COMPARISON OF SPEED OF ONSET OF FAZADINIUM, PANCURONIUM, TUBOCURARINE AND SUXAMETHONIUM

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SUMMARY

Under light general anaesthesia the speed of onset of action of fazadinium, pancuronium, tubocurarine and suxamethonium has been assessed by measuring the decrease in the twitch height of the adductor pollicis muscle following administration of the drugs. Suxamethonium produced 95% depression of the twitch height significantly faster than any of the other drugs, while the onset of fazadinium was significantly more rapid than that of the other non-depolarizing neuromuscular blocking drugs.

The effects in man of fazadinium, the latest non-depolarizing muscle relaxant to be introduced to clinical practice, have been described by Simpson and others (1972). This drug differs in configuration from other neuromuscular blocking drugs in that the distance between the two quaternary nitrogen atoms is 7.5 Å (compared with 12-16 Å for other competitive neuromuscular blocking drugs). The shorter distance is associated usually with ganglion blocking properties (Schuh, 1975).

The main advantage claimed for fazadinium is its rapidity of action. Several workers have compared its speed of onset with that of other neuromuscular blocking drugs by assessing conditions for tracheal intubation (Arora et al., 1973; Coleman et al., 1973; Young, Clarke and Dundee, 1975; Corall et al., 1977; Mehta, Lewin and Fidler, 1977). One of the earliest reports suggested that the speed of onset of fazadinium was as rapid as that of suxamethonium (Blogg et al., 1973).

Despite all efforts to eliminate bias, assessment of intubating conditions is of necessity a subjective phenomenon. Ease of intubation will depend not only on the degree of neuromuscular block, but also on the depth of anaesthesia at the time of attempted intubation, the anatomical configuration of the patient and, not least, the skill of the anaesthetist.

An objective comparison of the rate of onset of neuromuscular blocking drugs can be obtained by recording the response of a muscle to stimulation of the appropriate nerve. The speed of onset of action can be obtained by examining the percentage change of the twitch height from control values. In this study, the speeds of onset of fazadinium, pancuronium, tubocurarine and suxamethonium were compared using such a method.

METHODS

Studies were performed on 80 patients, who were allocated randomly to receive fazadinium 1 mg kg⁻¹, pancuronium 0.1 mg kg⁻¹, tubocurarine 0.5 mg kg⁻¹ or suxamethonium 1.0 mg kg⁻¹, in such a way that there were 20 patients in each group. Any adult patient in whom there was no contraindication to any of the neuromuscular blocking drugs and who was not in cardiac failure or suffering from any neurological or skeletal disease was included in the study. The doses of the non-depolarizing relaxants were those normally used clinically and were thought to be equipotent (Baird and Reid, 1967; Norman, Katz and Seed, 1970; Hughes, Payne and Sugai, 1976). The dose of suxamethonium was in the normal clinical range.

Premedication was not standardized. Anaesthesia was induced by injection via an indwelling needle in a large forearm vein. Fentanyl 50–100 μg was injected over a period of 1 min, followed by a dose of methohexitone sufficient to induce sleep. Anaesthesia was maintained with nitrous oxide in oxygen delivered via a Magill circuit and face mask, with incremental doses of methohexitone 10–20 mg as needed. The lungs of any patient who became apnoeic were ventilated artificially, but no myoneural blocking drug was given until spontaneous ventilation had returned and was judged to be adequate.

The ulnar nerve was stimulated supramaximally at the elbow at a frequency of 0.5 Hz and with a stimulus duration of 0.1 ms, using a Palmer stimulator (model 8048). Initially, the twitch response of the
adductor pollicis was recorded, on a Devices recorder using a Grass strain-gauge, for at least 2 min before the administration of the relaxant. The latter was then given rapidly via the indwelling needle. The times from the mid-point of the injection to depression of the twitch height by 25%, 50%, 75% and 95% of the control values were measured.

RESULTS

The groups of patients were comparable with regard to age, weight and sex distribution. In the tubocurarine group, one patient achieved only a 37% depression of twitch height 7 min after injection of the drug and was excluded from analysis of the results. A further patient in this group did not exhibit 95% block and hence only 18 patients are included in the tubocurarine group in the 95% block category.

The results obtained are shown in table I and illustrated graphically in figure 1. A one-way analysis of variance demonstrated a statistically significant difference at the time of 95% block \( F = 23.098; P<0.001 \). Student's t tests showed that the speed of onset of suxamethonium to this point was significantly faster than that of all the other drugs \( P<0.001 \) in each case.

<table>
<thead>
<tr>
<th>Time to depression of twitch height (s) by</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium</td>
<td>31.0</td>
<td>34.9</td>
<td>38.9</td>
<td>49.2</td>
</tr>
<tr>
<td>± 1.84</td>
<td>± 1.89</td>
<td>± 1.83</td>
<td>± 1.68</td>
<td></td>
</tr>
<tr>
<td>Fazadinium</td>
<td>37.9</td>
<td>46.4</td>
<td>64.7</td>
<td>103.1</td>
</tr>
<tr>
<td>± 2.69</td>
<td>± 3.59</td>
<td>± 5.61</td>
<td>± 10.85</td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>63.9</td>
<td>80.2</td>
<td>102.5</td>
<td>141.4</td>
</tr>
<tr>
<td>± 3.04</td>
<td>± 3.97</td>
<td>± 4.84</td>
<td>± 7.32</td>
<td></td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>47.7</td>
<td>64.6</td>
<td>102.7</td>
<td>173.2</td>
</tr>
<tr>
<td>± 2.87</td>
<td>± 4.10</td>
<td>± 11.83</td>
<td>± 19.50</td>
<td></td>
</tr>
</tbody>
</table>

If the results obtained for suxamethonium are excluded from the analysis, then a one-way analysis of variance showed again that the results were significantly different \( F = 7.306; P<0.01 \). Student's t tests then showed that fazadinium produced 95% depression of twitch height significantly faster than pancuronium \( P<0.01 \) and tubocurarine \( P<0.005 \). There was no significant difference in the time for 95% depression of twitch height between pancuronium and tubocurarine \( P>0.1 \).

Several factors influence the speed with which tracheal intubation can be achievedatraumatically. Apart from the degree of neuromuscular block these include the depth of anaesthesia, the anatomical configuration of the patient and the skill of the anaesthetist. Although intubation can be performed under deep general anaesthesia, modern techniques usually involve the administration of a dose of an i.v. induction agent sufficient to induce sleep, followed by a muscle relaxant, such light levels of anaesthesia being mandatory in ill patients and in obstetric practice.

Under thiopentone anaesthesia, Donlon, Ali and Savarese (1974) have shown that, although conditions were not perfect, intubation could be achieved easily by relatively inexperienced anaesthetists once the twitch height of the adductor pollicis had been depressed by 95% from its control value. Thus following the administration of various muscle relaxant drugs, a comparison of the times required to effect a 95% depression in the twitch height would be an indication of the speed at which intubation could be performed, while eliminating any subjective bias in an assessment of the manoeuvre.

The results reported here show that, in the doses used, depression of the twitch height to 95% of the
control values was achieved significantly more rapidly with suxamethonium than with any of the other drugs. There was no significant difference in the time to this point between pancuronium and tubocurarine. This is almost certainly a result of the very wide scatter in the results obtained with tubocurarine. Also, two patients in this particular group did not attain this degree of twitch depression. Harrison (1972) has shown that the time to 95% twitch depression and to intubation is more rapid following pancuronium than that following tubocurarine. The speed of onset of fazadinium was significantly faster than that of the other two non-depolarizing relaxants.

In 1961, Paton proposed that the speed of action of a blocking agent reflected its rate of reaction with receptors. However, Waud (1967) examined four neuromuscular blocking agents in animals and showed that, when they were applied directly to the receptors, they all acted rapidly and behaved as if access to the receptor was the rate-limiting factor. Thus, it may well be that the speed of onset of neuromuscular blocking drugs does not depend on the rate at which they combine with their receptors, but on the speed with which they diffuse from the plasma to the receptor site. This in turn would depend on such factors as molecular size, degree of ionization and protein binding. It is interesting to note that the distance between the two quaternary nitrogen atoms in the fazadinium molecule is 7.5 Å, compared with 12–16 Å in other competitive muscle relaxant drugs (Schuh, 1975).

Initial work with fazadinium indicated that rapid intubation was possible (Simpson et al., 1972; Arora et al., 1973) and Coleman and his colleagues (1973) achieved "crash intubation" in a comparable time following suxamethonium 75 mg or fazadinium 1.5 mg kg\(^{-1}\). Similarly, Mehta, Lewin and Fidler (1977) showed no significant difference in the time to intubation following suxamethonium 50 or 75 mg or fazadinium 1.0 or 1.5 mg kg\(^{-1}\). They showed further that intubation was performed most rapidly following suxamethonium 100 mg. This dose of suxamethonium gave also the highest incidence of excellent intubating conditions, a finding which substantiated that of other workers (Young, Clarke and Dundee, 1975; Hartley and Fidler, 1977).

Increasing the dose of fazadinium might well increase its speed of onset, but would result also in more prolonged paralysis. However, Hartley and Fidler (1977) and Mehta, Lewin and Fidler (1977) found that increasing the dose of fazadinium did not produce significantly better intubating conditions.

When rapid intubation is not essential then the choice of muscle relaxant will depend on such factors as the desirability of avoiding changes in heart rate and arterial pressure, the duration of surgery, etc. From the clinical work performed it appears that suxamethonium produces better intubating conditions than fazadinium. The results of the present study provide objective evidence that the speed of onset of suxamethonium is significantly faster than fazadinium and confirms that pancuronium and tubocurarine are unsuitable for rapid intubation. It is concluded that fazadinium cannot replace suxamethonium when rapid tracheal intubation is required under light general anaesthesia.

REFERENCES


VERGLEICH DER WIRKUNGSGESCHWINDIGKEIT VON FAZADINIUM, PANCURONIUM, TUBOCURARIN UND SUXAMETHONIUM

ZUSAMMENFASSUNG
Unter leichter Allgemeinnarkose wurde die Wirkungsgeschwindigkeit dieser vier Drogen verglichen, indem das Absinken der Zuckhöhe des Muskels adductor pollicis nach Verabreichung der Drogen gemessen wurde. Suxamethonium bewirkte eine 95%ige Depression der Zuckhöhe wesentlich schneller als die anderen Drogen, während das Einsetzen der Wirkung bei Fazadinium wesentlich rascher erfolgte als bei den anderen, nicht depolarisierenden, neuromuskulär blockierenden Drogen.

COMPARACION DE LA RAPIDEZ DE ACCION ENTRE FAZADINIO, PANCURONIO, TUBOCURARINA Y SUXAMETONIO

SUMARIO
Se ha evaluado bajo anestesia general liviana la rapidez de acción entre fazadinio, pancuronio, tubocurarina y suxametonio, midiendo la disminución en el nivel de sacudida del músculo aductor pollicis siguiendo la administración de las drogas. El suxametonio produjo una depresión de un 95% del nivel de sacudida en forma significativamente más rápida que cualquiera de las otras drogas, mientras que la acción del fazadinio fue significativamente más rápida que la de las demás drogas no depolarizadas para bloqueo neuromuscular.