Neuromuscular blocking agents are given to children to facilitate tracheal intubation, to relax the abdominal muscles during surgery, to assure immobility during critical portions of surgery and to facilitate mechanical ventilation in intensive care units. In recent years, several factors have influenced the practice of giving neuromuscular blocking agents to children. These include introduction of new drugs with different degrees of desirable qualities, concerns about the potential for severe adverse events with succinylcholine, and the introduction of new anaesthetic techniques and equipment, such as the laryngeal mask airway, that might obviate the need for tracheal intubation. This review addresses some of these issues and provides an overview of the pharmacology of neuromuscular blocking agents and their antagonists in children. Issues such as the role of governmental bodies and costs of anaesthetic drugs are presented from the author’s perspective in the USA.

Physiological and pharmacological differences between children and adults

Churchill-Davidson and Wise noted that neonates responded to tubocurarine and decamethonium (a depolarizing neuromuscular blocking agent) in a manner similar to that of patients with myasthenia gravis.4 5 Electrophysiological studies offer some insight into this observation. Whereas tetanic stimuli at frequencies as high as 50 Hz do not induce fade in adults, unanaesthetized premature neonates given tetanic stimuli at 20 Hz fade and full-term neonates fade at 50 Hz.30 Similarly, infants anaesthetized with methohexitol and nitrous oxide demonstrate fade at rapid stimulation rates.8

That neonates and infants cannot sustain a response to rapid stimulation suggests that their prejunctional reserves of acetylcholine are small. The clinical manifestation of this smaller margin of reserve is that neonates and infants need a lower steady-state plasma concentration of tubocurarine21 or vecuronium17 to depress twitch tension to 50% during anaesthesia with nitrous oxide and halothane. However, after infancy, maturational changes in sensitivity are complete (i.e. the response of a child is similar to that of an adult).

Maturation should also influence the response to neuromuscular blocking agents because age-related changes in body composition influence drug distribution. For example, neuromuscular blocking agents are polar and therefore distribute only to the extracellular fluid (ECF) space. This volume decreases markedly during the first year of life, thereafter reaching adult values. The finding that age-related changes in the weight-normalized volume of distribution at steady state21 (\(V_{ss}\)) of tubocurarine parallel these maturational changes in ECF (Fig. 1) is not surprising. Maturational changes for vecuronium17 and atracurium16 are similar. Thus, weight-normalized doses of non-depolarizing neuromuscular blocking agents yield smaller plasma concentrations in neonates or infants than in children or adults, counterbalancing the increased sensitivity in younger patients.

Maturational changes in organ function also alter clearance (\(Cl\)) and, in turn, elimination half-life. For tubocurarine (which is eliminated predominantly by glomerular filtration), age-related changes in \(Cl\)21 (normalized to body surface area) parallel those in glomerular filtration rate (Fig. 2). However, when \(Cl\) is normalized to body weight, it does not vary with age.21 The combination of no age-related change in weight-normalized \(Cl\) and a larger weight-normalized \(V_{ss}\) in younger patients results in the elimination half-life of tubocurarine and, presumably its rate of neuromuscular recovery, being longer in younger patients. Although vecuronium is eliminated by the liver rather than the kidney, its pharmacokinetic profile (no age-related change in \(Cl\) and a larger \(V_{ss}\), resulting in a longer half-life in younger patients) is similar. These findings are consistent with (and explain) recovery from vecuronium being slower in infants than in children.20 In contrast, \(Cl\) of atracurium decreases slightly with maturation,16 presumably because atracurium degrades throughout the larger ECF space (as a result of Hofmann degradation and/or ester hydrolysis) in younger patients. In turn, the elimination half-life of atracurium decreases minimally during maturation and age-related changes in 25–75% recovery time are small.35

Succinylcholine

Succinylcholine has been popular in both paediatric and adult anaesthesia for decades. However, because of its many
Neuromuscular blocking agents in paediatric anaesthesia

Fig 1 Age-related changes in the steady state volume of distribution ($V_{ss}$) of tubocurarine parallel maturational changes in the volume of the extracellular fluid space ($V_{ECF}$). Values for $V_{ss}$ are mean (SD). (Redrawn with permission from Fisher and colleagues.21)

Fig 2 Age-related changes in clearance ($Cl$) of tubocurarine (normalized by body surface area) parallel maturational changes in glomerular filtration rate (GFR) (mean (SD). (Redrawn with permission from Fisher and colleagues.21)

problems, several clinicians and investigators (including me) have encouraged that it be avoided, and eventually eliminated, from paediatric anaesthetic practice. During recent years, the controversy has reappeared.

In November 1992, Rosenberg and Gronert (two American anaesthetists with research interests in malignant hyperthermia) reported that ‘During the past 12 months, four boys... have died... during or following halothane and [succinylcholine]’.39 Simultaneously, they reported to the USA Food and Drug Administration (FDA) that a larger number of children given halothane and succinylcholine had suffered cardiac arrests. In retrospect, some or most of these children had muscular dystrophies10; however, as these dystrophies can be silent, clinicians cannot always purposefully avoid using succinylcholine in such cases. The FDA asked Burroughs Wellcome (the company now merged into Glaxo Wellcome that developed Anectine, the original succinylcholine) to revise the package insert. Burroughs Wellcome proposed a label stating ‘Except when used for emergency tracheal intubation or in 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’ (Burroughs Wellcome, Package Insert for Anectine, 1995).

This revised language appears as a ‘boxed warning’ rather than as a contraindication. Clinicians in the USA are now faced with a difficult situation: any complication associated with non-urgent use of succinylcholine would permit an attorney to argue that the clinician was sufficiently warned to avoid its use.

Malignant hyperthermia

The most significant problem associated with succinylcholine is malignant hyperthermia, a potentially fatal response that occurs rarely when both succinylcholine and a potent inhalation anaesthetic agent are given, and even less frequently when only one of these drugs is used. Of note, the sequence in which the two drugs is given is critical: malignant hyperthermia is more likely when the inhalation agent precedes succinylcholine. In the USA, the most common paediatric practice is to induce anaesthesia with an inhalation agent and then insert an i.v. catheter. This contrasts with the common practice of i.v. induction of anaesthesia for paediatric patients in the UK, possibly as a result of the more common use of EMLA. In that administration of succinylcholine during i.v. induction may not induce the same degree of risk of malignant hyperthermia as during inhalation induction, clinicians in the UK may not need to be as concerned about succinylcholine as their colleagues in the USA. In the USA, given a choice as to whether succinylcholine or potent inhalation agents
such a study). An interesting preliminary report from Dinner (one can imagine the difficulty of performing has been little formal evaluation of these newer drugs in onset of action approaching that of succinylcholine, there of choice for the treatment of laryngospasm. Although newer because succinylcholine has the most rapid onset of action

Masseter muscle rigidity
Of lesser significance than malignant hyperthermia, but occurring with greater frequency, is masseter muscle rigidity (MMR, also known as masseter spasm). In three North American pediatric hospitals, the incidence of MMR during inhalation induction of anaesthesia followed by succinylcholine was 1%, \textsuperscript{2} \textsuperscript{32} \textsuperscript{42} Van der Spek and colleagues\textsuperscript{45} found that succinylcholine routinely tightens the jaw muscles and decreases mouth opening (whereas vecuronium or pancuronium do not) and argued that MMR is nothing more than an extreme variant of the normal effect of succinylcholine. I disagree—if MMR occurs in only 1% of children given halothane and succinylcholine,\textsuperscript{2} \textsuperscript{42} Van der Spek and colleagues cannot conclude this by studying 24 patients. Interestingly, when anaesthesia in children is induced with thiopental rather than halothane, the incidence of MMR is reduced or eliminated.\textsuperscript{31} Thus timing of succinylcholine in relation to halothane again appears to be critical.

Other side effects
The third issue regarding succinylcholine given with halothane is that identified by the FDA—cardiac arrest in a small subset of patients, presumably those with undiagnosed muscular dystrophies, in whom succinylcholine triggers massive muscle breakdown. Succinylcholine can also cause cardiac arrest by increasing vagal tone, leading to bradycardia. This occurs more frequently with second doses of succinylcholine and is probably prevented by atropine pretreatment. Other issues with succinylcholine in children are less important but worthy of mention. Myalgias can occur, but are less likely than in adults. As in adults, succinylcholine increases serum potassium; however, children with myelomeningocele\textsuperscript{12} and cerebral palsy\textsuperscript{11} do not appear to be at risk of the massive hyperkalaemia that occurs in adults with certain neurological lesions.

Laryngospasm
Because succinylcholine has the most rapid onset of action of any neuromuscular blocking agent, it has been the drug of choice for the treatment of laryngospasm. Although newer non-depolarizing neuromuscular blocking agents have an onset of action approaching that of succinylcholine, there has been little formal evaluation of these newer drugs in this setting (one can imagine the difficulty of performing such a study). An interesting preliminary report from Dinner and Ward\textsuperscript{13} demonstrated that mivacurium 0.3 mg kg\textsuperscript{-1} had its initial effect at the vocal cords by 40 s (in contrast with 17 s for succinylcholine 1.5 mg kg\textsuperscript{-1}), suggesting that mivacurium may be a useful alternative to succinylcholine for emergency treatment of laryngospasm; there are no data for rocuronium or rapacuronium. Another important consideration is that the package insert for succinylcholine specifically permits it use to treat laryngospasm.

Availability of mivacurium and rocuronium (and soon rapacuronium) eliminates the need for routine i.v. administration of succinylcholine. The time course of each of these drugs is appropriate for almost all anaesthetics in children. I now routinely use mivacurium 0.3 mg kg\textsuperscript{-1} or rocuronium 0.5–1.2 mg kg\textsuperscript{-1} for routine and rapid sequence induction in infants and children.

Clinical effects of non-depolarizing neuromuscular blocking agents
The choice of which non-depolarizing neuromuscular blocking agent to administer to children should be based on concerns of safety, ease of use and cost (Table 1). Before the patent on pancuronium expired, the cost of a single dose exceeded that of comparable doses of atracurium, vecuronium, mivacurium, cisatracurium or rocuronium. However, the price of pancuronium has now decreased more than 10-fold, making it the least expensive non-depolarizing neuromuscular blocking agent; in addition, its longer duration of action means that fewer supplementary doses need to be given during lengthy procedures. Despite its lower cost, use of pancuronium in pediatric anaesthesia has decreased markedly. This is probably because many procedures in children are short—comparable with the time course of newer neuromuscular blocking agents—thereby popularizing the use of newer drugs.

Another consideration in selecting neuromuscular blocking agents is their effect on the cardiovascular system. Pancuronium typically increases heart rate; cisatracurium, vecuronium, and rocuronium have minimal effects; and atracurium\textsuperscript{1} and mivacurium may cause hypotension because of histamine release. Fortunately, infants and children typically tolerate any of these cardiovascular effects well. If the anaesthetic technique (e.g. fentanyl) decreases heart rate or if bradycardia is considered highly undesirable (as in the neonate), the tachycardia produced by pancuronium may be beneficial; alternatively, some clinicians precede vecuronium with atropine to induce tachycardia before tracheal intubation.

These neuromuscular blocking agents also differ in elimination pathways. Pancuronium, which is eliminated mainly by renal excretion, should be used cautiously in patients with renal failure. Vecuronium and rocuronium are eliminated mainly by the liver; despite this, their duration of action (in adults, and presumably in children) is minimally influenced by liver disease.\textsuperscript{24} \textsuperscript{29} Atracurium and cisatracurium have many elimination pathways, including some that do not depend on the kidney or liver,\textsuperscript{15} so duration of action is altered minimally by organ failure. Mivacurium is eliminated by plasma cholinesterase; its recovery is markedly prolonged in those rare (adult, and presumably pediatric) patients with deficient (genetically abnormal) cholinesterase.\textsuperscript{37}

The pediatric patient at risk of aspiration of residual gastric contents represents a particular challenge. Although
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Table 1 Onset, duration, cardiovascular effects, cost and special considerations of non-depolarizing neuromuscular blocking agents in children (listed alphabetically). Doses are my personal preference and, in some instances, exceed those recommended in the package insert. For onset and duration, specific values are omitted because of the difficulty in comparing studies and the influence of anaesthetic technique.

<table>
<thead>
<tr>
<th>Recommended dose (µg kg⁻¹)</th>
<th>Onset</th>
<th>Duration</th>
<th>Cardiovascular effects</th>
<th>Cost</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium 500</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Rare hypotension</td>
<td>Intermediate</td>
<td>Mild erythema common</td>
</tr>
<tr>
<td>Mivacurium 250–400</td>
<td>Intermediate</td>
<td>Short</td>
<td>Rare hypotension</td>
<td>Intermediate</td>
<td>Mild erythema common</td>
</tr>
<tr>
<td>Pancuronium 100</td>
<td>Intermediate</td>
<td>Intermediate–long</td>
<td>Tachycardia, occasional hypertension</td>
<td>Inexpensive</td>
<td>Effect prolonged in renal failure</td>
</tr>
<tr>
<td>Rapacuronium 1500–3000</td>
<td>Rapid</td>
<td>Short–intermediate</td>
<td>Minimal</td>
<td>Not known</td>
<td>Available late 1999 or later</td>
</tr>
<tr>
<td>Rocuronium 500–1200</td>
<td>Rapid</td>
<td>Intermediate</td>
<td>Slight increase in heart rate</td>
<td>Intermediate</td>
<td>Deltoid injection facilitates tracheal intubation</td>
</tr>
<tr>
<td>Vecuronium 100–400</td>
<td>Intermediate (Rapid with large doses)</td>
<td>Intermediate (Long with doses &gt;150 µg kg⁻¹)</td>
<td>Absent</td>
<td>Intermediate</td>
<td></td>
</tr>
</tbody>
</table>

Fig 3 In children, increasing the dose of vecuronium shortens time to 95% twitch depression and increases time to 25% recovery of twitch tension⁴³ (clinical duration). Succinylcholine (Succinyl.) is shown for comparison. Values are mean (SD).

neuromuscular blocking agents have a faster onset (defined as time to 100% depression of twitch tension in the adductor pollicis muscle) in infants than in adults, the tolerable apnoeic period is shorter in younger patients (because the ratio of oxygen consumption to functional residual capacity is larger); this must be considered in choosing between succinylcholine (with the risks mentioned above) and a non-depolarizing blocker.

Onset of pancuronium 0.15 mg kg⁻¹ is only slightly slower than that of succinylcholine 1 mg kg⁻¹ (80 vs 52 s in children);⁹ however, this large pancuronium dose yields prolonged paralysis. A smaller (and more typical) pancuronium dose of 0.1 mg kg⁻¹ is too slow in onset (151 s)⁹ to be appropriate for rapid i.v. induction. Onset of vecuronium 0.07 mg kg⁻¹ is 1.5 min in infants and 2.4 min in children; times to 90% recovery after these doses are 73 and 35 min in infants and children, respectively.²⁰ Increasing the dose shortens onset time⁴³ (but increases duration of action): in children, onset of vecuronium 0.4 mg kg⁻¹ is similar to that of succinylcholine (Fig. 3). Surprisingly, the onset of action of atracurium is not more rapid in infants and children than in adults.¹

Mivacurium 0.25 mg kg⁻¹ has an onset of mean 1.1 (SD 0.3) min and a clinical duration (time to 25% recovery) of 13.6 (3.9) min during halothane anaesthesia.⁴¹ During opioid anaesthesia, onset is 1.6 (0.4) min and duration 9.1 (2.6) min.⁴¹ The onset of action of rocuronium is even faster: during halothane anaesthesia, rocuronium 0.8 mg kg⁻¹ has an onset of 28 (9) s and a clinical duration of 32 (12) min.³⁶ A dose of rocuronium 0.6 mg kg⁻¹ depressed twitch tension by 90% (at which time the trachea can presumably be intubated) at 0.8 (0.3) min and 100% at 1.3 (0.7) min; clinical duration was 27 (7) min.⁴⁶

Organon’s newest neuromuscular blocking agent, rapacuronium (identified during clinical studies as ORG9487) is presently being evaluated in paediatric patients. In adults, its onset is nearly comparable with that of succinylcholine⁴⁷ and its duration of action is comparable with or less than that of mivacurium.²⁷ Preliminary data in children show a rapid onset and short duration. These initial data suggest that, with i.v. administration, rapacuronium rivals succinylcholine in its time course. It is likely that this compound will be available for clinical use in the USA late in 1999 and shortly thereafter in the UK.

The decision as to which neuromuscular blocking agent to give for rapid sequence induction lies between
succinylcholine (which has the fastest onset but may produce serious adverse effects) and mivacurium, rocuronium or rapacuronium. I use either mivacurium or rocuronium with consistent success. However, I recognize that, in addition to i.m. administration to treat laryngospasm, rapid sequence induction may represent one of the few roles remaining for succinylcholine. The clinician should also remember to flush thiopental through the i.v. tubing before giving rocuronium: thiopental precipitates when mixed with rocuronium (as with vecuronium), potentially occluding the tubing.

**Antagonism of paralysis**

Neostigmine was used traditionally to antagonize neuromuscular block in children and, despite little investigation of this drug, it was claimed that paediatric patients required larger doses (0.07 mg kg\(^{-1}\)) than adults (typically 2.0–3.5 mg/70 kg).\(^6\) A study from our laboratory contradicts this belief: neostigmine dose requirements are smaller in paediatric patients than in adults.\(^18\) Nevertheless, I rarely give neostigmine to children; I prefer edrophonium because of its more rapid onset. The \(ED_{50}\) (dose producing 50\% effect) of neostigmine for antagonism of tubocurarine-induced neuromuscular block is greater and somewhat more variable for infants and children than for adults.\(^18\) As a result, I recommend a larger dose of edrophonium for paediatric patients (1.0 mg kg\(^{-1}\)) than for adults (0.5 mg kg\(^{-1}\)).\(^7\) Extensive clinical experience indicates that this edrophonium dose is appropriate for antagonism of intermediate-duration non-depolarizing neuromuscular blocking agents.

Cardiovascular changes induced by edrophonium are minimized by giving atropine 10 \(\mu g\) kg\(^{-1}\) during halothane anaesthesia\(^9\); the dose of atropine should be 15 \(\mu g\) kg\(^{-1}\) during opioid anaesthesia. Atropine should be given 30 s before edrophonium\(^9\) because the vagotonia of edrophonium precedes the vagolysis of atropine. These doses of atropine may not induce tachycardia, but they do prevent bradycardia. The major advantage of edrophonium over neostigmine is its rapid onset—its effect peaks at approximately 2 min compared with 10 min with neostigmine (with both drugs, clinical effects precede these times to peak effect).

Edrophonium may not be the optimal antagonist if the patient has profound neuromuscular block (>95\% block) at the time of antagonism. In this situation, usual doses of edrophonium may not produce adequate antagonism\(^40\) and neostigmine may be more effective.

One final issue in respect of antagonism of mivacurium. Several studies demonstrated that both edrophonium and neostigmine impaired the elimination of mivacurium\(^23\) \(^44\) and that neostigmine may actually prolong recovery.\(^28\) Until this issue is resolved, I recommend not antagonizing profound mivacurium-induced paralysis. Instead, the clinician should wait until twitch tension has recovered partially before administering an antagonist.

If the anaesthetist uses clinical signs to assess neuromuscular function before tracheal extubation, the sign typically assessed in adults (sustained head lift) cannot reasonably be expected from neonates and infants. Instead, when infants can sustain bilateral leg lifts, they have adequate neuromuscular function.\(^34\)

**I.m. administration of non-depolarizing neuromuscular blocking agents**

In the USA, succinylcholine is often given i.m., either to treat laryngospasm or to facilitate routine tracheal intubation. Although onset of succinylcholine i.m. is reasonably rapid, the magnitude and time to peak effect are variable. For example, Liu and colleagues\(^35\) reported that succinylcholine 2–3 mg kg\(^{-1}\) i.m. occasionally produced minimal twitch depression. In addition, time to peak effect with doses of 2–4 mg kg\(^{-1}\) averaged approximately 4 min. This contrasts with the clinical observation that tracheal intubation can often be accomplished earlier.

Several investigators examined whether non-depolarizing neuromuscular blocking agents can be given i.m. Initial studies were disappointing. Iwasaki and colleagues\(^25\) gave pancuronium s.c. to adults and observed delayed onset and prolonged duration. Jöhr and Can\(^26\) reported that the onset of atracurium 0.375 mg kg\(^{-1}\) i.m. was 10 min. The moderately rapid onset of mivacurium i.v. (especially when given in larger than recommended doses) and its brief duration of action, suggested that it might work when given i.m. However, Cauldwell, Lau and Fisher\(^3\) demonstrated that onset of mivacurium i.m. at the adductor pollicis is slow (>10 min), despite administration of doses as large as 0.8 mg kg\(^{-1}\). Recognizing that the time course of the adductor pollicis differs from that of the respiratory muscles (the laryngeal adductors and the diaphragm), an ideal study would have measured laryngeal tone.\(^14\) However, these measurements require a tracheal tube positioned with its cuff at the vocal cords. Instead, Cauldwell, Lau and Fisher\(^3\) estimated strength of the respiratory muscles indirectly by measuring minute ventilation during spontaneous ventilation, assuming that a 50\% decrease in minute ventilation would indicate onset of diaphragmatic paralysis. Time to ventilatory depression exceeded 5 min even with large doses of mivacurium.

Studies with rocuronium i.m. were more successful. Reynolds and colleagues\(^38\) reported that doses of rocuronium 1.0 mg kg\(^{-1}\) in infants and 1.8 mg kg\(^{-1}\) in children permitted tracheal intubation in 3–4 min, despite a light plane of anaesthesia. However, time to initial recovery of twitch tension often exceeded 1 h, limiting its use for the majority of paediatric procedures with a duration <60 min.

In that onset of rapacuronium is more rapid than that of rocuronium and its duration of action is shorter, clinical studies of rapacuronium i.m. seem appropriate. These studies are presently being conducted and indicate that tracheal intubation can probably be accomplished.
approximately 1 min earlier than with rocuronium i.m. and twitch tension recovery begins at 30–45 min. If additional studies are consistent with these initial findings, I expect that rapacuronium i.m. will be used widely in paediatric anaesthesia.

**Summary**

Neuromuscular blocking agents are used commonly in paediatric anaesthesia, both to facilitate tracheal intubation and during surgery. Paediatric patients differ from adults in certain pharmacokinetic and pharmacodynamic characteristics. However, because maturational changes in certain of these characteristics counterbalance, dosing requirements do not differ markedly with age. In general, onset is more rapid in paediatric patients than in adults.

Succinylcholine is still used commonly in children, despite restrictions by regulatory authorities, because of its rapid onset and offset. However, newer non-depolarizing neuromuscular blocking agents, particularly mivacurium, rocuronium and rapacuronium, offer many of the advantages of succinylcholine without its severe adverse effects: rocuronium and rapacuronium have an onset comparable with that of succinylcholine whereas the onset of mivacurium is slightly longer. In addition, recovery from an intubating dose of either mivacurium or rapacuronium is nearly comparable with that of succinylcholine. If rapacuronium i.m. proves to have a rapid onset without prolonged duration, the remaining value of succinylcholine will diminish.

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