NEUROMUSCULAR BLOCKING AND AUTONOMIC EFFECTS OF VECURONIUM AND ATRACURIUM IN THE ANAESTHETIZED CAT

G. A. SUTHERLAND, I. B. SQUIRE, A. J. GIBB AND I. G. MARSHALL

SUMMARY

The effects of vecuronium and atracurium on neuromuscular transmission, on the responses of the heart rate to vagal stimulation and on the responses to preganglionic stimulation of the nictitating membrane were compared in the chloralose-anaesthetized cat. Vecuronium was four times more potent than atracurium as a neuromuscular blocking agent, whereas the two compounds had similar potencies in blocking the effects of stimulation of the cardiac vagus. The vagal/neuromuscular ratios measured at 50% inhibition were 96 for vecuronium and 25 for atracurium. Vecuronium possessed a slightly shorter recovery time than atracurium and shorter duration of action on the soleus muscle. The onset times of the two compounds were not significantly different. Both compounds had longer time-courses of action than suxamethonium. Very large doses of vecuronium decreased the responses of the preganglionic stimulation of the nictitating membrane, suggesting that at high doses the compound possesses ganglion blocking activity. Large doses of atracurium also decrease the nictitating membrane responses and, in some cats, contractions of the nictitating membrane associated with increases in heart rate and arterial pressure were observed.

Vecuronium (OrgNC45) and atracurium are recently developed non-depolarizing neuromuscular blocking agents, both of which possess, in experimental animals, a large safety margin between the doses required to produce neuromuscular blockade and those likely to lead to cardiovascular side-effects (Durant et al., 1979; Hughes and Chappie, 1981). The lack of cardiovascular side-effects at neuromuscular blocking doses has been confirmed in the initial clinical studies of vecuronium (Krieg, Crul and Booij, 1980; Fahey et al., 1981) and atracurium (Payne and Hughes, 1981; Katz et al., 1982).

This study is a comparison of the neuromuscular blocking potencies and time-courses of action of vecuronium and atracurium in the chloralose-anaesthetized cat. In addition, the effects of doses many times greater than those which produce neuromuscular blockade have been tested on the response of the heart rate to vagal stimulation and on the response of the nictitating membrane to preganglionic sympathetic stimulation.

MATERIALS AND METHODS

Cats of either sex were anaesthetized with a mixture of α-chloralose 80 mg kg⁻¹ and pentobarbitone sodium 5 mg kg⁻¹ i.p. In each animal the lungs were ventilated artificially with air via a tracheostomy at a rate of 26 b.p.m. and a tidal volume of 18 ml kg⁻¹. Drugs were administered i.v. via a cannula placed in a femoral vein. Systemic arterial pressure was recorded via a cannula placed in a femoral artery (Statham P23AC pressure transducer). Monitoring of heart rate was achieved by using the pulse pressure to trigger a Grass 7P4F cardiotachometer.

The right vagus nerve was separated in the neck region from the cervical sympathetic nerve and ligated. The vagus nerve was stimulated distally by trains of rectangular pulses of 0.5 ms duration for 10 s every 100 s. The stimulation strength was adjusted to produce maximal responses at any given stimulation frequency, and the frequency was then adjusted, generally within the range 1–5 Hz, to produce a decrease in heart rate of approximately 50%. In some experiments, the left cervical sympathetic nerve was separated from the vagus nerve, ligated and stimulated preganglionically by trains of rectangular pulses of 0.5 ms duration for 10 s every 100 s. The stimulation strength was adjusted to produce maximal contractile responses of the nictitating membrane.

The left sciatic nerve was ligated in the popliteal space and stimulated by rectangular pulses of 0.2 ms duration at a frequency of 0.1 Hz. The stimulation strength was greater than that required to produce maximal twitches of the tibialis anterior and soleus muscles. In one experiment, the right sciatic nerve was stimulated every 30 s with trains-of-four (2 Hz pulses).
for 2 s) and the contractions of the right tibialis anterior muscle were recorded. Contractions of the skeletal muscles and of the nictitating membrane were recorded by Grass FT03C and FT10C strain gauges connected to a Grass 7D ink-writing polygraph.

Dose–inhibition plots for neuromuscular blockade were constructed from the responses of the soleus and tibialis anterior muscles to sciatic nerve stimulation by injecting bolus doses of the drugs at a minimum interval of 1 h. In addition, at least 30 min was allowed after full recovery from one dose before a subsequent dose was administered. Vagal blockade and the effects on the nictitating membrane were assessed by cumulative additions of the drugs at 200-s intervals. Each drug was tested in six separate cats. Dose–inhibition lines were plotted from regression analysis of points lying between 20% and 80% of maximal blockade. \( ED_{20}, ED_{50} \) and \( ED_{90} \) values were calculated by linear interpolation from these lines. Neuromuscular blockade and vagal blockade were measured as a percentage depression of twitch tension or bradycardia, respectively, relative to control responses in the absence of either drug. The onset time of neuromuscular blockade was measured as the time from injection to maximal depression of twitch tension. Recovery time was measured as the time taken for the twitches to recover from 25% to 75% of the control twitch responses, and duration was measured as the time from injection until the twitches had recovered to 90% of control responses. All time-course measurements were made at doses of drugs that produced 75–95% depression of maximal twitch tension. In one cat, vecuronium and atracurium were both tested after the cat had initially received two doses of suxamethonium. The interval between the doses of suxamethonium, and between the last dose of suxamethonium and the first dose of vecuronium, was 1 h.

Results in the text, figures and tables are presented as mean ± standard error of the mean. Statis-

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**Fig. 1.** Comparison between the effects of suxamethonium and vecuronium in the same anaesthetized cat. Records show arterial pressure (AP), heart rate (HR), with responses to vagal stimulation shown as downward deflections, responses of the left soleus and tibialis anterior muscles to left sciatic nerve stimulation, and responses of the right tibialis anterior muscle to trains-of-four (TOF) stimulation of the right sciatic nerve. Drugs were injected at the arrow heads.
COMPARISON OF VECURONIUM AND ATRACURIUM

**RESULTS**

**Neuromuscular blockade**

Both vecuronium and atracurium produced a pattern of neuromuscular blockade that was consistent with a non-depolarizing mechanism of action. Thus, both compounds produced blockade of the twitch response which was not preceded by either twitch augmentation or muscle fasciculations. In addition, the compounds were more effective on the slow-contracting soleus muscle than on the fast-contracting tibialis anterior muscle. In contrast, the neuromuscular blockade produced in one cat by suxamethonium was preceded by fasciculations and twitch augmentation (fig. 1). Suxamethonium preferentially blocked the tibialis anterior muscle rather than the soleus muscle. The effects of suxamethonium and vecuronium in the same cat are illustrated in figure 1. The neuromuscular blockade produced by vecuronium, whilst short in duration for a non-depolarizing agent, was substantially longer than that of suxamethonium tested in the same cat. A similar result was found for atracurium in this cat.

From an analysis of the dose–inhibition lines (both of which were characteristically steep) and ED$_{50}$ values for vecuronium and atracurium, it can be concluded that vecuronium is around four times more potent than atracurium at the neuromuscular junction (figs 2, 3; table I).

As can be seen from the spread of the data points for neuromuscular blockade in figure 2 and from the standard error values for neuromuscular blocking ED$_{50}$ values in table I, there was a greater variation in the depth of neuromuscular blockade produced in response to vecuronium than to atracurium. Thus, for vecuronium the standard errors were 15.5% and 19% of the mean ED$_{50}$ values on the tibialis anterior and soleus muscles, respectively, compared with corresponding values of only 9% and 4% for atracurium.

When tested in separate cats, the time-courses for neuromuscular blockade were all longer for atracurium than for vecuronium (table II). In particular, the recovery times in both tibialis anterior and soleus muscles and the duration of activity in the

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED$_{50}$ (µg kg$^{-1}$)</th>
<th>ED$<em>{50}$ ratio (ED$</em>{50}$ vagus/ED$_{50}$ soleus)</th>
<th>ED$_{20}$ vagus (µg kg$^{-1}$)</th>
<th>ED$_{20}$ soleus (µg kg$^{-1}$)</th>
<th>ED$<em>{20}$ ratio (ED$</em>{20}$ vagus/ED$_{20}$ soleus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vecuronium</td>
<td>29.7 ± 4.6</td>
<td>26.8 ± 5.1</td>
<td>2275.7 ± 519.6</td>
<td>96.4 ± 22.6</td>
<td>32.3 ± 5.5</td>
</tr>
<tr>
<td>Atracurium</td>
<td>123.3 ± 11.5*</td>
<td>101.7 ± 4.1*</td>
<td>2448.3 ± 498.2</td>
<td>25.0 ± 56*</td>
<td>122.3 ± 4.8*</td>
</tr>
</tbody>
</table>

*Significantly different from vecuronium (P < 0.05)
soleus muscle were significantly ($P < 0.05$) longer for atracurium than for vecuronium.

However, in one cat, in which equieffective doses of the two agents were compared directly, the time-courses for the two compounds were almost identical (fig. 3).

In one experiment in which train-of-four stimulation was used, both vecuronium and atracurium produced train-of-four fade. In common with most non-depolarizing agents, the fade was greater at a given depth of block during recovery than during the onset of blockade. There were no apparent differences between the compounds with respect to the amount of fade, or the rate of recovery from fade. Suxamethonium produced virtually no fade of the trains-of-four (fig. 1).

**Autonomic effects**

At doses producing up to 100% neuromuscular blockade, neither vecuronium nor atracurium produced any change in the responses of the heart rate to vagal stimulation, or of the nictitating membrane to preganglionic stimulation. In addition, no significant or consistent changes in arterial pressure were observed.

As reported previously for both compounds (Durant et al., 1979; Hughes and Chappie, 1981; Coker et al., 1981), there was a wide separation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (µg kg$^{-1}$)</th>
<th>% Block</th>
<th>Onset (min)</th>
<th>Recovery (min)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tibialis</td>
<td>Soleus</td>
<td>Tibialis</td>
<td>Soleus</td>
<td>Tibialis</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>37 ± 6</td>
<td>34 ± 8</td>
<td>88 ± 4</td>
<td>89 ± 3</td>
<td>4.6 ± 0.3</td>
</tr>
<tr>
<td>Atracurium</td>
<td>125 ± 12*</td>
<td>121 ± 7*</td>
<td>83 ± 3</td>
<td>88 ± 2</td>
<td>5.8 ± 0.9</td>
</tr>
</tbody>
</table>

*Significantly different from vecuronium ($P < 0.05$)

**TABLE II. Time-course of neuromuscular block produced by vecuronium and atracurium. Results are expressed as mean ± SEM ($n = 5$).**
between doses producing neuromuscular blockade and those producing effects on these autonomic variables. Both compounds produced dose-inhibition lines for the responses of heart rate to vagal stimulation that were much shallower than the lines for neuromuscular blockade.

The ED₅₀ values for vagal blockade from vecuronium and atracurium were not significantly different and hence the difference in the vagal/neuromuscular blocking ED₅₀ ratios (table I) reflects purely the greater neuromuscular blocking potency of vecuronium—a factor of around 4. We have also used the ED₂₀/₅₀ ratio (table I), which compares the dose producing 20% vagal block with that producing 80% neuromuscular block (Drane and Evans, 1979). This value may give a more meaningful indication of the safety margin from autonomic side-effects at degrees of neuromuscular blockade likely to be used for intubation of the trachea in man (Marshall, Gibb and Durant, 1983). The use of this ratio produces a lower separation between neuromuscular and vagal blocking doses for both compounds, resulting in a three-fold difference between the ratios for vecuronium and atracurium as opposed to a four-fold difference if the ED₅₀ ratios are compared (table I).

In seven experiments in which responses to preganglionic stimulation of the nictitating membrane were recorded, no effects were seen with either compound until cumulative doses reached those already producing marked effects on vagal transmission. As reported previously (Durant et al., 1979) very large doses of vecuronium (5–15 mg kg⁻¹) produced a dose-related depression of the responses of the nictitating membrane. This was associated with a decrease in arterial pressure (fig. 4). With atracurium, two effects were seen with these very large doses. As reported previously (Coker et al., 1981), there was a decrease of the responses of the nictitating membrane but, in addition, in two of the cats drug-induced contractions of the nictitating membrane were observed (fig. 5). These contractions appeared to be related to the incremental increases in dose and were associated with short-
DISCUSSION

Vecuronium and atracurium have been studied previously in the anaesthetised cat, but by different groups of workers who used different skeletal muscles and different stimulation schedules to elicit the autonomic responses (Durant et al., 1979; Coker et al., 1981; Hughes and Chappie, 1981). The purpose of this study was to compare the two drugs under identical experimental conditions and to examine the effects of very large doses of the drugs which, in the case of atracurium, have not been reported previously.

Taking into account the spread of results, vecuronium was found to be of the same order of potency at the tibialis anterior and soleus muscles as reported by Durant and colleagues (1979). Atracurium was around 25% more potent at the soleus muscle than had been reported at the gastrocnemius muscle (Hughes and Chappie, 1981), the potency on the tibialis anterior muscle being similar to that on the gastrocnemius, as would be expected for the action of a non-depolarizing blocking drug. The onset times and time-courses of the neuromuscular blockade produced by vecuronium and atracurium were of the same order as reported previously, although precise comparisons are difficult. These results confirm that vecuronium is around four times more potent than atracurium at the cat neuromuscular junction. Studies in man have indicated that vecuronium is around five to 20 times more potent than atracurium (Agoston et al., 1980; Crul and Booij, 1980; Fahey et al., 1981; Payne and Hughes, 1981; Basta et al., 1982; Gramstad and Lilleaasen, 1982; Katz et al., 1982) although, in one study in man (Gramstad and Lilleaasen, 1982), in
which both atracurium and vecuronium were used, the potency ratio between the compounds was similar to that found in the present study. The spread of results for the neuromuscular blocking action of atracurium was much less than that for vecuronium. This may be, at least in part, a result of the chemical degradation of atracurium via Hofmann elimination (Stenlake, 1979). Thus, in the present study, the neuromuscular blocking potency of atracurium was easier to predict than that of vecuronium.

In addition, our results show that the two compounds had similar onset times, but that the recovery time and duration of action of atracurium were slightly longer than those of vecuronium. The relative, but not the absolute, time-courses of action of vecuronium and atracurium were similar to those reported from a comparison of the two drugs in man by Gramstad and Lilleaasen (1982). Both compounds may be classified as having a medium duration of action in the cat, being considerably longer-acting than suxamethonium but shorter-acting than tubocurarine or dimethyl tubocurarine (Hughes and Chapple, 1976).

The ED$_{50}$ values for vecuronium and atracurium in blocking the effects of vagal stimulation on the heart rate were very similar to those reported previously (Durant et al., 1979; Hughes and Chapple, 1981). In addition, the vagal ED$_{50}$ values for vecuronium and atracurium were not significantly different, indicating that the relationship between dose and the degree of vagal blockade was similar for the two drugs. The ED$_{50}$/ratio of vagal/neuromuscular blocking potencies was greater for vecuronium than for atracurium, reflecting the greater neuromuscular blocking potency of vecuronium. Neither drug has been reported to produce tachycardia in normal paralysing doses in man (Agoston et al., 1980; Crul and Booij, 1980; Fahey et al., 1981; Payne and Hughes, 1981; Basta et al., 1982; Gramstad and Lilleaasen, 1982; Katz et al., 1982) but because of the lower ED$_{50}$ and ED$_{50}$/ratio seen with atracurium, this drug would be expected to have a lower safety margin between doses producing muscle paralysis and those liable to produce tachycardia as a result of vagal blockade. In one study in man, doses of atracurium only slightly greater than those producing full neuromuscular blockade produced a small but statistically significant increase in heart rate (Basta et al., 1982).

The effects of very high doses of vecuronium and atracurium were also studied. At doses greater than 5 mg kg$^{-1}$, vecuronium decreased the responses to preganglionic stimulation of the nictitating membrane, confirming the results of Durant and colleagues (1979). These workers also found that responses to postganglionic stimulation of the nictitating membrane were not depressed by these doses of vecuronium. Hence, it is likely that the observed effect reflects ganglion blockade and would be likely to induce a decrease in arterial pressure, as was seen in the present study. High doses of atracurium also depressed responses to pre-ganglionic stimulation of the nictitating membrane, which suggests that this compound may possess ganglion blocking activity. A similar response has been noted by Coker and co-workers (1981). There is some evidence that large doses of atracurium cause histamine release in the dog and man (Hughes and Chapple, 1981; Basta et al., 1982) but in our experiments there was little evidence of effects on arterial pressure which might be associated with such an action. However, relative to the dog, the cat does not readily release histamine and, hence, such an action might be missed in this species. In two experiments large doses of atracurium, the lowest being 60 times the neuromuscular blocking ED$_{50}$ dose, produced increases in arterial pressure and heart rate associated with contractions of the nictitating membrane. No attempt was made to elucidate the mechanism underlying this apparently sympathomimetic effect.

In conclusion, both vecuronium and atracurium are medium duration non-depolarizing agents with a wide margin of safety between the neuromuscular blocking doses and doses likely to lead to autonomic side-effects. In this study vecuronium was slightly shorter in action than atracurium and had a lesser propensity to cause autonomic effects.

ACKNOWLEDGEMENTS

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REFERENCES


Les effets du vecuronium et de l'atracurium sur la transmission neuromusculaire, sur les réponses de la fréquence cardiaque à la stimulation vagale et sur les réponses de la membrane nicotinique à la stimulation préganglionaire ont été comparés chez le chat anesthésié au chloral. Le vecuronium s'est révélé quatre fois plus puissant que l'atracurium comme agent curarisant, alors que les deux produits étaient équivalents pour bloquer les effets de la stimulation parasympathique cardiaque. Le rapport vago-stimulant curarisant mesuré à 50% d'inhibition était de 96 pour le vecuronium et 25 pour l'atracurium. Le vecuronium avait un temps de récupération légèrement plus bref que l'atracurium et une durée d'action plus courte sur le muscle solaire. Les latences d'action des deux produits n'étaient pas significativement différentes. Les deux composés avaient une durée d'action supérieure à celle du suxaméthonium. Des doses très importantes de vecuronium diminuaient les réponses de la membrane nicotinique à la stimulation préganglionnaire, ce qui suggère qu'à fortes doses, le composé possède une activité ganglioplégique. De fortes doses d'atracurium diminuaient également les réponses de la membrane nicotinique et, chez certains chats, des contractions de la membrane nicotinique associées à des augmentations de fréquence cardiaque et de pression artérielle ont été observées.

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SUMARIO

En el gato anestesiado con cloralosa, se comparó los efectos del vecuronio y del atracurio sobre la transmisión neuromuscular, sobre las respuestas del ritmo cardíaco al estímulo vagal y sobre las respuestas al estímulo preganglionar de la membrana pestañera. El vecuronio fue cuatro veces más potente que el atracurio como agente de bloqueo muscular mientras que los dos compuestos tenían la misma potencia para bloquear los efectos del estímulo del nervio vago cardíaco. Las relaciones vago/neuromuscular medidas en un 50% de inhibición eran de 96 para el vecuronio y de 25 para el atracurio. El vecuronio demostró un tiempo de recuperación ligeramente más corto que el atracurio y más corta duración de acción sobre el músculo sóleo. Los tiempos de inicio de la acción de los dos compuestos fueron poco diferentes. Ambos compuestos tuvieron duración de acción más larga que el suxametonio. El vecuronio en dosis muy fuertes redujo las respuestas al estímulo preganglionar de la membrana de pestaña, lo que sugiere que en dosis mayores, el compuesto tiene una actividad bloqueadora de los ganglios. El atracurio en dosis mayores también redujo las respuestas de la membrana de pestañera y, en algunos gatos, se observaron unas contracciones de la membrana de pestañera asociadas con los aumentos del ritmo cardíaco y de la presión arterial.