SOME EFFECTS OF DIISOPROPYL PHENOL (ICI 35 868) ON THE PHARMACODYNAMICS OF ATRACURIUM AND VECURONIUM IN ANAESTHETIZED MAN

E. N. ROBERTSON, R. J. FRAGEN, L. H. D. J. BOOIJ, J. VAN EGMOND AND J. F. CRUL

SUMMARY

The effects of a bolus injection of diisopropyl phenol 2 mg kg\(^{-1}\) i.v. and an infusion (150 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) for 30 min and 75 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) thereafter) on the pharmacodynamics and dose–response curves of atracurium and vecuronium were studied in 52 healthy (ASA I or II) patients. Under anaesthesia with diisopropyl phenol, the cumulative dose–response curves of both myoneural blocking drugs were shifted to the left when compared with previously reported results. However, there was no clinically significant change in the pharmacodynamics of either drug after the bolus injection of the blocking drug. Diisopropyl phenol 2 mg kg\(^{-1}\) i.v. administered during steady-state infusions of vecuronium and atracurium increased the depth of the constant neuromuscular blockade. When diisopropyl phenol alone was given to four patients there was no change in the twitch height. These results show that diisopropyl phenol, given according to the regimen in this study, potentiates both of the neuromuscular blockers studied but does not prolong the duration of action of either drug. During the infusion of diisopropyl phenol, vecuronium was found to be five times more potent, to have a more rapid onset time, and to be shorter acting than an equipotent dose of atracurium.

The influence of volatile anaesthetic agents on the activity of non-depolarizing neuromuscular blocking drugs is well established. In addition, certain i.v. anaesthetic agents have been shown to influence the effects of neuromuscular blocking agents: for example, ketamine has been shown to potentiate tubocurarine (Johnstone, Miller and Way, 1974).

Diisopropyl phenol is a new hypnotic agent which can be used to induce and to maintain anaesthesia (Briggs et al., 1981; Major et al., 1981). Since in vitro studies have shown that diisopropyl phenol potentiates the neuromuscular blocking activity of pancuronium and vecuronium (Fragen et al., 1982) the influence of diisopropyl phenol (by bolus injection i.v. and by infusion), on the pharmacodynamics of atracurium and vecuronium has been studied in man.

PATIENTS AND METHODS

Studies were performed in 56 healthy (ASA I or II) patients aged between 18 and 65 yr. Informed consent was obtained at the time of the preoperative visit. The study was approved by the hospital Ethics Committee. Pregnant or nursing women were excluded from the study, as were patients with a history of allergy or atopy, and those exposed to Cremophor EL within the previous 6 months (Cremophor EL is the solvent for diisopropyl phenol).

The patients were premedicated with diazepam 10 mg orally 2 h, and droperidol 2.5–5 mg and piritramide 7.5–15 mg i.m. 0.5–1 h, before the induction of anaesthesia.

Two techniques of anaesthesia were used: "diisopropyl phenol anaesthesia" was used in four groups of 10 patients. In these groups, the induction of anaesthesia was with fentanyl 4 \(\mu\)g kg\(^{-1}\) and diisopropyl phenol 2 mg kg\(^{-1}\) given over 20 s i.v. Maintenance of anaesthesia was with diisopropyl phenol 150 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) i.v. for 30 min and 75 \(\mu\)g kg\(^{-1}\), thereafter. "Thiopentone anaesthesia" was used in 16 patients. Induction was with fentanyl 4 \(\mu\)g kg\(^{-1}\) i.v. followed by thiopentone 5 mg kg\(^{-1}\) i.v. Maintenance of anaesthesia was with incremental doses of thiopentone 50 mg, fentanyl 0.05 mg, or droperidol 2.5 mg, as judged by clinical signs such as arterial pressure and heart rate.

In all patients, intubation of the trachea was achieved shortly after induction (without muscle paralysis) after spraying the pharynx, larynx and trachea with 4% lignocaine spray (up to 4 ml). Mechanical ventilation of the lungs with 67% nitroxide.
ous oxide in oxygen was used to maintain the end-expired carbon dioxide concentration between 4.5 and 5 vol%.

The ulnar nerve was stimulated supramaximally through surface electrodes near the wrist at a rate of 0.1 Hz and a duration of 0.2 ms. The isometric twitch tension of the thumb produced by this stimulation, as measured by a force-displacement transducer, was recorded on a polygraph.

Patients were randomly assigned to each group. Four different investigations were undertaken:

(1) Determination of cumulative dose–response curves. When the twitch height had been stable for 10 min, small cumulative doses of atracurium (initial dose 0.075 mg kg\(^{-1}\) and subsequent smaller doses of 0.025 mg kg\(^{-1}\)) or vecuronium (initial dose 0.015 mg kg\(^{-1}\) then smaller doses of 0.005 mg kg\(^{-1}\)) were given i.v. to 20 patients under diisopropyl phenol anaesthesia (10 in each neuromuscular blocker group). Incremental doses were given when the previous dose had achieved its maximal effect, that is when three consecutive twitches of equal height were observed (Donlon et al., 1980). From the results, dose–response curves were constructed for each patient using the model where the blockade is described as a “normal probability integral” (NPI) function (integrated Gaussian; see Appendix). For each patient, ED\(_{50}\) (dose expected to give 50% block), sigma (\(\sigma\) = standard width of the underlying Gaussian; see Appendix), and ED\(_{90}\) (ED\(_{50}\) + 1.28 \(\times\) \(\sigma\)) were calculated. The mean ED\(_{50}\), ED\(_{90}\), and \(\sigma/ED_{50}\) of each neuromuscular blocker group were compared statistically using Student's \(t\) test.

(2) Determination of pharmacodynamic variables after bolus i.v. injection of neuromuscular blocking drug. Bolus injections of atracurium 0.188 mg kg\(^{-1}\) and vecuronium 0.043 mg kg\(^{-1}\) were given i.v. to 20 patients under diisopropyl phenol anaesthesia (10 in each neuromuscular blocking drug group). Previous studies in this department had shown these doses to be equipotent (Robertson et al., 1983). The onset time (from end of injection to maximum effect), duration 25 (time from end of injection to 25% twitch recovery), duration 90 (time from end of injection to 90% twitch recovery), recovery rate (time from 25% to 75% recovery) and degree of blockade were determined for each patient.

(3) Determination of influence of diisopropyl phenol on neuromuscular function without neuromuscular blocking agents. Four patients received “thiopentone anaesthesia” without any myoneural blockade. When the twitch height had been stable for 10 min, a bolus injection of diisopropyl phenol 2 mg kg\(^{-1}\) i.v. over 20 s was given and the effect on twitch height recorded to see if diisopropyl phenol alone had any effect.

(4) Determination of influence of diisopropyl phenol on neuromuscular function in the presence of steady-state neuromuscular blockade. Twelve patients (six in each myoneural blocker group) received thiopentone anaesthesia. A continuous infusion of atracurium i.v. (initial bolus of 0.1 mg kg\(^{-1}\) then an infusion at a rate of 8–12 mg h\(^{-1}\)) or vecuronium (initial bolus of 0.02 mg kg\(^{-1}\), then an infusion at a rate of 2–3 mg h\(^{-1}\)) was started once a stable twitch height had been obtained. A 30–60% block was obtained by this method. When stable blockade had existed for at least 15 min, a bolus injection of diisopropyl phenol 2 mg kg\(^{-1}\) over 20 s was given i.v. and the effect on the twitch height recorded while the infusion of the neuromuscular blocking drug was continued.

All results were analysed using Student's \(t\) test for paired or unpaired observations as required. \(P < 0.05\) was considered to be significant.

RESULTS

There were no differences in the ages or weights of patients in each group (table I).

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Number of patients</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Dose–response curves</td>
<td>Vecuronium</td>
<td>10</td>
<td>64.2 (2.9)</td>
<td>40.1 (4.1)</td>
</tr>
<tr>
<td></td>
<td>Atracurium</td>
<td>10</td>
<td>66.6 (2.5)</td>
<td>34.0 (4.1)</td>
</tr>
<tr>
<td>(2) Bolus injection</td>
<td>Vecuronium</td>
<td>10</td>
<td>59.0 (2.8)</td>
<td>30.1 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Atracurium</td>
<td>10</td>
<td>62.0 (3.6)</td>
<td>30.9 (1.9)</td>
</tr>
<tr>
<td>(3) Diisopropyl phenol without</td>
<td>Vecuronium</td>
<td>4</td>
<td>68.6 (2.9)</td>
<td>30.1 (1.6)</td>
</tr>
<tr>
<td>neuromuscular blocking drugs</td>
<td>Atracurium</td>
<td>6</td>
<td>63.3 (4.0)</td>
<td>39.7 (4.3)</td>
</tr>
<tr>
<td>(4) Steady-state infusion</td>
<td>Vecuronium</td>
<td>6</td>
<td>69.0 (3.3)</td>
<td>32.2 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Atracurium</td>
<td>6</td>
<td>63.3 (4.0)</td>
<td>39.7 (4.3)</td>
</tr>
</tbody>
</table>
(1) The ED$_{50}$ and ED$_{90}$ of vecuronium, as calculated from the dose–response curve, were 20.8 $\mu$g kg$^{-1}$ and 32.4 $\mu$g kg$^{-1}$, respectively, and of atracurium 103.7 $\mu$g kg$^{-1}$ and 157.6 $\mu$g kg$^{-1}$, respectively (fig. 1; table II). Using the ED$_{50}$ values, vecuronium was about five times more potent than atracurium. The ratio $\sigma$/ED$_{50}$ (dimensionless) expressed the slope of the dose–response relation if depicted on a logarithm (dimensionless) scale. The smaller the ratio, the smaller the dose of drug needed for an increase in neuromuscular blockade. These $\sigma$/ED$_{50}$ values were not significantly different.

(2) When the pharmacodynamics of equipotent bolus injections of vecuronium 0.043 mg kg$^{-1}$ and atracurium 0.188 mg kg$^{-1}$ were compared, vecuronium was found to have a more rapid onset time and a shorter duration of action than atracurium. The difference in degree of blockade produced by each drug was not, however, statistically significant (table III).

(3) Diisopropyl phenol 2 mg kg$^{-1}$ i.v. over 20 s had no recordable effect on the twitch height when no neuromuscular blocking drug was present.

(4) When diisopropyl phenol 2 mg kg$^{-1}$ over 20 s was given during a steady-state infusion of vecuronium or atracurium there was a decrease in the twitch height for each neuromuscular blocker. With vecuronium there was a 21.8 ± 4.1% decrease in twitch height and with atracurium an 18.5 ± 2.4% decrease. This change in twitch height was significant ($P < 0.01$). There was no difference in the actual decrease between atracurium and vecuronium.

**DISCUSSION**

Since the dose–response curves were parallel (the $\sigma$/ED$_{50}$ ratios were not different), the relative potency of vecuronium to atracurium is valid for other doses. Using the calculated ED$_{50}$ values, vecuronium is about five times more potent than atracurium. This is in agreement with previously reported results (Gramstad and Lilleaasen, 1982; Robertson et al., 1983). The values for ED$_{50}$ and ED$_{90}$ of vecuronium (20.8 $\mu$g kg$^{-1}$ and 32.4 $\mu$g kg$^{-1}$ respectively) and atracurium (103.7 $\mu$g kg$^{-1}$ and 157.6 $\mu$g kg$^{-1}$, respectively) appear, however, to be much smaller than most previously reported results.

**Table II.** ED$_{50}$, ED$_{90}$, and $\sigma$ calculated from dose–response curves of atracurium and vecuronium under diisopropyl phenol anaesthesia. Values are means with SEM in parentheses. $n =$ Number of patients.

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>ED$_{50}$ ($\mu$g kg$^{-1}$)</th>
<th>ED$_{90}$ ($\mu$g kg$^{-1}$)</th>
<th>$\sigma$ ($\mu$g kg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vecuronium</td>
<td>10</td>
<td>20.8 (1.3)</td>
<td>32.4 (1.6)</td>
<td>9.1 (0.6)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>10</td>
<td>103.7 (4.6)</td>
<td>157.6 (10.8)</td>
<td>42.1 (5.4)</td>
</tr>
</tbody>
</table>

**Table III.** Comparison of the pharmacodynamics of atracurium 188 $\mu$g kg$^{-1}$ and vecuronium 43 $\mu$g kg$^{-1}$ under diisopropyl phenol anaesthesia. Values are means with SEM in parentheses.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of patients</th>
<th>Onset time (min)</th>
<th>Duration 25 (min)</th>
<th>Duration 90 (min)</th>
<th>Recovery rate (min)</th>
<th>Maximum block (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vecuronium</td>
<td>10</td>
<td>4.8 (0.3)</td>
<td>12.9 (0.9)</td>
<td>23.2 (1.2)</td>
<td>7.1 (0.5)</td>
<td>95.7 (1.5)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>10</td>
<td>6.1 (0.4)</td>
<td>16.4 (1.8)</td>
<td>29.5 (2.1)</td>
<td>11.0 (1.1)</td>
<td>92.5 (2.7)</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>0.005</td>
<td>0.101</td>
<td>0.017</td>
<td>0.009</td>
<td>0.322</td>
</tr>
</tbody>
</table>

Fig. 1. Dose–response curves for atracurium and vecuronium under diisopropyl phenol anaesthesia ($n =$ 10 patients in each group). The bars are 1 SD.
Gramstad and Lilleaasen (1982) reported an ED50 for vecuronium of 30.3 µg kg⁻¹ and for atracurium 147.7 µg kg⁻¹. Robertson and colleagues (1983), using a technique similar to that used in this study, but without diisopropyl phenol, showed the ED50 and ED90 of vecuronium to be 31.1 µg kg⁻¹ and 43.2 µg kg⁻¹ respectively, and those of atracurium to be 131.1 µg kg⁻¹ and 188.7 µg kg⁻¹ respectively. Krieg, Hendrickx and Crul (1981) observed that vecuronium had an ED50 of 31.6 µg kg⁻¹. In one study (Krieg, Crul and Booij, 1980), vecuronium was demonstrated to have an ED50 of 19.0 µg kg⁻¹. However, this was later shown to be caused by potentiation of vecuronium by the previous administration of suxamethonium (Krieg, Hendrickx and Crul, 1981). Thus, the dose–response curves of vecuronium and atracurium would appear to be shifted to the left in this study. The most likely cause of this is diisopropyl phenol and this would be in agreement with the in vitro study of Fragen and co-workers (1983).

When the pharmacodynamics of bolus injections of vecuronium 43.0 µg kg⁻¹ and atracurium 188.0 µg kg⁻¹ were compared with each other, the degrees of blockade produced were not significantly different. The onset time of vecuronium was shorter than that of atracurium, and the duration 90 shorter for vecuronium when compared with atracurium. There was no statistical difference between the duration 25 of vecuronium and atracurium \((P = 0.1)\). Gramstad, Lilleaasen and Minsaas (1982) showed the duration 25 of atracurium 330 µg kg⁻¹ to be about 1.26 times greater than the duration 25 after vecuronium 66 µg kg⁻¹. This was the same as the relation between duration 25 for atracurium and vecuronium found in this study (1.27) and suggests that, if more patients had been used in this study, this difference would probably have reached significance.

The effect of diisopropyl phenol on the steady state infusion of vecuronium and atracurium during “thiopentone anaesthesia”, confirms the potentiation effect suggested by the dose–response curves. Although high doses of thiopentone enhance myoneural blockers (Foldes, 1959), we believe that such an effect of thiopentone on the neuromuscular junction is not relevant to this study. A normal clinical dose of thiopentone was given to these patients usually 30 min or more before the injection of diisopropyl phenol.

The lack of effect of diisopropyl phenol on twitch height when no myoneural blockade was present suggested that there was a large safety margin, as far as neuromuscular blocking effect is concerned, when this dose of diisopropyl phenol (2 mg kg⁻¹) was given. This may indicate that, with an impaired margin of safety (such as myasthenia gravis), diisopropyl phenol may influence muscle strength much more. How diisopropyl phenol produces this effect has yet to be studied. Of note, however, is the fact that, following the administration of diisopropyl phenol during the steady state infusion, the twitch height had not recovered to its original position after 15–20 min. This is long after the anaesthetic effect of diisopropyl phenol has ended and may suggest an effect of diisopropyl phenol on the muscle itself.

Thus, vecuronium and atracurium both appear to be potentiated by clinical doses of diisopropyl phenol. However, the time course of paralysis produced by these myoneural blockers was not altered by diisopropyl phenol. Vecuronium, in the doses used in this study, was found to be five times more potent and to be shorter-acting than an equipotent dose of atracurium.

**APPENDIX**

**Description of Dose–Response Relationship**

For the analytical description of dose–response relationships of neuromuscular blocking agents, several different mathematical functions have been used. Some authors use a linear relationship between neuromuscular blockade (often limited to a certain range, for example 20–80% blockade) and the logarithm of drug dose (Krieg, Crul and Booij, 1980). Others use an S-shaped curve because of the asymptotic character of the block (upper limit 100%; lower limit 0%) (Donlon et al., 1980). Both logistic curves (van der Veen and Bencini, 1980) and “normal probability integral functions” (Defares, Sneddon and Wise, 1973) are described, while both linear (van der Veen and Bencini, 1980) and logarithmic (Gramstad and Lilleaasen, 1982; Donlon et al., 1980) drug dose scales are used. In this
paper we describe the percentage block as a normal probability integral function of the drug doses in a linear scale. This allows us to use the greatest (100%) degrees of blockade recorded. Thus:

\[
\text{% block} = 100 \times \text{NPI} \frac{C - C_{50}}{\sigma}
\]

where:

- \( C \) = actual drug dose
- \( C_{50} \) = drug dose at which the block is 50%
- \( \sigma \) = standard width of actual underlying Gaussian (normal distribution function)

\[
\text{NPI}(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} e^{-t^2} dt
\]

ACKNOWLEDGEMENTS

The authors thank Drs P. Ponsioen (Chef de Clinique) for arranging clinical sessions, Organon for supplies of vecuronium, the Wellcome Foundation Ltd for supplies of atracurium, and I.C.I. Pharmaceutical Division for supplies of diisopropyl phenol.

REFERENCES


EINIGE EFFEKTE VON DI-ISOPROPYLPHENOL (ICI 35 868) AUF DIE PHARMAKODYNAMIK VON ATRACURIUM UND VECURONIUM BEIM NARKOTISIERTEN MENSCHEN

ZUSAMMENFASSUNG
Be 52 gesunden (ASA I oder II) Patienten wurden die Effekte einer Bolusinjektion von Di-isopropylphenol 2 mg kg⁻¹ und einer Infusion (150 µg kg⁻¹ min⁻¹ über 30 Minuten und 75 µg kg⁻¹ min⁻¹ danach) auf die Pharmakodynamik und Dosis-Wirkungskurve von Atracurium und Vecuronium untersucht. Im Rahmen einer Di-isopropylphenolnarkose wurden die kumulativen Dosis-Wirkungskurven beider Muskelrelaxantien nach links verschoben verglichen mit früher berichteten Ergebnissen. Nach Bolusinjektion des Muskelblockers gab es jedoch keine klinisch signifikante Veränderung in der Pharmakodynamik der beiden Medikamente. Di-isopropylphenolgabe (2 mg kg⁻¹) während steady-state-Infusion von Vecuronium und Atracurium verstärkte die Tiefe der konstanten Muskelrelaxation. Wurde Di-isopropylphenol bei vier Patienten alleine gegeben, ergab sich keine Veränderung in der Einzelreihe. Diese Ergebnisse zeigen, dass Di-isopropylphenolgabe nach dem Schema in dieser Studie die Wirkung beider beobachteten Muskelrelaxantien potenzierte, jedoch nicht die Wirkungsdauer der beiden Präparate verlängerte. Während der Infusion von Di-isopropylphenol zeigte sich Vecuronium 5mal stärker wirksam, mit schnellerem Wirkungseintritt und kürzerer Wirkungszeit als äquipotente Dosen von Atracurium.

BRITISH JOURNAL OF ANAESTHESIA
ALGUNOS EFECTOS DEL BI-ISOPROPILOFENOL (ICI 35868) EN LOS ASPECTOS FARMACODINAMICOS DEL ATRACURION Y DEL VENCURION EN EL HOMBRE ANESTESIADO

SUMARIO
Se estudiaron en 52 pacientes sanos (ASA I o II) los efectos de una inyección de un bolo de bi-isopropilofenol 2 mg kg⁻¹ intravenoso y de una infusión (150 µg kg⁻¹ min⁻¹ por espacio de 30 min y 75 µg kg⁻¹ min⁻¹ posteriormente), sobre los aspectos farmacodinámicos y las curvas de dosisrespuesta relativas al atracurion y al vencurionio. Las curvas acumulativas de dosisrespuesta de ambas drogas de bloqueo mioneural, bajo anestesia con bi-isopropilofenol, se desplazaron hacia la izquierda al compararlas con los resultados anteriormente presentados. No obstante, no hubo cambio clínico alguno de carácter significativo en los aspectos farmacodinámicos de ninguna de las drogas después de llevar a cabo la inyección del bolo de la droga de bloqueo. El bi-isopropilofenol 2 mg kg⁻¹ intravenoso administrado durante infusiones de estado de régimen de vecuronio y de atracurionio, aumentaron la profundidad del bloqueo neuromuscular constante. Cuando a cuatro de los pacientes se les administró de nuevo el bi-isopropilofenol al mismo tiempo, no hubo cambio alguno en el valor máximo de la altura de crisapación. Estos resultados muestran que si el bi-isopropilofenol se administra siguiendo el régimen de éste estudio, potencia ambos agentes de bloqueo neuromuscular estudiados, pero no prolonga el periodo de actividad de ninguno de ellos. Durante la infusión del bi-isopropilofenol se observó que el vencurionio era cinco veces más potente, un periodo de tiempo previo a la actividad que era más corto y de actividad más breve que una dosis equipotente de atracurionio.