CARDIOVASCULAR AND NEUROMUSCULAR EFFECTS OF DIMETHYL TUBOCURARINE IN ANAESTHETIZED CATS AND RHESUS MONKEYS

R. HUGHES AND D. J. CHAPPLE

SUMMARY

Intravenous dose–response relationships for dimethyl tubocurarine showed that vagal blockade only became appreciable (50–83%) at doses 8–16 times those sufficient for full neuromuscular paralysis in anaesthetized cats (0.0625 mg/kg) and rhesus monkeys (0.125 mg/kg); heart rate was unchanged. Sympathetic function was unimpaired by supramaximal paralysing doses of 0.5 and 1 mg/kg in cats, but was reduced (20–41%) by comparable neuromuscular paralysing doses of 1 and 2 mg/kg in rhesus monkeys; these doses decreased carotid arterial pressure by 22–36%. The duration of action of dimethyl tubocurarine was prolonged; more than 60 min was required for recovery from full neuromuscular paralysis; the drug was even more persistent in rhesus monkeys than in cats. Thus, the need remains for a drug resembling dimethyl tubocurarine in its highly specific action at the neuromuscular junction, but with a much shorter duration of action.

The clinical usefulness of a non-depolarizing neuromuscular blocking agent will depend upon the degree of separation between its neuromuscular paralysing effects and its inhibitory actions on peripheral autonomic nerve mechanisms.

Recently, we reported that neuromuscular paralysing doses of gallamine, pancuronium, alcuronium and fazadinium cause blockade of the cardiac vagus in anaesthetized cats (Hughes and Chapple, 1976). Such vagolytic effects in man may explain why these drugs can cause tachycardia and arterial hypertension in anaesthetic practice.

We found also that doses of dimethyl tubocurarine, sufficient to cause full neuromuscular paralysis, were devoid of effects on autonomic mechanisms and this distinctive feature has been investigated further in anaesthetized cats and rhesus monkeys.

A preliminary account of this work has been presented to the British Pharmacological Society (Chappie et al., 1976).

METHODS

Four male cats weighing 2.9–3.8 kg were studied after anaesthesia had been induced with 3–5% halothane and maintained with chloralose 60–80 mg/kg i.v. after cannulation of a jugular vein as described previously (Hughes and Chapple, 1976). Cannulae were placed in the trachea to record the respiratory pattern and to allow artificial ventilation, and in the carotid artery to measure the arterial pressure; the cannula inserted in the jugular vein also allowed the administration of drugs. Neuromuscular block was assessed by measuring the response of the gastrocnemius muscle to stimulation of the sciatic nerve with rectangular pulses of supramaximal voltage and duration at a frequency of 0.1 Hz and which was expressed as a percentage of the control response. The muscle load at rest was 0.2 kg and the maximum tension developed was 0.5–1 kg. Effects on parasympathetic activity were investigated by measuring the bradycardia which ensued when 10-s bursts of periodic stimulation were applied to the cardiac end of the cut right cervical vagus nerve. Effects on sympathetic activity were measured by recording the contractions of the nictitating membrane when the central end of the cut right preganglionic cervical sympathetic nerve was stimulated for 60 s at supramaximal voltage. Atropinic effects were confirmed by inducing bradycardia with metacholine 100 μg i.v.

Four male rhesus monkeys weighing 3.2–3.9 kg were anaesthetized with thiopentone 25 mg/kg i.v. Anaesthesia was maintained with a mixture of 50% nitrous oxide in oxygen, supplemented by thiopentone 5–12 mg i.v. when required. The methods of study were similar to those described for cats, but effects on sympathetic mechanisms were investigated by measuring the vasopressor response to carotid occlusion for 10 s.

Dimethyl tubocurarine dibromide was dissolved (9 mg/ml) in saline and administered i.v. During neuromuscular paralysis the cats were ventilated with air using a Starling Ideal pump (rate 20/min, tidal...
FIG. 1. Tracing from a 3-kg male cat anaesthetized with chloralose. An i.v. dose of dimethyl tubocurarine 0.125 mg/kg, twice that necessary to abolish the twitches of the gastrocnemius muscle and to arrest breathing, reduced the bradycardia response to vagal nerve stimulation only marginally; the contraction of the nictitating membrane (sympathetic response) was unchanged. The small transient changes in carotid artery pressure and heart rate during the bolus injection were artefacts.

RESULTS

Cats

Figure 1 shows a typical tracing from an anaesthetized cat which received dimethyl tubocurarine 0.125 mg/kg i.v., sufficient to arrest breathing and abolish the single twitches of the gastrocnemius muscle. This dose had no appreciable effect on the carotid artery pressure, heart rate, bradycardia induced by vagal nerve stimulation or on the response of the nictitating membrane to sympathetic nerve stimulation.

Dose–response curves were obtained by plotting percentage inhibition against dose for a group of four cats. They show that full neuromuscular paralysis was achieved with a dose of 0.0625 mg/kg (fig. 2). Vagal blockade became of importance only at doses of 0.5 and 1 mg/kg, which were 8–16 times the dose necessary for complete paralysis; sympathetic function was virtually unimpaired. These doses also reduced the carotid artery pressure, the mean reduction in the four cats being 25 and 36% respectively; heart rate was not changed significantly (table I).

Dimethyl tubocurarine was long-acting. A dose of 0.0625 mg/kg caused full neuromuscular paralysis within about 1 min, and a mean time of 64 min was required for full recovery in three cats (table I). In the fourth cat, full recovery had not occurred after 75 min. At higher doses complete recovery occurred rarely. For example, in two cats receiving 0.125 mg/kg the neuromuscular responses had recovered fully in 78 and 88 min, but in the other two cats of the group recovery was incomplete after 75 and 92 min. Furthermore, after doses of 0.25 mg/kg in two cats no recovery had occurred after 75 and 90 min. Of the
two remaining cats, one showed some recovery after 92 min and the other had recovered fully after 117 min. None of the four cats showed any recovery at 75 min after doses of 0.5 mg/kg (table I). Even while neuromuscular blockade was complete, vagal blockade was only partial and recovery could be observed; similarly, in the following experiments in rhesus monkeys partial vagal and sympathetic blockade were evident at high doses.

**Rhesus monkeys**

The dose–response curves show that dimethyl tubocurarine was about half as potent in rhesus monkeys as in cats; a dose of 0.125 mg/kg was required for complete paralysis (fig. 3). As in cats, vagal blockade was appreciable only at 8–16 times the full neuromuscular paralysing dose. These doses of 1 and 2 mg/kg reduced the vasopressor response to carotid occlusion, which was evidence of sympathetic blockade, and also reduced the carotid artery pressure.
TABLE I. Neuromuscular, cardiovascular and autonomic effects of dimethyl tubocurarine in groups of four anaesthetized cats and four rhesus monkeys. Maximal inhibition of the twitches of the gastrocnemius muscle to indirect stimulation at 0.1 Hz, of the vagal-induced bradycardia, of the contraction of the nictitating membrane caused by sympathetic nerve stimulation in cats and of the vasopressor response to carotid occlusion in monkeys, are expressed as percentages; carotid artery pressure and heart rate are shown as percentage of initial values. Mean of results from four animals are quoted (± SEM)

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg i.v.)</th>
<th>Gastrocnemius muscle</th>
<th>Arterial (a) pressure (initial = 100)</th>
<th>Heart (b) rate (initial = 100)</th>
<th>Vagal response (% inhibition)</th>
<th>Sympathetic response (% inhibition)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% inhibition</td>
<td>Onset time (min)</td>
<td>Recovery time (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>0.0156</td>
<td>16 ± 10.9</td>
<td>5.3 ± 0.8</td>
<td>13 ± 2.8</td>
<td>103 ± 1.9</td>
<td>98 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>0.03125</td>
<td>93 ± 3.7</td>
<td>3.1 ± 0.3</td>
<td>40 ± 13</td>
<td>94 ± 4.0</td>
<td>98 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>0.0625</td>
<td>100 ± 0.8</td>
<td>0.8 ± 0.1</td>
<td>64 ± 6.4*</td>
<td>96 ± 1.5</td>
<td>99 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>0.125</td>
<td>100 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>&gt; 75</td>
<td>91 ± 1.8</td>
<td>98 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>100 ± 0.8</td>
<td>0.8 ± 0.4</td>
<td>&gt; 75</td>
<td>89 ± 4.0</td>
<td>99 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>100 ± 0.8</td>
<td>&gt; 75</td>
<td></td>
<td>75 ± 7.6</td>
<td>101 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>100 ± 0.8</td>
<td>&gt; 30</td>
<td></td>
<td>64 ± 5.5</td>
<td>99 ± 7.4</td>
</tr>
</tbody>
</table>

| Rhesus monkey | 0.0156            | 0                     | —                                     | —                              | 99 ± 2.2                      | 101 ± 0.9                          | 0                                 | 0                                 |
|              | 0.03125           | 15 ± 12.2            | 2.8 ± 0.8                             | 13 ± 2.8                       | 101 ± 3.9                     | 106 ± 4.5                          | 0                                 | 0                                 |
|              | 0.0625            | 83 ± 6.4             | 3.6 ± 0.5                             | 26 ± 7.8                       | 99 ± 8.7                      | 106 ± 3.6                          | 0                                 | 0                                 |
|              | 0.125             | 100 ± 0.1            | 1.9 ± 0.5                             | 184 ± 81†                      | 98 ± 9.4                      | 102 ± 1.5                          | 4 ± 2.2                           | 0                                 |
|              | 0.25              | 100 ± 0.8            | 0.5 ± 0.2                             | > 60                           | 100 ± 7.8                     | 95 ± 2.0                           | 14 ± 7.8                          | 2 ± 2.0                           |
|              | 0.5               | 100 ± 0.8            | > 60                                  |                                | 90 ± 6.7                      | 102 ± 1.3                          | 34 ± 6.2                          | 11 ± 6.4                          |
|              | 1.0               | 100 ± 0.8            | > 60                                  |                                | 78 ± 1.5                      | 100 ± 2.1                          | 50 ± 6.7                          | 20 ± 8.2                          |
|              | 2.0               | 100 ± 0.8            | > 30                                  |                                | 73 ± 1.1                      | 99 ± 4.4                           | 82 ± 5.3                          | 41 ± 13.8                         |

* Results from 3 cats only; † estimated by extrapolation.

Cat (a) Resting arterial pressure = mean 150 mm Hg, range 135–180.
(b) Resting heart rate = mean 203 beat/min, range 185–220.

Monkey (a) Resting arterial pressure = mean 113 mm Hg, range 90–140.
(b) Resting heart rate = mean 198 beat/min, range 185–215.

by 22 and 27% respectively; the heart rate was not changed significantly (table I).

Dimethyl tubocurarine was even longer acting in rhesus monkeys than in cats. A dose of 0.125 mg/kg produced complete paralysis of the single twitches of the gastrocnemius muscle in about 2 min, and after 60 min a mean recovery of only 65% occurred in the four monkeys. Only one of the four monkeys which received 0.25 mg/kg showed any signs of recovery after 60 min and no recovery was seen at the same time after doses of 0.5 and 1 mg/kg.

DISCUSSION

We have reported previously that dimethyl tubocurarine has no important effects on vagal or sympathetic mechanisms at i.v. doses about twice those required for full neuromuscular blockade in anaesthetized cats (Hughes and Chappie, 1976). In the present study, employing much larger doses of the drug, we found that vagal blockade became appreciable in cats at doses 8–16 times that necessary to abolish the twitch responses of the gastrocnemius muscle. Thus, dimethyl tubocurarine, in sufficient doses, is similar to other non-depolarizing neuromuscular blocking agents in that it antagonizes the effects of acetylcholine released by the vagal postganglionic nerve endings in the heart. However, the degree of separation between neuromuscular and vagal blockade was considerably greater than that found previously for gallamine, alcuronium, pancuronium and fazadinium (Hughes and Chappie, 1976). Such vagolytic effects of these drugs in man may cause tachycardia and hypertension in anaesthetic practice. Furthermore, dimethyl tubocurarine, unlike tubocurarine, even at the high doses used was devoid of inhibitory effects on sympathetic mechanisms in cats.

When the investigation was extended to rhesus monkeys, although the drug was only about half as potent as in cats, the degree of separation between neuromuscular and vagal blockade was considerably greater than that found previously for gallamine, alcuronium, pancuronium and fazadinium (Hughes and Chappie, 1976). Such vagolytic effects of these drugs in man may cause tachycardia and hypertension in anaesthetic practice. Furthermore, dimethyl tubocurarine, unlike tubocurarine, even at the high doses used was devoid of inhibitory effects on sympathetic mechanisms in cats.
paralyzing dose in the primate, but the dose–response curves show that this was less in magnitude than was the vagal blockade.

In cats and rhesus monkeys, arterial pressure was reduced by 22–36% following large doses (0.5–2 mg/kg); changes in heart rate were minimal. McCullough and others (1972) found no significant cardiovascular effects following tubocurarine 0.4 mg/kg in cats. These workers anaesthetized the cats with pentobarbitone which is known to impair sympathetic function and, as a consequence, may have obscured the mild arterial hypotension that we observed with similar doses in cats anaesthetized with chloralose.

Our results show also that the duration of action of dimethyl tubocurarine was so prolonged that often it was not possible to follow complete recovery after full neuromuscular blocking doses; paralysis was even more persistent in rhesus monkeys than in cats. It is reported elsewhere that the drug is also long-acting in anaesthetized man (Hughes, Ingram and Payne, 1976).

It seems, therefore, that although dimethyl tubocurarine has desirable clinical properties there remains a need for a neuromuscular blocking agent with a similar highly specific action at the neuromuscular junction but of shorter duration.

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REFERENCES
disminuyeron la tensión arterial carótida entre el 22 al 36%. La duración de la acción de la dimetil-tubocurarina fue prolongada; se necesitaron más de 60 min para recuperarse de la plena parálisis neuromuscular; el fármaco fue incluso más persistente en los monos rhesus que en los gatos. Así pues, sigue haciendo falta disponer de un fármaco parecido a la dimetil-tubocurarina en cuanto a su acción altamente específica en el punto de unión mioneural, pero con una duración mucho más corta de su acción.