New Developments in Nondepolarizing Muscle Relaxants

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Anesthesiologists perceive that the ideal muscle relaxant is not yet available, particularly the nondepolarizing one with a rapid onset and a short duration of action. There is also a need for relaxants with different durations of action but which would be free from side effects. During the process of this development several new compounds have been tested and four have reached an advanced state of study; three of these, doxacurium, pipecuronium, and mivacurium are already licensed and rocuronium is likely to be licensed in the near future. Doxacurium and pipecuronium are slow onset and long duration of action compounds but singularly free from cardiovascular side effects. Mivacurium has an onset comparable to that of atracurium and vecuronium but with a duration of action which is intermediate in duration between these drugs and succinylcholine. Rocuronium is a drug with a fast onset of action capable of being used in place of succinylcholine but with a duration of action which is similar to that of vecuronium.

Nondepolarizing relaxants have been an integral part of anesthetic practice ever since the introduction of curare in 1942. These agents act predominantly by competing with Achb for the postsynaptic receptor. Occupation of even only one of the binding sites on the receptor complex by these agents prevents Ach from opening the ion channel and initiating the process that ultimately leads to muscle contraction. The blocking drug does not remain in contact with the receptors but like Ach keeps on associating and dissociating from it [1]. The neuromuscular blocking drug does, therefore, not prevent the interaction of Ach with the receptor but merely reduces the chances of it doing so; this is the basis of the reversible block by competition [1]. Nondepolarizing neuromuscular blockers also exert varying degrees of effect on the prejunctional cholinceptors and this is reflected by fade in response to the train-of-four and tetanic stimulations [2]. Only in large doses do relaxants produce true ion channel block.

New muscle relaxants have been developed and introduced at regular intervals in order to meet the criteria of an ideal neuromuscular blocking agent. Although an ideal muscle relaxant has been defined as an agent with non-cumulative, nondepolarizing action, with rapid onset and recovery, Savarese and Kitz [3] have suggested that clinical anesthesia needs three different types of nondepolarizing neuromuscular agents, rapid and short-acting, intermediate acting and long-acting. These would fill the needs of different durations of surgery. Within all three categories of relaxants absence of side effects is a desirable feature.

The introduction of pancuronium in 1967 was a major breakthrough in the development of neuromuscular blocking agents. This was one of the few agents which was not associated with any significant histamine liberation or ganglion blockade, thus providing an agent with significant cardiovascular advantages [4]. Although pancuronium has been a very popular muscle relaxant since then, it has in common with d-tubocurarine a rela-

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bAbbreviations used: Ach, acetylcholine.
tively slow onset and a long duration of action. In addition some consider the cardiovascular stimulating effects of pancuronium undesirable [5]. The early 1980's saw the introduction of atracurium and vecuronium, the two most commonly used neuromuscular blocking agents in the UK and probably the rest of Europe [6]. These, however, fulfilled only the group described by Savarese and Kitz as "intermediate duration agents." A common shortcoming of both these drugs is that neither approach the speed of onset or duration of action of succinylcholine. Since atracurium and vecuronium have been well described in the literature and have admirably fulfilled the intermediate duration category of muscle relaxant these will not be described here any more. Instead, this review will focus on two longer-acting agents, doxacurium and pipercuronium, and two other agents, mivacurium and rcuronium, which have been designed in an effort to fulfill the criteria required of a short duration and fast action nondepolarizing drug.

**Doxacurium chloride**

Doxacurium is a bisquaternary benzylisoquinolinium compound which has been approved for use in the United States since 1991. It is currently the most potent nondepolarizing neuromuscular blocking agent available with an estimated $ED_{95}$ of approximately $30 \mu g/kg$ [7, 8].

The onset and duration of action of doxacurium are characteristic of a slow and long-acting drug. Onset times are very variable and show a lot of individual variability. Doses equal to $1 \times ED_{95}$ have been reported to produce maximum block in times ranging from 3 to 13 min, with a duration of clinical relaxation of between 30 min and over 1.5 hrs [8, 9]. The onset of action is faster, with less variability and in the region of about 4–5 min if the dose is increased to 40–60 $\mu g/kg$. However, this is at the expense of a further increase in the duration of clinical relaxation [7, 10]. Increasing the dose further to 80 $\mu g/kg$ results in a duration of clinical relaxation of over 2.5 hrs [11]. Because of such a long duration of action, it is likely that doxacurium will cumulate although there are no data to support this because the effect of even a single dose lasts quite a long time. Because of the slow onset of action, doxacurium is not suitable for facilitating intubation within 2–3 min of administration of the drug.

Although antagonism of doxacurium block by neostigmine is satisfactory provided adequate spontaneous recovery has taken place, the time taken to achieve adequate antagonism is extremely variable and may take more than 20 min, even when greater than 25% recovery of the twitch has taken place [7, 8]. If antagonism is attempted at very deep levels of block, it is perhaps inadequate and extremely slow. For this reason, it is advocated that doxacurium block is not antagonised unless considerable spontaneous recovery has taken place.

The elimination half-life of doxacurium has been reported to vary between 86 and 99 min, but this is considerably prolonged in patients with renal failure [12, 13]. The same authors have described the rate of clearance to be between 0.13 and 0.16 L/kg/hr and the volume of distribution of 0.15–0.22 L/kg in adult subjects with a dose of 25 $\mu g/kg$. The volume of distribution may be increased in the elderly and in those with hepatic and renal failure. Patients with renal failure show a markedly increased mean residence time, but those with liver failure show only moderate increase both in the mean residence time as well as the duration of action. The increased duration of action of doxacurium in patients with renal failure has been confirmed in a study reported by Cashman et al. [14].

A singular property of doxacurium chloride is the lack of any significant cardiovascular effects. In fact, it appears that this is the only advantage of this drug in clinical use. This has been confirmed by detailed hemodynamic studies which have shown no significant changes in mean arterial pressure or cardiac index with doxacurium, in contrast to a
significant increase in these parameters following pancuronium and a small, but significant decrease following vecuronium [15, 16]. There may, however, be some reduction in heart rate which, though statistically significant, is of little clinical consequence. Doxacurium is generally free from causing any increase in plasma histamine levels, although a case with transient systemic arterial hypotension and cutaneous flushing has been reported [17].

The commonly used doses of doxacurium range from 25 to 50 μg/kg.

**Pipecuronium bromide**

Pipecuronium bromide, in contrast to doxacurium chloride, is a bisquaternary steroidal neuromuscular blocking agent originally used in Hungary [18]. In recent years, the drug has been investigated in the Western world and recently introduced in the USA. The potency of pipecuronium in terms of its ED$_{95}$ is approximately 45 μg/kg using mechanomyography, although the ED$_{95}$ has been reported to be somewhat higher at just under 60 μg/kg using electromyography [19, 20].

The neuromuscular blocking effects of pipecuronium are dose-dependent, higher doses leading to shorter onset times and longer durations of action. A dose of 45 to 50 μg/kg produces maximum block in 3.5 to 5 min and has a duration of clinical relaxation of approximately 40 min [20–22]. The onset of block is significantly shorter at 2 to 2.5 min following a dose of approximately 2 x ED$_{95}$, but with a duration of clinical relaxation which is close to 2 hrs [22, 24]. Although similar durations of effect have been reported with up to three repeat doses of the agent, it is likely that the drug will cumulate over a period of time once given in repeated doses. It is difficult, as with doxacurium, to determine the cumulative potential of a very long-acting drug. Pipecuronium, like doxacurium, is not suitable for situations where intubation needs to be carried out rapidly although the conditions have been described as good or excellent at 3 min following a dose of 70 μg/kg [24].

The antagonism of neuromuscular block with neostigmine can be carried out satisfactorily as long as there is spontaneous recovery in excess of 20% or so [25]. The recovery occurs at a relatively slow speed and adequate antagonism may take more than 10 min., particularly if anesthesia has been maintained with isoflurane [26]. Edrophonium appears to be an unreliable and ineffective antagonist [25]. The neuromuscular effects of pipecuronium, therefore, do not provide any advantage over agents like pancuronium.

Like doxacurium, the main virtue of pipecuronium appears to be cardiovascular stability. In a comparative study of pancuronium and pipecuronium, there was an increase of 22% in heart rate and significant increases in mean arterial pressure, cardiac index, and rate-pressure product following administration of pancuronium, whereas these parameters showed very little change following the administration of pipecuronium in patients undergoing coronary artery surgery [27]. Cardiovascular stability is generally maintained even with doses as high as 200 μg/kg, although there may be some reduction in cardiac output [28].

As with doxacurium, the elimination half-life of pipecuronium is in the region of 2 hrs and is almost doubled in patients with significant renal failure [29]. The steady-state volume of distribution is similar to that of doxacurium at about 300 mL/kg increasing somewhat in patients with renal failure. The clearance is reduced in patients with renal dysfunction [29]. Although this increase in elimination half-life and reduced clearance was not associated with a significant increase in duration of clinical relaxation in the study of Caldwell et al., the patients with renal dysfunction showed extremely large inter-patient variability. The effects of pipecuronium may also be prolonged in patients with
significant hepatic disease.

In conclusion, therefore, pipecuronium, like doxacurium, appears to be an agent which resembles pancuronium in its neuromuscular effects. The main advantage of this drug is in its cardiovascular stability which might be an advantage in patients with cardiovascular disease undergoing prolonged surgery. The usual clinical dose is 50–80 μg/kg.

**Mivacurium chloride**

This agent is a bisquaternary benzylisoquinolinium compound which resembles atracurium in its structure. The drug has been recently released for use in the US, the UK, and parts of Europe.

The ED₉₅ of mivacurium has been shown to vary between 60 and 80 μg/kg depending upon the anesthetic technique used and the method of stimulation applied [30–32]. As with other muscle relaxants, the onset of block following mivacurium administration is dose-related. It varies between 2 and 4 min after doses of mivacurium varying from 0.1 to 0.25 mg/kg [30, 33]. These times are similar to those observed after equipotent doses of atracurium but longer than the onset time of succinylcholine. The duration of clinical relaxation is 15–20 min following doses of 0.1 to 0.2 mg/kg with complete spontaneous recovery taking up to 30 min with a dose of 0.2 mg/kg [30, 33]. The duration of action is also dose-related, although not as marked as observed with other neuromuscular blocking agents. The duration of action is roughly half that of atracurium and vecuronium and 2 to 3 times that of succinylcholine [34].

Although intubating conditions at 1.5 to 2 min following 0.2 mg/kg of mivacurium were initially reported to be good, some studies have subsequently shown that the best intubating conditions may be obtained at 2.5 to 3 min following administration of this dose or at 2 min with a dose of 0.25 mg/kg [33, 35]. As mivacurium is metabolised by plasma cholinesterase, it has been suggested that antagonism of residual block is rarely required [30]. However, if required, neostigmine or edrophonium can be administered to get a more rapid recovery [35]. It is believed that there is an inverse relationship between plasma cholinesterase activity and the duration of mivacurium block. Moreover, dependence of the agent on plasma cholinesterase for metabolism can result in prolonged neuromuscular block in patients with abnormal enzymes [36–38].

Because of a shorter duration of action it is more convenient to administer mivacurium as a continuous infusion for surgery which is longer than a few minutes. The dose of mivacurium necessary for maintaining a 90 to 95% block is 4–8 μg/kg/min, depending upon the anesthetic used [35, 39, 40].

Mivacurium has been found to consist of a mixture of three stereoisomers, the equipotent and most active cis-trans and trans-trans isomers as well as the markedly less active cis-cis isomer. It is believed that the last of these isomers contributes little to the neuromuscular blocking effect of mivacurium. The rate of clearance of mivacurium is very high at 12.2 L/kg/hr and this is consistent with its short duration of action. The elimination half-life of the two active isomers has been given as 2.1 and 2.3 min, respectively, with very high rates of clearance of 4.2 and 8.3 L/kg/hr [41, 42]. Mivacurium is associated with a prolonged half-life and prolonged duration of action in patients with liver disease as well as in patients with renal disease, although not to the same extent as other relaxants [43, 44]. The effects are believed to be mainly due to reduction in plasma cholinesterase activity.

Although mivacurium is associated with good cardiovascular stability when used in doses of up to 0.15 mg/kg, doses higher than this may cause a transient decrease in arterial pressure due to histamine liberation, an effect which can be reduced by slow administration of the drug [45]. Similar changes have been observed using more detailed hemo-
dynamic monitoring in patients undergoing coronary artery surgery [46].

In summary, therefore, mivacurium appears to be an agent with a shorter duration of action although not as short as that of succinylcholine but with an onset of action which is similar to that of other intermediate acting agents. The drug may be, therefore, useful for outpatient surgery when there is no need for rapid tracheal intubation. The usual clinical initial dose is 0.15–0.2 mg/kg.

Rocuronium (ORG 9426)

Rocuronium is a desacetoxy derivative of vecuronium and is a monoquaternary steroidal neuromuscular blocking agent. The potency, in terms of ED₉₅ is approximately 300 µg/kg making it a relatively low potency compound [47, 48]. This low potency is a deliberate design feature of the drug which is believed to result in a more rapid onset of effect as it provides for delivery of more molecules of the drug to the neuromuscular junction [49]. Doses of approximately 2 x ED₉₅ (0.6 mg/kg) have been reported to produce maximum block in about 1.5 min with a duration of action which is similar to that of vecuronium and takes about 30 min for recovery of T1 to 25% [50]. Doses greater than this and in the region of 0.9 mg/kg have been reported to produce complete block in about 45 sec, with a duration of clinical relaxation of 45–50 min [51]. The rapid onset of block is associated with provision of good to excellent intubating conditions within 60 to 90 sec [50]. The conditions are not significantly different when compared with suxamethonium [50]. The reversibility of the agent has been described to be easy [47].

With a rapid onset of effect and a duration of action similar to that of vecuronium the agent has been found to be useful for use by continuous infusion [52]. The required dose by infusion is approximately 10 µg/kg/min.

Routine cardiovascular measurements carried out in the course of neuromuscular block have suggested no significant cardiovascular effects with doses of 0.5 to 0.6 mg/kg [51]. Previous studies in dogs have suggested that doses of greater than 5 x ED₉₅ may increase the heart rate significantly [53]. A more recent detailed cardiovascular study comparing vecuronium and rocuronium in equipotent doses (2 x ED₉₅) in patients undergoing coronary artery bypass surgery under high dose fentanyl anesthesia have shown an increase of 1 to 7% in heart rate with the use of rocuronium and a similar change in the other direction with vecuronium [54]. These workers also showed a small but statistically significant increase in cardiac index with the use of 0.6 mg/kg rocuronium. All the cardiovascular changes however are within acceptable clinical limits. The agent has not been shown to have any significant histamine liberating effect with doses of up to 4 x ED₉₅ [55].

The elimination half-life of rocuronium has been observed to be approximately 97 min. in normal patients, with a slight but insignificant increase in patients with renal failure who however showed a reduced clearance and an increased mean residence time [56]. This is also associated with a greater variability of clinical relaxation in patients with renal disease. A more marked prolongation of the effect has been reported in patients with liver disease [57]. Rocuronium would, therefore, appear to be an agent with a duration of action similar to that of vecuronium but with an onset which is much more rapid and closer to that of succinylcholine. As a result, the intubating conditions with its use have been described to be similar to those of succinylcholine. The drug is still undergoing clinical evaluation and is not yet licensed for general use. The clinical dose is likely to be 0.6 mg/kg.

The main neuromuscular features of these agents are summarised in Table 1.

In summary, the anesthesiologist now has the long and the intermediate duration relaxants which are relatively free from side effects [58]. We now have a fast acting non-
Table 1. Main neuromuscular features of the new relaxants in comparison to pancuronium, atracurium and vecuronium.

|               | ED$_{50}$ (µg/kg) | Intubating dose (mg/kg) | Onset time of the intubating dose (min) | Duration of clinical relaxation (min) |
|---------------|-------------------|-------------------------|----------------------------------------|---------------------------------------|
| Doxacurium    | 30                | 0.03–0.05               | 5–10                                   | 50–150                                |
| Pimecuronium   | 45                | 0.05–0.07               | 4–7                                    | 45–100                                |
| Mivacurium     | 70                | 0.15–0.2                | 2–4                                    | 15–20                                 |
| Rocuronium     | 300               | 0.5–0.6                 | 1–2                                    | 25–35                                 |
| Pancuronium    | 60                | 0.08–0.1                | 3–5                                    | 50–100                                |
| Atracurium     | 225               | 0.4–0.5                 | 2–4                                    | 25–35                                 |
| Vecuronium     | 40                | 0.08–0.1                | 2–4                                    | 25–35                                 |

The variability in the onset times and the duration of clinical relaxation is greater in agents which are slower in onset and longer acting.

depolarizing relaxant and a relatively shorter acting nondepolarizing relaxant but not the one which has both these properties.

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