DOXACURIUM CHLORIDE: A PRELIMINARY CLINICAL TRIAL

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Doxacurium, in common with atracurium, is a benzylisoquinolinium, non-depolarizing neuromuscular blocking drug containing two quarternary nitrogen groups. Initial clinical studies in the U.S.A. suggest that it is a potent, long acting drug devoid of cardiovascular and histamine releasing side effects at clinically effective doses [1, 2]. The ED_{95} dose to block contraction of the adductor pollicis muscle is approximately 25 μg kg^{-1} [1]. Unlike atracurium, it is not susceptible to Hofmann degradation, and is probably excreted largely unchanged by the kidney.

This study of doxacurium was designed to assess its onset, intubation conditions, effect of multiple increments and ease of antagonism with edrophonium and neostigmine. A preliminary report of this study was presented to the Anaesthetic Research Society.

PATIENTS AND METHODS

We studied 27 ASA I or II adult patients (weights 45–100 kg) scheduled to undergo elective surgery expected to last 120 min. Each gave written informed consent for the study which was also approved by the local Hospital Ethics Committee.

The patients were premedicated with papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. 1 h before surgery. Before induction of anaesthesia the skin over one forearm and the hand was degreased using an alcohol solution. Five silver-silver chloride electrodes were placed, two over the ulnar nerve, one over the mid-point of the distal skin crease at the wrist, one over the palmar aspect of the head of the fifth metacarpal and one over the belly of the adductor pollicis muscle.


Summary

The onset, duration of action and reversibility of doxacurium were studied in 27 anaesthetized patients, using doses of 37.5 μg kg^{-1} (1.5 × ED_{95}) and 62.5 μg kg^{-1} (2.5 × ED_{95}). Onset was slow and, whilst tracheal intubation was always possible 3 or 4 min after injection, the conditions were not ideal. With the higher dose a mean 97.6 (SD 5.2)% block of the response of adductor pollicis to ulnar nerve stimulation was obtained in 9.85 (6.17) min and recovery of the integrated EMG response to 20% of control took 102 min (42 min). After these initial doses, when incremental doses were given there was no sign of cumulation of effect. Antagonism of block with edrophonium 1 mg kg^{-1}, whilst fast in onset, was rarely complete; with neostigmine 50 μg kg^{-1} antagonism was satisfactory. No adverse haemodynamic effect was seen, although a gradual onset of bradycardia, which responded to atropine or glycopyrrolate, was noted in 12 of the patients. No histamine release or other adverse effects were noted.

These were connected to a Datex Relaxograph. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} i.v. and fentanyl 2–3 μg kg^{-1} i.v.

Neuromuscular monitoring was commenced using a train-of-four stimuli (2 Hz at 20-s intervals) to the ulnar nerve and the gated, rectified and integrated EMG from the adductor pollicis was recorded. The size of the gain setting, supramaximal stimulus and the stimulus artefact were noted. Anaesthesia was maintained with 66% nitrous oxide in oxygen and the lungs were ventilated artificially to maintain normocapnia. The patients were allocated to three groups of nine and patient order was randomized. Following randomization the first 18 patients studied (and hence the last nine also) were equally divided.
between the three groups. When an initially stable record was obtained, doxacurium 37.5 \( \mu g \) kg\(^{-1}\) i.v. (1.5 \( \times \) ED\(_{50}\)) was administered to group A, and 62.5 \( \mu g \) kg\(^{-1}\) i.v. (2.5 \( \times \) ED\(_{50}\)) to groups B and C, with the bolus being given either into a continuous infusion or flushed through a cannula with a 5-ml bolus of saline. The bolus was given to coincide with a train-of-four sequence, to give an accurate time mark on the record.

Intubation conditions were assessed by the same investigator (R.S.) each time at 4 min after the administration of doxacurium in groups A and B and at 3 min in group C. The conditions were graded on a scale of 1–4 (excellent, good, poor or not possible) [3].

The onset of block was determined as the time from injection to the appearance of either complete block or the maximum degree of block. Following maximal block, anaesthesia was maintained with nitrous oxide in oxygen plus 0.5% halothane. Additional doses of fentanyl and thiopentone were administered as required. When the first response of the train-of-four (T1) had recovered to 20% of control, a bolus of doxacurium 5 \( \mu g \) kg\(^{-1}\) was given; this was repeated when T1 had recovered again to 20%. The duration and degree of block produced by each increment were noted.

At the end of surgery, when T1 had recovered to greater than 10% of control, the residual block was antagonized with edrophonium 1 \( mg \) kg\(^{-1}\) i.v. in the first 18 patients (six in each of groups A, B and C), and neostigmine 50 \( \mu g \) kg\(^{-1}\) i.v. in the last nine patients (\( n = 3 \) in each group). Glycopyrrolate or atropine i.v. in an appropriate dose was given concurrently. The percentage recovery of T1 following the injection of the anticholinesterase agent was continuously recorded.

Heart rate was observed continuously from a Hewlett-Packard ECG monitor and the arterial pressure measured every 2 min using a Hewlett-Packard non-invasive monitor. To minimize decreases in core and hand temperatures during the operation, nasopharyngeal temperature was measured, all infusions were warmed to body temperature, a condenser humidifier was used in the breathing system and the forearm was insulated by wrapping in towelling.

Neuromuscular monitoring was stopped when the patient was awake, and neuromuscular function was evaluated clinically during the recovery period by assessing patient's grip strength and ability to head lift for 5 s [4]. Each patient was reassessed 24–48 h after surgery and questioned with regard to any adverse experience noted.

Non-parametric and Student's \( t \) test were used as appropriate to assess statistical significance.

**RESULTS**

There were no significant differences between the ages, weights or ASA groups of the three groups of patients studied (table I). The duration of surgery was defined as the time from administration of the initial bolus of doxacurium until administration of the antagonizing agent. Intubation conditions ranged between grades excellent and poor in all three groups, but only one patient in each group achieved excellent conditions (table II). Intubation was accomplished successfully in all patients, although 100% block of adductor pollicis was not achieved before intubation was performed.

Because patients in groups B and C all received doxacurium 62.5 \( \mu g \) kg\(^{-1}\), these two groups were analysed together and compared with group A

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**Table I. Patient characteristics (mean (SD))**

<table>
<thead>
<tr>
<th>Group</th>
<th>Doxacurium (( \mu g ) kg(^{-1}))</th>
<th>( n )</th>
<th>Age (yr) (SD)</th>
<th>Weight (kg) (SD)</th>
<th>Duration of surgery (min) (SD)</th>
<th>Sex (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>37.5</td>
<td>9</td>
<td>52.5 (11.8)</td>
<td>67.3 (10.7)</td>
<td>127.8 (58.4)</td>
<td>5/4</td>
</tr>
<tr>
<td>Group B</td>
<td>62.5</td>
<td>9</td>
<td>60.7 (11.2)</td>
<td>69.8 (15.8)</td>
<td>161.4 (48.6)</td>
<td>7/2</td>
</tr>
<tr>
<td>Group C</td>
<td>62.5</td>
<td>9</td>
<td>49 (14.0)</td>
<td>74.5 (15.0)</td>
<td>139.6 (38.7)</td>
<td>6/3</td>
</tr>
</tbody>
</table>
(doxacurium 37.5 µg kg⁻¹) (table III). Three patients in group A failed to achieve 80% block following the initial bolus and one patient was antagonized at 10% recovery. In the remaining five it took an average of 51 min to recover to T1 of 20%. With the higher dose, in one patient the initial block was only to 75%, and in two the recording was lost following movement of the patient by theatre staff and loss of electrode placement. In the remaining 15, the time to 20% T1 recovery was on average 102 min after the initial dose (table III). There was no significant correlation between the age of the patients and duration of block at this higher dose.

Only 13 patients received increments of doxacurium as, in the remainder, the initial bolus dose of doxacurium was adequate to last throughout the operation. The incremental doses administered at 20% recovery of T1 produced a moderately wide between-patient variation in response, both with regard to percent increase in block of T1 and time to return to 20% T1. However, the response in any one patient was consistent, with increments producing the same increase in paralysis and a constant duration of effect (table IV).

Two patients with poor recovery recordings were omitted from the antagonism data analysis. The mean percent recovery of T1 at the time of administration of the antagonist was almost the same in the edrophonium and neostigmine groups (table V). The first twitch of the train-of-four was antagonized well after neostigmine. The T1 antagonism response to edrophonium was rapid.

### TABLE II. Intubation data. Score 1 = excellent, 2 = good; 3 = poor; 4 = not possible

<table>
<thead>
<tr>
<th></th>
<th>Time of intubation (min)</th>
<th>Intubation score (No. patients)</th>
<th>Reduction in T1 at intubation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxacurium 37.5 µg kg⁻¹</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxacurium 62.5 µg kg⁻¹</td>
<td>4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxacurium 62.5 µg kg⁻¹</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

### TABLE III. Onset and duration data (mean (SD) [range]). *Three patients failed to achieve 80% block

<table>
<thead>
<tr>
<th></th>
<th>Max. block achieved (T1 %)</th>
<th>Time to max. block (min)</th>
<th>Duration to 20% recovery of T1 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxacurium 37.5 µg kg⁻¹</td>
<td>9</td>
<td>83.6 (18.3) [55–100]</td>
<td>10.5 (2.2) [6–14]</td>
</tr>
<tr>
<td>Groups B + C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxacurium 62.5 µg kg⁻¹</td>
<td>18</td>
<td>97.6 (5.2) [78–100]</td>
<td>9.85 (6.17) [5–31]</td>
</tr>
</tbody>
</table>

### TABLE IV. Response to increments (5 µg kg⁻¹) (mean (SD) [range]), †Group A n = 4; group B n = 4; group C n = 5

<table>
<thead>
<tr>
<th></th>
<th>Increase in block T1 (%)</th>
<th>Duration to return to 20% (min)</th>
<th>No. increments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients receiving increments at 20% recovery T1</td>
<td>Total 13†</td>
<td>8 (3.3) [2.5–15]</td>
<td>31.3 (31.1) [9.5–42]</td>
</tr>
</tbody>
</table>
in onset but was incomplete and subsequently appeared to be similar to that of a spontaneous recovery. In eight (47%) patients in the edrophonium group a train-of-four (TOF) ratio less than 0.5 was still present when recording had to be stopped. Only four (24%) patients achieved a TOF ratio greater than 0.7. One patient, with a TOF ratio of 0.6 at the end of recording, failed a 5-s head lift 30 min after administration of edrophonium. Ten minutes later he had a successful head lift following administration of neostigmine 2.5 mg. In the neostigmine group, no neuromuscular block could be detected by clinical assessment in the recovery room. One patient had a train-of-four ratio less than 0.5 following antagonism at the end of the recording. Four patients (50%) achieved a TOF ratio greater than 0.7. The mean period of recording following administration of both agents was approximately 14 min.

Twelve (44.4%) patients required administration of an i.v. anticholinergic agent during operation to correct a heart rate of less than 50 beat min⁻¹. The bradycardias were gradual in onset and generally occurred 30-60 min after induction of anaesthesia and seemed unrelated to the administration of doxacurium.

No adverse experiences were reported by the patients on follow-up at 24 h.

**DISCUSSION**

This study confirms that doxacurium is a potent, long acting neuromuscular blocking agent. Although a formal dose-response study was not carried out in our patients the drug appeared to be less potent than might have been anticipated from previous reports. Other studies [1, 2, 5, 6] suggest that the ED₉₅ lies between 13.6 and 25 µg kg⁻¹ [1]. In our study, group A received 1.5 times this ED₉₅ and groups B and C received 2.5 times the ED₉₅. Our data, however, showed that at 37.5 µg kg⁻¹ (1.5 × ED₉₅) the maximum block achieved was 83.6 % T1. This apparent difference in potency may result from the fact that we compared EMG responses to mechanomyographic forms of measurement [1, 2]. In addition, the drug may appear less potent because of the lighter depth of anaesthesia during induction. Alternatively, there may be an Anglo–American difference in potency for doxacurium, as had been described previously for tubocurarine [7].

Intubating conditions were similar to those described by other workers [8, 9] and could only be described as excellent in one patient in each group; in no patient was 100% blockade of T1 achieved before intubation. In two patients the intubating conditions were between grades 2 and 3 by the intubation criteria of Twohig and his colleagues [3] and therefore they scored 2.5. Even at the high dose (62.5 µg kg⁻¹) the mean onset time to 90% block of T1 was some 4.9 min (n = 17). Nevertheless, in no patient was intubation impossible and the mean conditions in all three groups could be said to be good.

In the patients receiving multiple maintenance increments of doxacurium there was no evidence of an increase in duration or degree of block following each bolus.

In all patients except the two with poor recordings, in whom antagonism was blind, the block was antagonized between 10 and 37% recovery of T1. It could be argued that the poor antagonism with edrophonium was related to baseline drift of the electromyographic recording, which has been well documented by other authors [10, 11]. However, the antagonism of T1 by neostigmine was complete; this would confirm a real difference in ability to antagonize doxacurium by these two anticholinesterase agents. As a result of time constraints imposed on this clinical study, TOF fade was still present in several patients when stimulation had to be stopped as the patient

<table>
<thead>
<tr>
<th>Recovery of T1 (%) at</th>
<th>1 min</th>
<th>3 min</th>
<th>5 min</th>
<th>10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium</td>
<td>23.8 (8.8) [10–37]</td>
<td>59.2 (22.8)</td>
<td>70.9 (17.3)</td>
<td>76.4 (17.4)</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>22.5 (6.7) [10–32.5]</td>
<td>40.6 (21.2)</td>
<td>70.5 (28.2)</td>
<td>81.8 (21.0)</td>
</tr>
</tbody>
</table>
awakened. Nevertheless, with the exception of one patient who received edrophonium, all other patients appeared to have appropriate clinical antagonism of block and had satisfactory grip strength and 5-s head lift when tested between 2u and 40 min after admission to the recovery ward.

It is unlikely that the gradual onset of bradycardia could be attributed to doxacurium; our measurements of heart rate and arterial pressure confirm the findings of others that doxacurium is a haemodynamically stable agent [1, 12]. There was no clinical evidence of histamine release. Konstadt also noted a decrease in heart rate and attributed this to progressive reduction in sympathetic tone resulting from anaesthesia [13]. The effect of opioids and volatile agents on heart rate is well documented [14].

In conclusion, we found doxacurium to be a potent, long acting, haemodynamically stable, non-depolarizing neuromuscular blocker. Although intubation was possible in all patients in the three groups studied and with the doses used in this study, doxacurium did not provide intubating conditions which could be described as excellent. In common with vecuronium and atracurium, this drug does not have the protective vagolytic effect of pancuronium and it is recommended that an anticholinergic agent be available immediately if vagal stimuli are likely to be encountered during surgery. Neostigmine would appear to be more suitable than edrophonium as an antagonist for doxacurium.

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REFERENCES