neuromuscular drugs.[32]

The use of suxamethonium chloride is associated with a high incidence (73%) of muscle pains.[32] There seems to be no relationship between the degree of fasciculation and the degree of postoperative myalgia.[32,113] Several drugs, such as nondepolarising neuromuscular blockers,[32,113] lidocaine[114] and diazepam,[115] have been found to be useful in reducing suxamethonium chloride–induced myalgia. The hypothesis that production of prostaglandins might be involved in the generation of suxamethonium chloride–induced myalgia was tested by Naguib et al.[32] They demonstrated that the use of intravenous aspirin (acetylsalicylic acid) 13 mg/kg 3 minutes before the administration of suxamethonium chloride reduced the incidence and intensity of suxamethonium chloride–induced myalgia.[32]

Mivacurium chloride is metabolised by plasma cholinesterase (PCHE) at about 70 to 88% of the rate of suxamethonium chloride.[116] In patients with atypical forms of PCHE, the action of both suxamethonium chloride and mivacurium chloride is prolonged.[117-119] In individuals who are heterozygous for the gene producing atypical PCHE (incidence 1 in 25), the duration of action is lengthened by 30 to 50%. In patients who are homozygous

for atypical PCHE (incidence 1 in 3000), the duration of action is markedly prolonged; full paralysis after an intubating dose of suxamethonium chloride 1 mg/kg or mivacurium chloride 0.2 mg/kg will last 4 hours on average. The incidence of the gene producing silent PCHE is much rarer than the other types; patients who are homozygous for silent PCHE (approximately 0.0006% of the population) have virtually no plasma cholinesterase activity, and complete paralysis after suxamethonium chloride usually lasts many hours. The best course of action for patients who are homozygotes for silent or atypical PCHE or heterozygote for atypical and silent PCHE is either administration of exogenous human PCHE[120,121] or mechanical ventilation of the lungs until full recovery of neuromuscular function can be demonstrated. Administration of exogenous human PCHE resulted in a dose-related acceleration of recovery indices of mivacurium chloride–induced blockade (fig. 5).[122]

Several reports have recently implicated non-depolarising neuromuscular blockers in cases of generalised weakness, following their long term administration to patients on intensive care units (ICUs), which required recovery periods from 2 days to 6 months.[123-128] However, it is not clear whether muscle relaxants were a precipitating factor, since other possible contributing conditions were present, for example, polyneuropathy of critical illness,[129] disuse atrophy,[33] and aminoglycoside and corticosteroid administration.[126,127,130,131] In one study, prolonged paralysis after vecuronium bromide was associated with renal failure and higher plasma concentrations of a potentially active metabolite, 3-desacetyl-vecuronium.[132] Recovery of neuromuscular function after discontinuation of neuromuscular blocker infusion in patients on ICUs was found to be significantly faster with cisatracurium besilate than with vecuronium bromide.[133] The data from the aforementioned studies suggest that the incidence of post-paralysis weakness is probably higher than initially believed, and can probably be limited (but not eliminated) by monitoring of neuromuscular function. However, others[133] have concluded that routine neuromuscular monitoring was not sufficient to eliminate prolonged recovery time and myopathy in ICU patients.

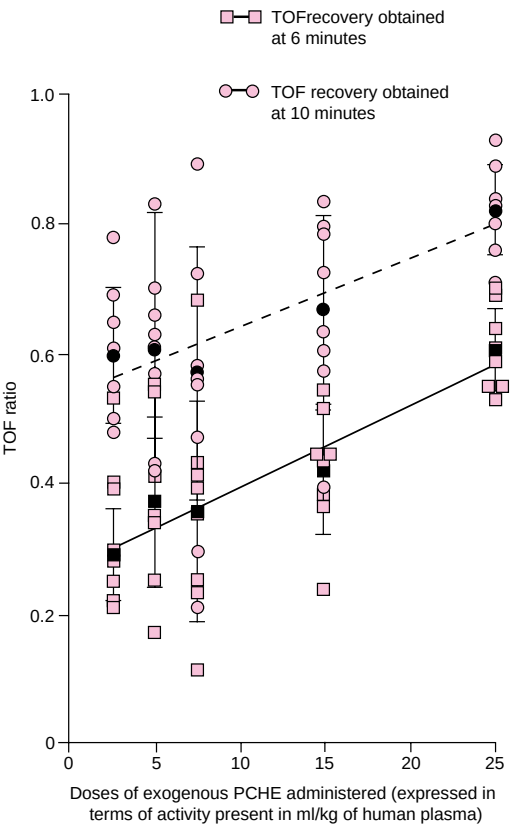

Fig. 5. Dose-response plot of train-of-four (TOF) recovery obtained at 6 minutes and at 10 minutes after administration of human plasma cholinesterase (PCHE). Black symbols represent mean TOF attained with each dose, the bars represent the standard deviation, and the solid and dotted lines represent the approximate dose-response at 6 at 10 minutes, respectively (reproduced from Naguib et al.,[122] with permission).

The use of suxamethonium chloride for changing tracheal tubes or for re-intubation is not uncommon in ICUs because of its rapid action and short duration. However, cardiac arrest with lethal potassium levels has been reported in some of these instances.[134] It is likely that up-regulation of acetylcholine receptors induced by immobilisation and long term neuromuscular blockade contributed to

such episodes of cardiac arrest.[135] For this reason, it is wise to avoid the use of suxamethonium chloride in ICU patients.

Lack of complete jaw relaxation has been described in children who were anaesthetised with halothane and paralysed with suxamethonium chloride.[136-138] This phenomenon has also been called 'incomplete jaw relaxation', 'masseter muscle rigidity' (MMR), 'masseter spasm' or 'trismus'. MMR may be regarded as an early sign of MH. However, most existing studies that have examined this adverse effect were retrospective, and lacked agreement on the magnitude and incidence of this phenomenon.[139] Some reports suggest that the incidence of MMR in children receiving suxamethonium chloride approximates 1%.[136,138] Other studies report that 50% of patients with MMR will go on to develop MH.[140,141] This means that either the susceptibility to MH is much greater than is generally believed, or the diagnosis of 'masseter spasm' was incorrectly made. It is probable that the high incidence of MMR reported by some investigators was the result of inadequate doses of suxamethonium chloride administered to children.[139] In a recent prospective study, the incidence of MMR was reported to be 0.2%.[139]

3.9 Allergic Reactions

Dose-related histamine release has been noted with tubocurarine and atracurium besilate both *in vivo* and *in vitro*.[142] Histamine liberation often elicits harmless cutaneous reactions, more serious incidents being mainly associated with unusually high doses.[143]

Neuromuscular blockers are responsible for 80% of anaphylactic reactions during anaesthesia;[144] 85% of patients who have an anaphylactic reaction to such drugs have not received the drug before.[11] IgE antibodies that are specific to neuromuscular blockers may be detected 6 weeks after the reaction in 87.9% of individuals who have had a reaction.[145] In adults, suxamethonium chloride remains the most frequent cause of anaphylactic reactions, although a recent series reported that vecuronium bromide accounted for 36% of cases.[146] Atracurium besilate, despite its direct histamine-releasing effect, is associated with a low incidence (0.2 to 5%) of anaphylactoid response.[147,148]

The sporadic occurrence of evidence showing histamine release after vecuronium bromide administration in clinical practice, and the occasional patients with unusually severe effects, may be attributed to a qualitatively different phenomenon (such as cross-reactivity between vecuronium bromide and chemically related compounds) from that causing histamine release in the majority of patients.[149-151] All neuromuscular blockers can cause noncompetitive inhibition of histamine-*N*-methyltransferase, but the plasma concentrations required for inhibition far exceed those that would be obtained in clinical situations, the exception being vecuronium bromide, for which the effect becomes manifest at doses of 0.1 to 0.2 mg/kg.[152,153]

Neuromuscular blockers contain 2 quaternary ammonium ions, which are the epitopes commonly recognised by specific IgE.[154] They also exhibit cross-reactivity, as evident in intradermal skin tests. Cross-reactivity can be observed in 66% of patients with a history of anaphylaxis to a neuromuscular blocking agent.[154,155] Vecuronium bromide and pancuronium bromide have the highest concordance rate in cross-reactivity, followed by suxamethonium chloride.[155] Cross-reactivity has been reported between neuromuscular blockers and food, cosmetics, disinfectants and industrial materials.[154] There is a significantly greater proportion of life-threatening reactions to neuromuscular blockers in women than in men. Sensitisation to ammonium ion epitopes in cosmetics has been postulated to explain the predominance of reaction in females.[154]

Drug interactions are among the factors that determine the sensitivity to muscle relaxants in general. Certain combinations of drugs may be associated with an increased frequency of such reactions, for example, the combination of atracurium besilate and propofol.[156] It would therefore seem advisable not to administer propofol at the same time as atracurium besilate, which is well known as a

histamine releaser.[157] The coadminstration of propofol and tubocurarine, another histamine releasing drug, may produce the same phenomenon and this combination is also best avoided.

An anaphylactic reaction to atropine, mediated by IgE antibodies, has been reported in a female patient.[158]

3.10 Teratogenicity and Effects During Pregnancy

It has been shown that the clinically used nondepolarising muscle relaxants tubocurarine, pancuronium bromide, atracurium besilate and vecuronium bromide produce dose-dependent developmental toxicity in rat embryos cultured from the presomite stage to the forelimb bud stage.[159] However, the lowest concentrations of relaxants that caused any adverse effects were at least 30-fold greater than plasma concentrations achieved in humans under normal clinical circumstances. This suggests that these muscle relaxants have little potential to disrupt embryonic development during organogenesis when used clinically.[159]

3.11 Other Effects

Severe burning pain has been associated with the administration of subparalysing doses of rocuronium bromide.[160,161] In one report, 52 of 105 patients (51%) had pain on injection with rocuronium bromide; of these patients, 12% reported severe pain.[161] Prior administration of lidocaine may reduce the pain. Otherwise, priming doses, usually one-tenth of the total dose, of rocuronium bromide should be administered after induction of anaesthesia and loss of consciousness.

4. Conclusions

Adverse drug reactions are a major complication of modern drug therapy. Neuromuscular blockers are rarely administered in isolation. However, among all drugs used for general anaesthesia, neuromuscular blockers seem to play a predominant role in the incidence of severe adverse reactions.

It has been noted that, despite advances in patient monitoring and the introduction of newer drugs in clinical practice, the incidence of serious, immediate hypersensitivity–type reactions has remained virtually unchanged (table II).[2,3] Allergic reactions remain a prominent cause of anaesthetic morbidity, although mortality remains low with improved understanding of the subject.[3] However, a recent study has suggested a serious problem in the identification, as well as documentation, of drug allergies in surgical patients;[162] approximately 20 to 30% of healthcare personnel did not document a history of drug allergies in patients' admission notes.[162]

The development of myopathy and paresis has been increasingly recognised after prolonged use of neuromuscular blockers in the ICU. Contributing factors to this phenomenon include changes in the pharmacokinetics of neuromuscular blockers in critically ill patients, pathophysiological changes in the nerve, muscle or neuromuscular junction, and the effect of active metabolites of neuromuscular blockers. In addition, many of the drugs given in the intensive care unit influence the pharmacodynamics of neuromuscular blockers.[163] Further investigation is needed to fully characterise this phenomenon, identify patients at risk, and outline a mechanism to prevent or limit the injury.[164]

Adequate knowledge of drug pharmacology, experience, proper perioperative assessment of the patient, proper documentation of adverse drug reactions, and slow administration of intravenous drugs, are needed to prevent adverse drug effects in anaesthesia.

References

1. Anaesthetists and the reporting of adverse drug reactions. BMJ 1986; 292: 949
2. Watkins J. Second report from an anaesthetic reactions advisory service. Anaesthesia 1989; 44: 157-9
3. Watkins J. Adverse reaction to neuromuscular blockers: frequency, investigation, and epidemiology. Acta Anaesthesiol Scand 1994; 38 Suppl. 102: 6-10
4. McKinnon RP, Wildsmith JAW. Histaminoid reactions in anaesthesia. Br J Anaesth 1995; 74: 217-28
5. Boston Collaborative Drug Surveillance Program. Drug induced anaphylaxis. JAMA 1973; 224: 613-5
6. Laxenaire M-C, Moneret-Vautrin DA, Watkins J. Diagnosis of causes of anaphylactoid anaesthetic reactions: a report of the recommendations of the joint Anaesthetic and Immuno-

Allergological Workshop: 1982 Mar 19; Nancy, France. Anaesthesia 1983; 38: 147-8
7. Fisher MMcD, More DG. The epidemiology and clinical features of anaphylactic reactions in anaesthesia. Anaesth Intensive Care 1981; 9: 226-34
8. Laxenaire M-C, Moneret-Vautrin DA, Widmer S, et al. Anaesthetic drugs responsible for anaphylactic shock: French multicenter study. Ann Fr Anesth Reanim 1990; 9: 501-6
9. Laxenaire M-C, Moneret-Vautrin DA, Vervloet D. The French experience of anaphylactoid reactions. Int Anesthesiol Clin 1985; 23: 145-60
10. Thornton JA, Lorenz W. Histamine and antihistamine in anaesthesia and surgery: report of a symposium. Anaesthesia 1983; 38: 373-9
11. Fisher MMcD, Munro I. Life-threatening anaphylactoid reactions to muscle relaxants. Anesth Analg 1983; 62: 559-64
12. Stoelting RK. Allergic reactions during anesthesia. Anesth Analg 1983; 62: 341-56
13. Raper RF, Fisher MMcD. Profound reversible myocardial depression after anaphylaxis. Lancet 1988; I: 386-8
14. Parker CW. Drug allergy. N Engl J Med 1975; 292: 732-6
15. Van Arsdel PP. Diagnosing drug allergy. JAMA 1982; 247: 2576-81
16. Ryan JR, Kagen LJ, Hyman AI. Myoglobinemia after a single dose of succinylcholine. N Engl J Med 1971; 285: 824-7
17. Goudsouzian NG, Ryan JR. Recent advances in pediatric anesthesia. Pediatr Clin North Am 1976; 23: 345-60
18. Watters DJ, Mapleson WW. Suxamethonium pains: hypothesis and observation. Anaesthesia 1971; 26: 127-41
19. McLoughlin C, Leslie K, Caldwell JE. Influence of dose of suxamethonium on suxamethonium-induced muscle damage. Br J Anaesth 1994; 73: 194-8
20. Blanc VF, Vaillancourt G, Brisson G. Succinylcholine, fasciculations and myoglobinemia. Can Anaesth Soc J 1986; 33: 178-84
21. Cozanitis DA, Erkola O, Klemola U, et al. Precurarization in infants and children less than three years of age. Can J Anaesth 1987; 34: 17-20
22. Bennike KA, Jarnum S. Myoglobinuria with acute renal failure possibly induced by suxamethonium. Br J Anaesth 1964; 36: 730-6
23. Farmer JC. Rhabdomyolysis. In: Civetta JM, Taylor RW, Kirby RR, editors. Critical care. Philadelphia: JB Lippincott, 1988: 1569-73
24. Delphin E, Jackson D, Rothstein P. Use of succinylcholine during elective pediatric anesthesia should be reevaluated. Anesth Analg 1987; 66: 1190-2
25. Rosenberg H, Gronert GA. Intractable cardiac arrest in children given succinylcholine [letter]. Anesthesiology 1992; 77: 1054
26. Sullivan M, Thompson WK, Hill GD. Succinylcholine-induced cardiac arrest in children with undiagnosed myopathy. Can J Anaesth 1994; 41: 497-501
27. Goudsouzian NG. Recent changes in the package insert for succinylcholine chloride: should this drug be contraindicated for routine use in children and adolescents? (Summary of the discussions of the anesthetic and life support drug advisory meeting of the Food and Drug Administration, FDA building, Rockville, MD, June 9, 1994) [letter]. Anesth Analg 1995; 80: 207-8
28. Badgwell JM, Hall SC, Lockhart C. Revised label regarding use of succinylcholine in children and adolescents [letter]. Anesthesiology 1994; 80: 243-5
29. Bevan RB. Succinylcholine [editorial]. Can J Anaesth 1994; 41: 465-8
30. Schulte-Sasse U, Eberlein HJ, Schmucker I, et al. Should the use of succinylcholine during pediatric anesthesia be re-evaluated? [in German] Anaesthesiol Reanim 1993; 18: 13-9
31. Hopkins PM. Use of suxamethonium in children [editorial]. Br J Anaesth 1995; 75: 675-7
32. Naguib M, Farag H, Magbagbeola JAO. Effect of pre-treatment with lysine acetyl salicylate on suxamethonium-induced myalgia. Br J Anaesth 1987; 59: 606-10
33. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 1975; 43: 89-99
34. Mazze RI, Escue HM, Houston JB. Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. Anesthesiology 1969; 31: 540-7
35. Belin RP, Karleen CI. Cardiac arrest in the burned patient following succinylcholine administration. Anesthesiology 1966; 27: 516-8
36. Cooperman LH. Succinylcholine-induced hyperkalemia in neuromuscular disease. JAMA 1970; 213: 1867-71
37. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. Anesthesiology 1984; 61: 173-87
38. Kohlschutter B, Baur H, Roth F. Suxamethonium-induced hyperkalemia in patients with severe intra-abdominal infections. Br J Anaesth 1976; 48: 557-61
39. Stevenson PH, Birch AA. Succinylcholine-induced hyperkalemia in a patient with a closed head injury. Anesthesiology 1979; 51: 89-90
40. Durant MM, Katz RI. Suxamethonium. Br J Anaesth 1982; 54: 195-208
41. Craythorne NWB, Turndorf H, Dripps RD. Changes in pulse rate and rhythm associated with the use of succinylcholine in anesthetized children. Anesthesiology 1960; 21: 465-70
42. Gibb DB. Suxamethonium – a review. Anaesth Intensive Care 1974; 2: 9-26
43. Bevan DR, Donati F. Neuromuscular relaxants: complications. Semin Anesth 1985; 4: 65-72
44. Galindo AHF, Davis TB. Succinylcholine and cardiac excitability. Anesthesiology 1962; 23: 32-40
45. Mathias JA, Evans-Prosser CD, Churchill-Davidson HC. The role of the non-depolarizing drugs in the prevention of suxamethonium bradycardia. Br J Anesth 1970; 42: 609-13
46. Basta SJ, Savarese JJ, Ali HH, et al. Histamine-releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. Br J Anaesth 1983; 55 Suppl. 1: 105S-6S
47. Moss J, Philbin DM, Rosow CE, et al. Histamine release by neuromuscular blocking agents in man. Klin Wochenschr 1982; 60: 891-5
48. Naguib M, Samarkandi AH, Bakhamees HS, et al. Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. Br J Anaesth 1995; 75: 588-92
49. Naguib M, Abdulatif M, Absood A. Comparative effects of pipecuronium and tubocurarine on plasma histamine in humans. Br J Anaesth 1991; 67: 320-2
50. Watkins J. Histamine release by atracurium. Br J Anaesth 1986; 58: 19S-22S
51. Murray DJ, Mehta MP, Choi WW, et al. The neuromuscular blocking and cardiovascular effects of doxacurium chloride in patients receiving nitrous oxide narcotic anesthesia. Anesthesiology 1988; 69: 472-7
52. Lien CA, Belmont MR, Abalos A, et al. The cardiovascular effects and histamine-releasing properties of 51W89 in pa-

tients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 1995; 82: 1131-8
53. Scott RPF, Savarese JJ, Basta SJ, et al. Atracurium: clinical strategies for preventing histamine release and attenuating the haemodynamic response. Br J Anaesth 1985; 57: 550-3
54. Flacke W, Gillis RA. Impulse transmission via nicotinic and muscarinic pathways in the stellate ganglion. J Pharmacol Exp Ther 1968; 163: 266-76
55. Bowman WC. Non-relaxant properties of neuromuscular blocking drugs. Br J Anaesth 1982; 54: 147-60
56. Hammer R, Berrie BC, Birdsall NJM, et al. Pirenzepine distinguishes between different subclasses of muscarinic receptors. Nature 1980; 283: 90-2
57. Doods HN, Mathy MJ, Davidesko D, et al. Selectivity of muscarinic antagonists in radioligand and *in vivo* experiments for the putative M_1, M_2 and M_3 receptors. J Pharmacol Exp Ther 1987; 242: 257-62
58. Bonner TI, Buckley NJ, Young AC, et al. Identification of a family of muscarinic acetylcholine receptor genes. Science 1987; 237: 527-32
59. Kubo T, Fukuda K, Mikami A, et al. Cloning, sequencing and expression of complementary DNA encoding the muscarinic acetylcholine receptor. Nature 1986; 323: 411-6
60. Bonner TI, Young AC, Brann MR, et al. Cloning and expression of the human and rat m5 muscarinic acetylcholine receptor genes. Neuron 1988; 1: 403-10
61. Buckley NJ, Bonner TI, Buckley CM, et al. Antagonist binding properties of five cloned muscarinic receptors expressed in CHO-K1 cells. Mol Pharmacol 1989; 35: 469-76
62. Lazareno S, Buckley NJ, Roberts FF. Characterization of muscarinic M_4 binding sites in rabbit lung, chicken heart, and NG108-15 cells. Mol Pharmacol 1990; 38: 805-15
63. Appadu BL, Lambert DG. Studies on the interaction of steroidal neuromuscular blocking drugs with cardiac muscarinic receptors. Br J Anaesth 1994; 72: 86-8
64. Tassonyi E, Neidhart P, Pittet JF, et al. Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 1988; 69: 793-6
65. Ivankovich AD, Miletich DJ, Albrecht RF, et al. The effect of pancuronium on myocardial contraction and catecholamine metabolism. J Pharm Pharmacol 1975; 27: 837-41
66. Durant NN, Marshall IG, Savage DS, et al. The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45 and other pancuronium analogues, in the cat. J Pharm Pharmacol 1979; 31: 831-6
67. Gottlieb JD, Sweet RB. The antagonism of curare: the cardiac effect of atropine and neostigmine. Can Anaesth Soc J 1963; 10: 114-21
68. Naguib M, Gomaa M, Absood GH. Atropine-edrophonium mixture: a dose-response study. Anesth Analg 1988; 67: 650-5
69. Naguib M, Gomaa M. Atropine-neostigmine mixture: a dose-response study. Can Anaesth Soc J 1989; 36: 412-7
70. O'Sullivan EP, Childs D, Bush GH. Peri-operative dreaming in paediatric patients who receive suxamethonium. Anaesthesia 1988; 43: 104-6
71. Cottrell JE, Hartung J, Giffin JP, et al. Intracranial and hemodynamic changes after succinylcholine administration in cats. Anesth Analg 1983; 62: 1006-9
72. Hennis PJ, Fahey MR, Canfell PC, et al. Pharmacology of laudanosine in dogs. Anesthesiology 1986; 65: 56-60
73. Scheepstra GL, Vree TB, Crul JF, et al. Convulsive effects and pharmacokinetics of laudanosine in the rat. Eur J Anaesthesiol 1986; 3: 371-83
74. Shi WZ, Fahey MR, Fisher DM, et al. Laudanosine (a metabolite of atracurium) increases the minimum alveolar concentration of halothane in rabbits. Anesthesiology 1985; 63: 584-8
75. Chapple DJ, Miller AA, Ward JB, et al. Cardiovascular and neurological effects of laudanosine: studies in mice and rats, and in conscious and anaesthetized dogs. Br J Anaesth 1987; 59: 218-25
76. Fahey MR, Canfell PC, Taboada T, et al. Cerebrospinal fluid concentrations of laudanosine after administration of atracurium. Br J Anaesth 1990; 64: 105-6
77. Fahey MR, Rupp SM, Canfell C, et al. Effect of renal failure on laudanosine excretion in man. Br J Anaesth 1985; 57: 1049-51
78. Lawhead RG, Matsumi M, Peters KR, et al. Plasma laudanosine levels in patients given atracurium during liver transplantation. Anesth Analg 1993; 76: 569-73
79. Boyd AH, Eastwood NB, Parker CJR, et al. A comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in the intensive therapy unit. Br J Anaesth 1996; 76: 382-8
80. Matteo RS, Pua EK, Khambatta HJ, et al. Cerebrospinal fluid levels of d-tubocurarine in man. Anesthesiology 1977; 46: 396-9
81. Szenohradszky J, Trevor AJ, Bickler P, et al. Central nervous system effects of intrathecal muscle relaxants in rats. Anesth Analg 1993; 76: 1304-9
82. Greenblatt DJ, Shader RI. Drug therapy: anticholinergics. N Engl J Med 1973; 288: 1215-9
83. Schneck HG, Rupreht J. Central anticholinergic syndrome (CAS) in anesthesia and intensive care. Acta Anaesthesiol Belg 1989; 40: 219-28
84. Granacher RP, Baldessarini RJ, Messner E. Physostigmine treatment of delirium induced by anticholinergics. Am Fam Physician 1976; 13: 99-103
85. Britt BA, Kalow W. Malignant hyperthermia: aetiology unknown. Can Anaesth Soc J 1970; 17: 316-30
86. Gronert GA. Malignant hyperthermia. Anesthesiology 1980; 53: 395-423
87. Strazis KP, Fox AW. Malignant hyperthermia: a review of published cases. Anesth Analg 1993; 77: 297-304
88. Britt BA. Dantrolene. Can Anaesth Soc J 1984; 31: 61-75
89. Few JD, Davies CT. The inhibiting effect of atropine on growth hormone release during exercise. Eur J Appl Physiol 1980; 43: 221-8
90. Miller RD, Way WL. Inhibition of succinylcholine-induced increased intragastric pressure by nondepolarizing muscle relaxants and lidocaine. Anesthesiology 1971; 34: 185-8
91. Lind JF, Warrian WG, Wankling WJ. Responses of the gastroesophageal junctional zone to increases in abdominal pressure. Can J Surg 1966; 9: 32-8
92. Smith G, Dalling R, Williams TI. Gastro-oesophageal pressure gradient changes produced by induction of anaesthesia and suxamethonium. Br J Anaesth 1978; 50: 1137-43
93. Cotton BR, Smith G. Single and combined effects of atropine and metoclopramide on the lower oesophageal sphincter pressure. Br J Anaesth 1981; 53: 869-74
94. Wilkins JL, Hardcastle JD, Mann CV, et al. Effects of neostigmine and atropine on motor activity of ileum, colon, and rectum of anaesthetized subjects. BMJ 1970; 1: 793-4
95. Whitaker BL. Observations on the blood flow in the inferior mesenteric arterial system and the healing of colonic anastomoses. Ann R Coll Surg Eng 1968; 43: 89-110
96. King MJ, Milazkiewicz R, Carli F, et al. Influence of neostigmine on postoperative vomiting. Br J Anaesth 1988; 61: 403-6

97. Hovorka J, Korttila K, Nelskylä, et al. Reversal of neuromuscular blockade with neostigmine has no effect on the incidence or severity of postoperative nausea and vomiting. Anesth Analg 1997; 85: 1359-61
98. Bell CM. Neostigmine and anastomotic disruption. Proc R Soc Med 1970; 63: 752
99. Morisot P, Loygue J, Guilmet C. Influence of postoperative decurarization with neostigmine on digestive anastomoses. Can Anaesth Soc J 1975; 22: 144-8
100. Freeman J, Lesko SM, Mitchell AA, et al. Hyperbilirubinemia following exposure to pancuronium bromide in newborns. Dev Pharmacol Ther 1990; 14: 209-15
101. Atracurium [editorial]. Lancet 1983; I: 394-5
102. Vetterman J, Beck KC, Lindhahl SHE, et al. Actions of enflurane, isoflurane, vecuronium, atracurium, and pancuronium on pulmonary resistance in dogs. Anesthesiology 1988; 69: 688-95
103. Okanlami OA, Fryer AD, Hirshman C. Interaction of nondepolarizing muscle relaxants with M_2 and M_3 muscarinic receptors in guinea pig lung and heart. Anesthesiology 1996; 84: 155-61
104. Eriksson LI, Lennmarken C, Johnson A. Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. Acta Anaesthesiol Scand 1992; 36: 710-5
105. Polarz H, Bohrer H, Fleischer F, et al. Effects of thiopentone/suxamethonium on intraocular pressure after pretreatment with alfentanil. Eur J Clin Pharmacol 1992; 43: 311-3
106. Pandey K, Badola RP, Kumar S. Time course of intraocular hypertension produced by suxamethonium. Br J Anaesth 1972; 44: 191-6
107. Meyers EF, Krupin T, Johnson M, et al. Failure of nondepolarizing neuromuscular blockers to inhibit succinylcholine-induced increased intraocular pressure: a controlled study. Anesthesiology 1978; 48: 149-51
108. Kelly RE, Dinner M, Turner LS, et al. Succinylcholine increases intraocular pressure in the human eye with extraocular muscles detached. Anesthesiology 1993; 79: 948-53
109. Gooding JM, Holcomb MC. Transient blindness following intravenous administration of atropine. Anesth Analg 1977; 56: 872-3
110. Garde JF, Aston R, Endler GC, et al. Racial mydriatic response to belladonna premedication. Anaesth Analg 1978; 57: 572-6
111. Cunningham AJ, Barry P. Intraocular pressure – physiology and implications for anaesthetic management. Can Anaesth Soc J 1986; 33: 195-208
112. Hartman GS, Fiamengo SA, Riker Jr WF. Succinylcholine: mechanism of fasciculations and their prevention by d-tubocurarine or diphenylhydantoin. Anesthesiology 1986; 65: 405-13
113. Pinchak AC, Smith CE, Shepard LS, et al. Waiting time after non-depolarizing relaxants after muscle fasciculation response to succinylcholine. Can J Anaesth 1994; 41: 206-12
114. Usubiaga JE, Wikinski JA, Usubiaga LE, et al. Intravenous lidocaine in the prevention of postoperative muscle pain caused by succinylcholine administration. Anesth Analg 1967; 46: 225-30
115. Fahmy NR, Malek NS, Lappas DG. Diazepam prevents some adverse effects of succinylcholine. Clin Pharmacol Ther 1976; 26: 395-8
116. Savarese JJ, Ali HH, Basta SJ, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): a short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 1988; 68: 723-32
117. Whittaker M. Plasma cholinesterase variants and the anaesthetist. Anaesthesia 1980; 35: 174-97
118. Viby-Mogensen J, Hanel HK. Prolonged apnoea after suxamethonium: an analysis of the first 225 cases reported to the Danish cholinesterase research unit. Acta Anaesthesiol Scand 1978; 22: 371-80
119. Goudsouzian NG, d'Hollander AA, Viby-Mogensen J. Prolonged neuromuscular block from mivacurium in two patients with cholinesterase deficiency. Anesth Analg 1993; 77: 183-5
120. Benzer A, Luz G, Oswald E, et al. Succinylcholine-induced prolonged apnea in a 3-week-old newborn: treatment with human plasma cholinesterase. Anesth Analg 1992; 74: 137-8
121. Naguib M, El-Gammal M, Daoud W, et al. Human plasma cholinesterase for antagonism of prolonged mivacurium-induced neuromuscular blockade. Anesthesiology 1995; 82: 1288-92
122. Naguib M, Daoud W, El-Gammal M, et al. Enzymatic antagonism of mivacurium-induced neuromuscular blockade: by human plasma cholinesterase. Anesthesiology 1995; 83: 694-701
123. Gooch JL, Suchyta MR, Balbierz JM, et al. Prolonged paralysis after treatment with neuromuscular junction blocking agents. Crit Care Med 1991; 19: 1125-31
124. Vanderheyden BA, Reynolds HN, Gerold KB, et al. Prolonged paralysis after long-term vecuronium infusion. Crit Care Med 1992; 20: 304-7
125. Op de Coul AA, Lambregts PC, Koeman J, et al. Neuromuscular complications in patients given Pavulon® (pancuronium bromide) during artificial ventilation. Clin Neurol Neurosurg 1985; 87: 17-22
126. Apte Kakade S. Rehabilitation of patients with quadriparesis after treatment of status asthmaticus with neuromuscular blocking agents and high-dose corticosteroids. Arch Phys Med Rehabil 1991; 72: 1024-8
127. Danon MJ, Carpenter S. Myopathy with thick filament (myosin) loss following prolonged paralysis with vecuronium during steroid treatment. Muscle Nerve 1991; 14: 1131-9
128. Partridge BL, Abrams JH, Bazemore C, et al. Prolonged neuromuscular blockade after long-term infusion of vecuronium bromide in the intensive care unit. Crit Care Med 1990; 18: 1177-9
129. Bolton CF, Gilbert JJ, Hahn AF, et al. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry 1984; 47: 1223-31
130. Vital Brazil O, Prado-Franceschi J. The nature of neuromuscular block produced by neomycin and gentamicin. Arch Int Pharmacodyn Ther 1969; 179: 78-85
131. Sanders Jr WE, Sanders CC. Toxicity of antibacterial agents: mechanisms of action on mammalian cells. Ann Rev Pharmacol Toxicol 1979; 19: 53-83
132. Segredo V, Caldwell JE, Matthay MA, et al. Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med 1992; 327: 524-8
133. Prielipp RC, Coursin DB, Scuderi PE, et al. Comparison of the infusion requirements and recovery profiles of vecuronium and cisatracurium 51W89 in intensive care unit patients. Anesth Analg 1995; 81: 3-12
134. Horton WA, Fergusson NV. Hyperkalaemia and cardiac arrest after the use of suxamethonium in intensive care. Anaesthesia 1988; 43: 890-1
135. Martyn JAJ, White DA, Gronert GA, et al. Up-and-down regulation of skeletal muscle acetylcholine receptors: effects on neuromuscular blockers. Anesthesiology 1992; 76: 822-43

136. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: incidence and implications. Anesthesiology 1984; 61: 772-5
137. Donlon JV, Newfeld PA, Streter F, et al. Implications of masseter spasm after succinylcholine. Anesthesiology 1987; 49: 298-301
138. Carroll JB. Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. Anesthesiology 1987; 67: 599-61
139. Hannallah RS, Kaplan RK. Jaw relaxation after a halothane/succinylcholine sequence in children. Anesthesiology 1994; 81: 99-103
140. Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. Anesth Analg 1986; 65: 161-4
141. Ellis FR, Halsall PJ. Suxamethonium spasm: a differential diagnosis conundrum. Br J Anaesth 1984; 56: 381-4
142. North FC, Kettelkamp N, Hirshman CA. Comparison of cutaneous and *in vitro* histamine release by muscle relaxants. Anesthesiology 1987; 66: 543-6
143. Rowlands DE. Harmless cutaneous reactions associated with the use of atracurium: a report of 1200 anaesthetics. Br J Anaesth 1987; 59: 693-6
144. Laxenaire MC, Moneret-Vautrin DA, Widmer S, et al. Anaesthetic drugs responsible for anaphylactic shock. French multicenter study. Ann Fr Anesth Reanim 1990; 9: 501-6
145. Guéant JL, Mata E, Monin B, et al. Evaluation of a new reactive-solid phase for radioimmunoassay of seric specific IgE against muscle relaxant drugs. Allergy 1991; 46: 452-8
146. Moneret-Vautrin DA, Laxenaire MC. Predictive check-up for risk of anaphylactoid shock in anesthesia. Monogr Allergy 1992; 30: 156-61
147. Birnbaum J, Vervloet D. Mechanisms of anaphylactic reactions to muscle relaxants: role of allergenic determinants. Monogr Allergy 1992; 30: 15-23
148. Fisher MMcD, Baldo BA. The incidence and clinical features of anaphylactic reactions during anaesthesia in Australia. Ann Fr Anesth Réanim 1993; 12: 97-104
149. O'Callaghan AC, Scadding G, Watkins J. Bronchospasm following the use of vecuronium. Anaesthesia 1986; 41: 940-2
150. Durrani Z, O'Hara J. Histaminoid reaction from vecuronium priming: a case report. Anesthesiology 1987; 67: 130-2
151. Holt AW, Vedig AE. Anaphylaxis following vecuronium [letter]. Anaesth Intens Care 1988; 16: 378-9
152. Futo J, Kupferberg JP, Moss J, et al. Vecuronium inhibits histamine *N*-methyltransferase. Anesthesiology 1988; 69: 92-6
153. Futo J, Kupferberg JP, Moss J. Neuromuscular relaxants inhibit HNMT *in vitro*. Biochem Pharmacol 1990; 39: 415-20
154. Baldo BA, Fisher MMcD. Substituted ammonium ions as allergenic determinants in drug allergy. Nature 1983; 306: 262-4
155. Abel M, Book WJ, Eisenkraft JB. Adverse effects of nondepolarizing neuromuscular blocking agents: incidence, prevention and management. Drug Saf 1994; 10: 420-38
156. Naguib M. Anaphylactoid reactions following propofol-atracurium sequence. Can J Anaesth 1989; 36: 358-9
157. Laxenaire MC, Mata-Bermjo E, Moneret-Vautrin DA, et al. Life-threatening anaphylactoid reactions to propofol (Diprivan®) Anesthesiology 1992; 77: 275-80
158. Aguilera L, Martinez-Bourio R, Cid C, et al. Anaphylactic reaction after atropine. Anaesthesia 1988; 43: 955-7
159. Fujinaga M, Baden JM, Mazze RI. Developmental toxicity of nondepolarizing muscle relaxants in cultured rat embryos. Anesthesiology 1992; 76: 999-1003
160. Moorthy SS, Dierdorf SF. Pain on injection of rocuronium bromide [letter]. Anesth Analg 1995; 80: 1067
161. Steegers MAH, Robertson EN. Pain on injection of rocuronium bromide [letter]. Anesth Analg 1996; 83: 203
162. Ricardo O, Bands C, Laney G, et al. Drug allergies in the surgical population. Can J Anaesth 1994; 41: 1149-55
163. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for sustained neuromuscular blockade in the adult critically ill patient: an executive summary. Crit Care Med 1995; 23: 1601-5
164. Prielipp RC, Coursin DB, Wood KE. Complications associated with sedative and neuromuscular blocking drugs in critically ill patients. Crit Care Clin 1995; 11: 983-1003

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