Neuromuscular blocking drugs (NMBDs), are given to infants and children for anaesthesia to provide muscle relaxation, to reduce the quantity of anaesthetic agent required and to facilitate controlled ventilation. The effective use of NMBDs in paediatric practice requires a knowledge of certain fundamental differences in the responses of paediatric patients and adults to these drugs, and the physiological factors that underlie them. This review presents a brief account of these differences and an overview of the clinical pharmacology of the most commonly used NMBDs in infants and children.

Factors affecting paediatric responses to neuromuscular blocking drugs
Development of the neuromuscular system
Acetylcholine receptors (AChRs) appear over the entire surface of human muscle fibres at about 8 weeks of gestational age. From 9 to 16 weeks, AChRs cluster to form primitive motor-end plates on one side of the muscle fibres. From 16 to 24 weeks the number of nerve terminals is reduced reflecting the transition from poly- to mononeuronal innervation. From 24 to 31 weeks, the neuromuscular junctions attain a mature appearance, although they continue to grow until the end of the first year of life.

The nicotinic AChR in mammalian muscles exists in fetal and adult forms. The fetal form is composed of five subunits designated α, β, γ, and δ (Fig. 1). In the adult form, the γ subunit is replaced by a subunit designated ε. When two molecules of acetylcholine (ACh) combine with the α subunits, the central pore opens, allowing mainly sodium ions to enter the cell. Compared with the adult receptor, the fetal receptor has a longer open time when combined with ACh, allowing more sodium ions to enter the cell and creating a larger depolarising potential. Effectively, the fetal receptor is sensitive to the agonist ACh and resistant to antagonists such as tubocurarine. The presence of a receptor which is sensitive to AChs may compensate for reduced stores of the transmitter in immature nerve endings, thereby facilitating spontaneous fetal movements which are essential for normal neuromuscular development.

The number and disposition of AChRs on developing muscle fibres are regulated by neural ‘trophic’ factors and muscle activity. The neurotrophic factors appear to be more important in establishing and maintaining early synaptic clusters, whereas muscle activity plays a critical role in the developmental loss of the predominantly fetal type extrajunctional receptors. Fetal AChRs are not normally detected on human muscle fibres after 31 weeks of gestational age, but they may reappear at extrajunctional sites in pathological states associated with prolonged inactivity (e.g. burns, denervation injury, prolonged muscle paralysis) giving rise to an exaggerated response to succinylcholine and a reduced response to non-depolarizing NMBDs.

Maturation of neuromuscular transmission
Maturation of neuromuscular transmission is incomplete at birth. Experiments in young rats suggest that the principal deficiency is a three-fold reduction in the availability of ACh in developing motor nerves. A similar reduction in the release of AChs from motor nerves in the human neonate probably underlies the three-fold increase in sensitivity of the neuromuscular junction to tubocurarine and other non-depolarizing neuromuscular blocking agents. A prejunctional locus for the weakness in neuromuscular transmission in human neonates is consistent with the mature appearance of the motor end-plate and the absence of fetal ACh receptors after 31 weeks of gestational age. It is also consistent with the apparently normal response of the motor end-plate to succinylcholine in the newborn period (see below).
In this case, doses of 5 mg kg\(^{-1}\) succinylcholine are not available, and succinylcholine may be given by i.m. injection. In such circumstances, reliable conditions for intubation are necessary. The duration of action of these drugs is the same or somewhat less than that of the standard 1 mg kg\(^{-1}\) dose of succinylcholine.5 Elimination depends on hydrolysis by butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase).

The unique mode of action of succinylcholine (sustained depolarisation) and its activity at muscarinic acetylcholine receptors produce a large number of side effects. These include tachycardia, bradycardia (most reliably treated with atropine 20–30 \(\mu\)g kg\(^{-1}\) i.v.), increase in intraocular pressure, hyperkalaemia (which may be severe in patients with burns, paraplegia, and disuse atrophy), myoglobinemia, and masseter muscle spasm. Of particular concern have been the instances of life-threatening malignant hyperpyrexia and reports of rare, but often fatal, hyperkalaemic cardiac arrests in young boys with undiagnosed muscular dystrophy. As a result of these reports, in 1994, the US Food and Drug Administration (FDA) recommended that ‘the use of succinylcholine in children should be reserved for emergency intubation and instances where immediate securing of the airway is necessary, e.g. laryngospasm, difficult airway, full stomach, or for i.m. use when a suitable vein is inaccessible’. Since the publication of this recommendation, the use of succinylcholine in routine anaesthesia in children has been declining.

### Depolarizing neuromuscular blocking drugs

#### Succinylcholine

Succinylcholine is the only depolarizing neuromuscular blocking agent in clinical use. Structurally, it resembles two molecules of acetylcholine joined back to back by an ester linkage. A unique combination of rapid onset and ultra-short duration of action makes succinylcholine especially useful for facilitating tracheal intubation. Elimination depends on hydrolysis by butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase).

Dose-response studies suggest that infants require at least 3 mg kg\(^{-1}\) and children 2 mg kg\(^{-1}\) of succinylcholine to produce reliable conditions for intubation.2 The duration of action of these doses is about the same or somewhat less than that of the standard 1 mg kg\(^{-1}\) intubating dose in adults (6–8 min). If an i.v. line is not available, succinylcholine may be given by i.m. injection. In this case, doses of 5 mg kg\(^{-1}\) for infants and 4 mg kg\(^{-1}\) for children are required to produce 85–100% twitch depression. Maximum block is achieved in 3–4 min and lasts for about 15–20 min.

The increased dose requirement of succinylcholine in younger patients is thought to result from its rapid distribution into an enlarged volume of extracellular fluid rather than an altered response to the action of the drug at postjunctival AChRs. The fact that expressing the dose of succinylcholine in mg m\(^{-2}\) abolishes the differences in dose requirements between the age groups supports this suggestion, as extracellular fluid volume and surface area bear a close relationship throughout life (Table 1).5,6

Because succinylcholine is hydrolysed by butyrylcholinesterase, a deficiency in this enzyme may result in prolonged neuromuscular block requiring ventilation and sedation to be continued until spontaneous resolution occurs. Although neonates and infants aged less than 6 months have only half the concentration of butyrylcholinesterase activity of adults, this does not prolong the effect of succinylcholine.

### Non-depolarizing neuromuscular blocking drugs

Neuromuscular transmission studies in the 1960s and 1970s produced conflicting results about the sensitivity of paediatric patients to non-depolarizing relaxants. The question was largely resolved in 1982 by a study which showed that the steady-state concentration of tubocurarine corresponding to 50% depression of EMG twitch (\(C_{pss50}\)) in neonates was only one-third of that in adults, while that of infants was about one-half. However, when the dose corresponding to 50% depression of EMG twitch (\(D_{50}\)) was calculated for each patient by multiplying the \(C_{pss50}\) by the volume of distribution (\(V_{dis}\)) there were no significant

### Table 1 Ed90 of succinylcholine is greater in neonates, infants and children than in adults when expressed in mg kg\(^{-1}\), but not when expressed in mg m\(^{-2}\)

<table>
<thead>
<tr>
<th></th>
<th>mg kg(^{-1})</th>
<th>mg m(^{-2})</th>
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<tbody>
<tr>
<td>Neonates</td>
<td>0.517</td>
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</tr>
<tr>
<td>Infants</td>
<td>0.608</td>
<td>12.04</td>
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<tr>
<td>Children</td>
<td>0.352</td>
<td>8.45</td>
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<tr>
<td>Adults</td>
<td>0.290</td>
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Developmental changes in other body systems

Weight-normalized cardiac output and extracellular fluid volumes decline exponentially from birth to adulthood. The relatively high cardiac output in infants and children translates into faster circulation times, so that NMBDs are transferred to and from their sites of action more rapidly. The relatively high volume of extracellular fluid in infants and children corresponds to an increase in the volume of distribution of NMBDs and influences dose requirements.

#### Fig. 1

Fetal acetylcholine receptor. Five glycoprotein subunits designated \(\alpha, \beta, \gamma, \delta\) are grouped around a central pore. In the adult acetylcholine receptor subunit \(\gamma\) is replaced by a subunit designated \(\epsilon\). Adapted from Goudsouzian and Standaert\(^5,6\) and reproduced with permission from G Meakin.\(^14\)
differences between the groups (Table 2). It was concluded that, although neonates and infants were sensitive to tubocurarine in terms of requiring a lower plasma concentration to produce a given effect, this was countered by an increased volume of distribution, such that dose did not vary significantly with age. The same appears to be true for all other non-depolarizing neuromuscular blocking agents. The increased sensitivity of the neuromuscular junction of the human neonate and infant to non-depolarizing neuromuscular blocking agents is the result of reduced release of ACh from immature motor nerves.

The clinically available non-depolarizing neuromuscular blocking agents can be classified into benzylquinolinium or aminosteroidal compounds. Benzylquinolinium drugs are associated with histamine release and hypotension, whereas aminosteroidal compounds are associated with tachycardia and hypertension.

**Benzylquinolinium compounds**

**Atracurium**

Atracurium is a bisquaternary benzylquinolinium diester with an intermediate duration of clinical action. The molecule is eliminated mainly by Hofmann elimination, a process dependent on pH and temperature.

When compared during nitrous-oxide narcotic anaesthesia, the ED$_{95}$ of atracurium was found to be significantly lower in neonates and infants than in children (119 and 163 µg kg$^{-1}$ vs. 195 µg kg$^{-1}$). Following a standard dose of atracurium 0.5 mg kg$^{-1}$, 95% depression of twitch occurred more rapidly in neonates than in children (0.9 min vs. 1.4 min), while recovery to 10% of the control twitch height occurred more rapidly in neonates compared with the other two groups (22.7, 29.7 vs. 28.6 min). Prompt recovery in all age groups makes atracurium a very attractive drug for use in paediatric anaesthesia.

The adverse effects associated with atracurium relate mainly to histamine release. This commonly results in a macular rash or erythema along the course of the vein of injection, which may subsequently spread peripherally. Occasionally, the rash may be accompanied by more serious histamine-mediated effects such as hypotension, tachycardia or bronchospasm. The cardiovascular changes are dose-related and usually occur at doses greater than twice the ED$_{95}$.

**Cisatracurium**

Cisatracurium is the $1R$-$cis$, $1'R$-$cis$ isomer of atracurium, and one of the 10 stereoisomers that make up the commercially available atracurium mixture. Like atracurium, it is an intermediate duration relaxant that undergoes spontaneous degradation at body pH and temperature.

The potency of cisatracurium is about three times that of atracurium. When measured in children during thiopental-nitrous oxide-opioid anaesthesia, the ED$_{95}$ of cisatracurium is 0.45 mg kg$^{-1}$, which is similar to that found in adults. Increased potency is associated with greater specificity of drug action and fewer side effects; accordingly, cisatracurium has less propensity for histamine release and provides greater cardiovascular stability than atracurium. Doses of cisatracurium of 3 x ED$_{95}$ in children and up to 8 x ED$_{95}$ in adults produce no signs of histamine release or significant changes in heart rate or blood pressure. The main disadvantage of increased potency is a slower onset of action which necessitates a relative high dose (3 x ED$_{95}$) to achieve reliable intubating conditions at 2 min.

After a dose of 0.15 mg kg$^{-1}$ ($\sim 3 \times$ ED$_{95}$) onset of maximum block occurred more rapidly in infants than in children (2.0 min vs. 3.0 min), whereas recovery to 25% of control twitch height occurred more rapidly in children than in infants (36 min vs. 43 min). The 25% recovery time in children was comparable with that reported for atracurium 0.5 mg kg$^{-1}$ under similar anaesthetic conditions. However, the clinical duration in infants appeared to be 5–10 min longer after cisatracurium 0.15 mg kg$^{-1}$ than after atracurium 0.5 mg kg$^{-1}$, which could have clinical importance in infants undergoing short surgical procedures. Onset and recovery times following cisatracurium 0.15 mg kg$^{-1}$ appeared to be somewhat shorter in infants and children than in adults.

**Mivacurium**

Mivacurium has a structure similar to that of atracurium but a shorter duration of action due to its metabolism by butyrylcholinesterase. Plasma clearance of mivacurium decreases with age consistent with the faster recovery times and greater infusion requirements reported in infants and children compared with adults.

The potency of mivacurium has been determined in infants and children during nitrous oxide-halothane and nitrous oxide-opioid anaesthesia. The ED$_{95}$ values for children varied between 89 and 110 µg kg$^{-1}$ whereas those for infants tended to be less, varying between 65 and 94 µg kg$^{-1}$. Mivacurium 0.2 mg kg$^{-1}$ ($\sim 2 \times$ ED$_{95}$) provides satisfactory intubating conditions in 98% of children 90s after administration during thiopental-nitrous oxide anaesthesia. Onset of maximum block occurs in 1–2 min and recovery of T1 to 25% in 9–10 min; these times are less than those reported in adults. As mivacurium is hydrolysed by butyrylcholinesterase, a deficiency in this enzyme may result in prolonged block. Mivacurium, like atracurium, has significant histamine-releasing properties that may be evident at therapeutic doses.
Aminosteroidal compounds

**Pancuronium**

Pancuronium is a potent, long-acting, bisquaternary aminosteroidal neuromuscular blocking agent lacking the histamine releasing and hypotensive properties of tubocurarine. As it is mainly eliminated via the kidney its duration of action may be prolonged in patients with renal failure.

When measured during nitrous oxide-halothane anaesthesia, the ED₉₅ of pancuronium in infants is approximately 46 µg kg⁻¹ in infants and 58 µg kg⁻¹ in children. In children anaesthetised with halothane, a dose of 0.12 mg kg⁻¹ (~2 × ED₉₅) produced 95% depression of controlled twitch height in about 2 min with recovery to 25% control twitch height taking more than 1 h. Increases in heart rate of 30–40% and systolic blood pressure of 10–15% were also found after this dose of pancuronium. The vagolytic effect of pancuronium may be an advantage in infants, in whom bradycardia is highly undesirable, or in patients undergoing anaesthesia with high-dose opioids, which tend to decrease heart rate and blood pressure. The latter group may include cardiac and other high-risk cases, in whom the use of pancuronium to facilitate postoperative ventilation can reduce oxygen consumption by up to 13%.

**Vecuronium**

Vecuronium is a monooquaternary aminosteroid relaxant produced by N-demethylation in the 2-piperidino substitution of pancuronium. This single alteration to the molecular structure of pancuronium results in a molecule with greater selectivity of pharmacological profile, a shorter duration of action, and less cumulative properties. Minimal cardiovascular effects and histamine release have made vecuronium a popular choice for use in critically ill children.

When studied during nitrous oxide-opioid anaesthesia, the ED₉₅ of vecuronium was found to be significantly lower in neonates and infants than in children aged 3–10 yrs (48 and 47 vs. 81 µg kg⁻¹). Furthermore, a dose of 100 µg kg⁻¹ maintained > 90% neuromuscular block for almost an hour in the neonates and infants compared with only 18 min in children. Vecuronium is clearly a long-acting neuromuscular blocking agent in newborns and infants, in agreement with its increased residence time (a parameter similar to half-time) in younger patients.

**Rocuronium**

Rocuronium (rapid onset-curonium) is a desacetoxy analogue of vecuronium with a more rapid onset of action. Rapid onset is the result of reduced potency, which necessitates an increase in dose, and hence the injection of larger number of drug molecules. When compared with nitrous oxide-opioid anaesthesia, the ED₉₅ of rocuronium was significantly lower in infants than in children (248 µg kg⁻¹ vs. 396 µg kg⁻¹) whereas the duration of clinical effect after a standard intubating dose of 0.6 mg kg⁻¹ (~2 × ED₉₅) was much longer (42 min vs. 27 min). These results confirm that rocuronium, like vecuronium is longer acting in infants than in children. However, unlike vecuronium, rocuronium retains the characteristics of an intermediate-acting NMBD in infants.

In three clinical trials, rocuronium 0.6 mg kg⁻¹ produced satisfactory intubating conditions in 100% of children 60 s after injection. Rocuronium would appear to be an acceptable alternative to succinylcholine for rapid sequence intubation after a careful assessment of the airway to exclude possible difficulty with intubation. Doses of 1–2 × ED₉₅ of rocuronium produce a negligible increase in heart rate with no change in arterial blood pressure.

**Antagonism of neuromuscular blocking drugs**

At conclusion of anaesthesia, any residual neuromuscular block due to a non-depolarizing neuromuscular blocking agent should be antagonized by an anticholinesterase. This is especially important in neonates and small infants because of their reduced respiratory reserve. The most commonly used anticholinesterases are neostigmine and edrophonium.

Rates of recovery from a 90% pancuronium-induced neuromuscular block after one of two doses of neostigmine (36 and 71 µg kg⁻¹) or edrophonium (0.71 and 1.43 mg kg⁻¹) have been compared in paediatric and adult patients. Recovery after edrophonium was significantly faster than that after neostigmine for the first 2 min after injection, but doubling the doses of the antagonists had no significant effect on recovery. Recovery after either antagonist was significantly faster in paediatric patients than in adults. These results suggest that in the presence of 10% recovery of twitch height, about 35 µg kg⁻¹ of neostigmine or 0.7 µg kg⁻¹ edrophonium should provide maximal antagonism in all age groups. For convenience, and to provide a margin of safety, somewhat larger doses of 50 µg kg⁻¹ of neostigmine or 1 mg kg⁻¹ of edrophonium are usually given. Atropine 20 µg kg⁻¹ or glycopyrrolate 10 µg kg⁻¹ should be administered before, or with, the anticholinesterase to prevent muscarinic effects.

**References**