Long-acting nondepolarizing neuromuscular blocking agents

PATRICIA B. EMBREE, CRNA
Ashland, Massachusetts

Patients with compromised cardiovascular function who are undergoing cardiothoracic or other lengthy surgical procedures are at risk of complications from the hemodynamic effects of the long-acting nondepolarizing neuromuscular blocking agents (NMBs), which have been in use for several decades. The development of agents that maintain a stable hemodynamic profile is a potential advantage to this patient population.

This literature review, which was completed in May 1992, describes the profiles of doxacurium and pipecuronium, two recently developed long-acting NMBs with increased potency over d-tubocurarine, metocurine, and pancuronium. Doxacurium is a benzylisoquinolinium compound with an ED₉₅ of 0.025 mg/kg. Pipecuronium, a steroidal agent, has an ED₉₅ of 0.04 mg/kg. Twice the ED₉₅ of either agent produces a duration of action comparable to that with 2 times ED₉₅ of pancuronium, but neither doxacurium nor pipecuronium possesses vagolytic or histamine-releasing properties at therapeutic doses.

Although no significant differences in serum elimination half-life or plasma clearance of doxacurium have been noted between young and elderly patients, as with other NMBs, the duration of action of doxacurium may be somewhat prolonged and seems to be more variable in older patients and in patients with impaired hepatic or renal function. A similar pattern appears to occur with pipecuronium. Children seem to require higher doses of doxacurium than adults to achieve the same degree of neuromuscular block but recover from the effects more rapidly.

Doxacurium and pipecuronium produce no dose-dependent or clinically significant changes in heart rate, mean arterial pressure, or cardiac output either in patients with normal cardiac function or in those with coronary artery disease. For prolonged cardiovascular procedures, the increased potency and cardiovascular safety profiles of these newer, long-acting nondepolarizing agents provide attractive alternatives to other compounds currently available.

Key words: Cardiac patients, doxacurium, neuromuscular blocking agents, pipecuronium.

Introduction

The introduction of succinylcholine and d-tubocurarine as neuromuscular blocking agents (NMBs) represented historic landmarks in anesthesia and paralleled cardiothoracic surgical advances during the 1950s.¹ However, their hemody-
namic effects were a disadvantage and posed a special risk to patients with cardiovascular disorders. Recent research has emphasized the development of alternative agents that would provide adequate neuromuscular block without clinically significant cardiovascular effects. Such research has produced nondepolarizing muscle relaxants with varying durations of action in both the steroidal and benzylisoquinolinium classes.

**History**

Steroidal NMB development began in the 1960s with the formulation of pancuronium, a long-acting agent with increased neuromuscular blocking potency but without the propensity to cause hypotension or stimulate histamine release. Pancuronium became the most popular nondepolarizing NMB during the 1970s. Because of its autonomic actions, however, pancuronium may cause tachycardia and related hypertension, possibly increasing the complication risk for certain patients with coronary artery disease. Anesthetists soon recognized the need for nondepolarizing, reversible NMBs free of cardiovascular effects: short-acting agents to replace succinylcholine, intermediate-acting drugs for versatility in a variety of surgical procedures, and long-acting agents to replace curare.

Modification of pancuronium's chemical structure removed the vagolytic moiety and produced compounds virtually free of cardiovascular effects: vecuronium, an intermediate-acting relaxant; rocuronium, an intermediate-acting vecuronium analog; and pipecuronium, a long-acting agent. Alterations in the structures of the older benzylisoquinoliniums reduced their histamine-releasing potential and produced atracurium, an intermediate-acting agent. High doses of atracurium administered rapidly may stimulate histamine release, causing a decrease in blood pressure and an increase in heart rate. Therefore, other benzylisoquinolinium structures were considered for clinical use. Two of these compounds were (1) doxacurium, a long-acting agent free of cardiovascular side effects at clinically relevant doses, and (2) mivacurium, a short-acting agent metabolized by plasma cholinesterase.

**Discussion**

Perioperative hemodynamic changes are related to many factors. For patients with heart disease, hemodynamics are affected by preexisting conditions and preoperative medications, as well as by induction and maintenance agents. Administration of an NMB free of cardiovascular effects may minimize the need for vasoactive agents to maintain hemodynamic stability during surgery. This type of relaxant would be beneficial not only for the patient undergoing cardiac surgery but also for the cardiac patient undergoing prolonged noncardiac surgery. These agents might also be considered for the patient with an incomplete or unknown cardiac history.

Both doxacurium and pipecuronium have a duration of action similar to that of pancuronium and exhibit excellent hemodynamic stability. At clinically relevant doses, neither doxacurium nor pipecuronium caused tachycardia, hypotension, or histamine release.

**Pharmacokinetics.** Following a dose of 0.015 or 0.025 mg/kg during isoflurane anesthesia, healthy adult surgical patients (n < 10) had mean doxacurium elimination half-lives ($t_{1/2}$) of 99 and 86 minutes, respectively, similar to those of other nondepolarizing NMBs. The mean corresponding plasma clearance rates were 2.7 and 2.2 mL/kg/min (Table I). Approximately 30% of the dose was excreted unchanged in the urine in 6 to 12 hours. A pipecuronium dose of 0.07 mg/kg had an elimination half-life of 137 minutes and was cleared from the plasma at a rate of 2.4 mL/kg/min during halothane anesthesia. Clearance and elimination half-life of both doxacurium and pipecuronium in elderly patients were not significantly different from those in younger individuals (Table I).

Although the steady-state volume of distribution ($V_{ds}$) of doxacurium in patients with impaired renal function was not significantly different from that of individuals with normal renal function during isoflurane anesthesia (Table I), the clinical duration (time to 25% recovery) appeared to be longer. Pipecuronium was also cleared more slowly in patients with renal failure. As a result, the duration of action of both long-acting NMBs may be prolonged and variable in the patient with renal failure.

Since pancuronium is eliminated through both biliary and renal excretion, its clearance and elimination half-life are significantly altered, resulting in a prolonged block in patients with liver disease. Doxacurium, on the other hand, is eliminated primarily by the kidneys; therefore, hepatic failure does not significantly affect its pharmacokinetics. Values for clearance and elimination half-life for the hepatic failure patient increased slightly but remained within the normal range (Table I). The clearance of pipecuronium may also be prolonged by hepatic dysfunction.

**Pharmacodynamics.** The potency of pipecuronium is approximately one and one-half times that of its analog pancuronium, whereas the potency of doxacurium is two to three times greater.
than that of pancuronium. As a result, the calculated doxacurium ED$_{95}$ during balanced anesthesia was approximately one-half that of the pipecuronium ED$_{95}$ (0.023-0.03 versus 0.04-0.06 mg/kg). After administration of equipotent doses (1.5 times ED$_{95}$), the onsets of action of pancuronium and pipecuronium were comparable, while that of doxacurium was slower. However, time to 25% recovery (clinical durations) of the three agents appeared similar (Table II).

Maximum twitch suppression was achieved in 2.5 and 2.8 minutes after a dose of 0.08 mg/kg of pipecuronium and 0.1 mg/kg of pancuronium; time to 25% recover after these doses was 91 and 107 minutes, respectively. Comparison of 0.04 mg/kg of doxacurium and 0.1 mg/kg of pancuronium reported onset times of 6.5 and 2.4 minutes, respectively. The corresponding clinical durations were 78 minutes for doxacurium and 83 minutes for pancuronium. Both the onset of maximum block and the clinical duration of doxacurium and pipecuronium appeared to be dose-dependent (Table II).

Patients receiving chronic anticonvulsant therapy seemed slightly resistant to and recovered more quickly from doxacurium- and pipecuronium-induced block. Although several studies have demonstrated this interaction with other NMBs, the exact mechanism for this phenomenon is unknown.

In clinical practice, NMBs are frequently administered during the early stages of recovery from succinylcholine. There were no significant differences in either the onset or duration of action of doxacurium, whether it was administered alone or at 10% or 95% recovery from succinylcholine. Patients who were given pipecuronium at 75% recovery from succinylcholine experienced a shorter onset of block than those given pipecuronium alone.

Following an initial bolus dose, patients may require additional doses of an NMB, depending on the length of the procedure. Over the years, there has been some debate about the cumulative effect of pancuronium seen with multiple-dose administration. In clinical studies, the interval between maintenance doses of doxacurium or pipecuronium appeared consistent, suggesting a lack of cumulative effects.

Rapid reversal of doxacurium or pipecuronium-induced neuromuscular block was easily achieved during balanced anesthesia with neostigmine and atropine or glycopyrrolate administered at recovery greater than 25%. However, as with pancuronium, reversal of deep block (<25% recovery) induced by doxacurium or pipecuronium may require additional time for full recovery.

Effect of inhalation agents on pharmacodynamics. Neuromuscular block produced by nondepolarizing muscle relaxants is enhanced by inhalation anesthetics, the extent of which varies with the anesthetic used. Patterns similar to those shown with previously available agents were found with doxacurium and pipecuronium-induced block. Initially, it was noted that the doxacurium cumulative dose-response curve shifted to the left by 43% with enfurane, 31% with isoflurane, and 20% with halothane, reflecting a decrease in the calculated ED$_{95}$. However, the onset and duration of doxacurium block after administration of the ED$_{95}$ did not differ during anesthesia with any of the three inhalation agents. Administration of 2 times ED$_{95}$ produced a more rapid onset (5-7 minutes) and a longer duration (106-109 minutes) with all three

### Table I

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent/Population</th>
<th>Number</th>
<th>Dose (mg/kg)</th>
<th>$t_{1/2}$ (min)</th>
<th>Vd$_{ss}$ mL/kg</th>
<th>Clearance (mL/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dresner et al$^6$</td>
<td>Doxacurium</td>
<td>8</td>
<td>0.025</td>
<td>86</td>
<td>150</td>
<td>2.22</td>
</tr>
<tr>
<td></td>
<td>Young (22-49 yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elderly (67-72 yr)</td>
<td>8</td>
<td>0.025</td>
<td>96</td>
<td>220</td>
<td>2.47</td>
</tr>
<tr>
<td>Matteo et al$^{10}$</td>
<td>Pipecuronium</td>
<td>9</td>
<td>0.07</td>
<td>113</td>
<td>417</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Young (27-59 yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elderly (70-82 yr)</td>
<td>10</td>
<td>0.07</td>
<td>122</td>
<td>433</td>
<td>2.7</td>
</tr>
<tr>
<td>Cook et al$^7$</td>
<td>Doxacurium</td>
<td>9</td>
<td>0.015</td>
<td>99</td>
<td>200</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic failure</td>
<td>7</td>
<td>0.015</td>
<td>115</td>
<td>290</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>8</td>
<td>0.015</td>
<td>221</td>
<td>270</td>
<td>1.2</td>
</tr>
<tr>
<td>Caldwell et al$^9$</td>
<td>Pipecuronium</td>
<td>20</td>
<td>0.07</td>
<td>137</td>
<td>307</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>20</td>
<td>0.07</td>
<td>263</td>
<td>442</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Effect of inhalation agents on pharmacodynamics. Neuromuscular block produced by nondepolarizing muscle relaxants is enhanced by inhalation anesthetics, the extent of which varies with the anesthetic used. Patterns similar to those shown with previously available agents were found with doxacurium and pipecuronium-induced block. Initially, it was noted that the doxacurium cumulative dose-response curve shifted to the left by 43% with enfurane, 31% with isoflurane, and 20% with halothane, reflecting a decrease in the calculated ED$_{95}$. However, the onset and duration of doxacurium block after administration of the ED$_{95}$ did not differ during anesthesia with any of the three inhalation agents. Administration of 2 times ED$_{95}$ produced a more rapid onset (5-7 minutes) and a longer duration (106-109 minutes) with all three

Journal of the American Association of Nurse Anesthetists
Table II
Comparative pharmacodynamics of neuromuscular blocking agents in normal adults under balanced anesthesia (mean values)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent</th>
<th>Dose (mg/kg)</th>
<th>Time to maximum block</th>
<th>Time to 25% recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>Minutes</td>
<td>Number</td>
</tr>
<tr>
<td>Basta et al(^{14})</td>
<td>Doxacurium</td>
<td>0.015</td>
<td>9</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.02</td>
<td>10</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04</td>
<td>26</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.05</td>
<td>9</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.08</td>
<td>9</td>
<td>3.5</td>
</tr>
<tr>
<td>Murray et al(^{16})</td>
<td>Pancuronium</td>
<td>0.10</td>
<td>8</td>
<td>2.4</td>
</tr>
<tr>
<td>Pittet et al(^{15})</td>
<td>Pipecuronium</td>
<td>0.06</td>
<td>10</td>
<td>12.5</td>
</tr>
<tr>
<td>Larijani et al(^{13})</td>
<td>Pipecuronium</td>
<td>0.07</td>
<td>26</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.085</td>
<td>10</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.10</td>
<td>10</td>
<td>3.0</td>
</tr>
<tr>
<td>Dubois et al(^{18})</td>
<td>Pancuronium</td>
<td>0.10</td>
<td>12</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.08</td>
<td>12</td>
<td>2.8</td>
</tr>
</tbody>
</table>

inhalation agents. Time from 25-75% recovery (recovery index) after administration of the ED\(_{95}\) or 2 times ED\(_{95}\) of doxacurium appeared similar under balanced and inhalation anesthesia.\(^{34}\) Administration of 3 times ED\(_{95}\) (0.08 mg/kg) decreased the onset of doxacurium block during enflurane anesthesia from 5.4 minutes after administration of 2 times ED\(_{95}\) (0.05 mg/kg) to 3.5 minutes, and the duration of action increased from 84.7 to 164.4 minutes.\(^{32}, 34\)

The calculated ED\(_{95}\) of pipecuronium in adults was significantly reduced under isoflurane anesthesia, from 0.06 to 0.04 mg/kg; however, halothane did not appear to influence the effective dose.\(^{15}, 29\) Onset of pipecuronium block was not influenced by enflurane, isoflurane, or halothane anesthesia. Enflurane, but not isoflurane or halothane, significantly prolonged the duration of pipecuronium block from 85-125 minutes.\(^{15, 35}\)

*Effects of age on pharmacodynamics.* Pharmacokinetic differences of long-acting NMBs between young and elderly patients are paralleled by pharmacodynamic differences. However, similar dose regimens for doxacurium and pipecuronium can be administered to both populations. During isoflurane anesthesia in elderly patients, the onset of doxacurium block was longer than in the younger patients (7.8 minutes versus 5.7 minutes), and the duration of action was somewhat prolonged (97.1 minutes versus 67.5 minutes) and more variable.\(^9\) These differences may be caused by changes in pharmacokinetic profiles resulting from increases in initial fluid loading, blood loss, and fluid replacement or by normal physiologic changes in the elderly. The calculated pipecuronium ED\(_{95}\) was comparable in young and elderly populations, approximately 0.035 mg/kg.\(^{35}\)

As with other long-acting nondepolarizing agents, during halothane anesthesia children required higher doses of doxacurium than adults to achieve a comparable degree of block; however, the recovery time in children was approximately one-half that in adults.\(^{27}, 28, 34, 36\) The doxacurium ED\(_{95}\) in children under halothane anesthesia was 0.027-0.032 mg/kg, compared with 0.019 mg/kg in adults.\(^{27}, 28\) Bolus doses of 0.0275 and 0.05 mg/kg of doxacurium provided maximum block in 6.7 and 5.3 minutes, respectively, with corresponding clinical durations of 28 and 51 minutes.\(^{27}\)

By contrast, the calculated pipecuronium ED\(_{95}\) in children under halothane anesthesia was comparable to that in adults (0.046 mg/kg (1-3 years) or 0.049 mg/kg (3-6 years) versus 0.047 mg/kg (adults)). Yet the duration of action was shorter.\(^{30}, 36\) Time to 25% recovery after cumulative bolus doses of 0.046 and 0.049 mg/kg required 31.5 and 29.9 minutes, respectively, and the corresponding recovery indices (25-75% recovery time) were 31.3 and 25.3 minutes.\(^{29}\) Under balanced anesthesia, the pipecuronium ED\(_{95}\) in children is slightly but not...
significantly higher than that in adults (0.079 versus 0.059 mg/kg), and the duration of action is slightly shorter (39 versus 45 minutes).\textsuperscript{15, 37}

- **Effect of renal or hepatic dysfunction on pharmacodynamics.** The pharmacodynamics of NMBs in the presence of organ system dysfunction are important considerations in patients with cardiac disease. Hepatic or renal impairment appeared to slow the onset of doxacurium block slightly but not significantly (11 minutes versus 8 minutes).\textsuperscript{7, 38} The duration of doxacurium block was also slightly prolonged in patients with hepatic failure (52 versus 36 minutes) as well as in those with renal failure (80 versus 36 minutes) after a 0.015-mg/kg dose. However, the differences were not statistically significant and, in the case of renal failure, may have been due to wide interpatient variation.\textsuperscript{7}

Onset and duration of pipecuronium block were not significantly different between patients with normal (3 and 98 minutes, respectively) and impaired (4 and 103 minutes, respectively) renal function after administration of a 0.07-mg/kg dose.\textsuperscript{9}

- **Hemodynamic effects.** Because doxacurium and pipecuronium do not stimulate histamine release at clinically relevant doses, no clinically significant hemodynamic effects or increases in plasma histamine levels occurred in adults with normal or impaired cardiac function.\textsuperscript{14, 16, 25, 29, 39-42} Small, clinically insignificant changes in heart rate (usually decreases) were observed with all dose levels of doxacurium up to and including 0.08 mg/kg (2.7 times \textit{ED\textsubscript{95}}) in adults and 0.05 mg/kg (1.7 \textit{ED\textsubscript{95}}) in children. These changes were probably related to the effects of opioids administered during anesthesia induction.\textsuperscript{14, 29, 28, 31} Similar decreases in heart rate and mean arterial pressure occurred after administration of 0.07 or 0.08 mg/kg of pipecuronium (1.5 or 2 times \textit{ED\textsubscript{95}}).\textsuperscript{13, 29, 39}

In patients undergoing elective coronary artery bypass grafting or valve replacement procedures, pancuronium caused significant increases in heart rate, mean arterial pressure, and cardiac index at a dose of 0.09 mg/kg (1.5 times \textit{ED\textsubscript{95}}), whereas no clinically significant changes in cardiovascular hemodynamics or clinical signs of histamine release were observed after administration of doxacurium at doses up to 0.08 mg/kg (3 times \textit{ED\textsubscript{95}}) or pipecuronium at 0.2 mg/kg (4 times \textit{ED\textsubscript{95}}).\textsuperscript{12, 39, 41} Similarly, patients undergoing abdominal aortic aneurysm repair showed no clinically significant changes in left or right ventricular function after a bolus dose of 0.05 mg/kg of doxacurium.\textsuperscript{42}

**Summary**

The long-acting nondepolarizing neuromuscular blocking agents that have been in clinical use for several decades are associated with cardiovascular side effects which may be noteworthy in patients with cardiovascular disease. Of the recently developed NMBs with long durations of action, doxacurium is the most potent, with an \textit{ED\textsubscript{95}} of 0.025 mg/kg, and does not release histamine at doses as high as 0.08 mg/kg. Pipecuronium is also potent, with an \textit{ED\textsubscript{95}} of 0.04-0.05 mg/kg. In therapeutic doses, doxacurium and pipecuronium produced no dose-dependent or clinically significant changes in heart rate, mean arterial pressure, or cardiac output. Because of their increased potency and excellent cardiovascular safety profiles, these new long-acting neuromuscular blocking agents offer appropriate alternatives for the patient undergoing cardiovascular surgical procedures, as well as for the patient with compromised cardiac function who is scheduled for noncardiac surgery.

**REFERENCES**


AUTHOR

Patricia B. Embree, CRNA, is a graduate of the Carney Hospital School of Nurse Anesthesia, Dorchester, Massachusetts. She received her nursing diploma from Massachusetts General Hospital School of Nursing and her BA from Emmanuel College, Boston, Massachusetts. Ms. Embree previously held the position of clinical research coordinator, Department of Anesthesiology, New York Hospital Cornell Medical Center, New York, and the position of staff nurse anesthetist/neuromuscular research coordinator, Anesthesiology Department, Massachusetts General Hospital, Boston. She is currently a clinical research manager at Aspect Medical Systems, Framingham, Massachusetts.

ACKNOWLEDGMENT

The author is most grateful to John Savarese, MD, and Marjorie Hale for their editorial assistance.