COMPARISON OF CUMULATIVE AND SINGLE BOLUS DOSE TECHNIQUES FOR DETERMINING THE POTENCY OF VECURONIUM

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Vecuronium, a recently introduced, relatively shorter-acting monoquaternary analogue of pancuronium, is considered to be almost equipotent to pancuronium (Gramstad and Lilleaasen, 1982; Ferres et al., 1984) when the potency is determined using a cumulative dose technique. Although the potency of longer-acting agents such as pancuronium and tubocurarine, as judged by the 95% blocking dose (ED$_{95}$), has been shown to be similar using either single bolus or cumulative dose techniques (Donlon et al., 1980), this has not been determined for vecuronium. Fisher and his colleagues (1982) showed that vecuronium was more potent when assessed by the single bolus dose technique in comparison with a cumulative dose technique; however, these workers did not provide any information on the traditionally used index of ED$_{95}$ and, in addition, were using halothane anaesthesia, which in itself could affect the potency of vecuronium. In the present study, the potency of vecuronium has been determined using a single bolus dose method and the results compared with our previously published results (Ferres et al., 1984) using a cumulative dose method.

PATIENTS AND METHODS

The study was carried out in 28 adult patients conforming to ASA grade I, who were to undergo elective surgery for repair of retinal detachments or follow-up surgery for trauma to the eye. All patients gave informed consent and the investigation was approved by the regional ethics committee.

SUMMARY

The potency of vecuronium was determined using single bolus dose administrations of 10–50 \( \mu g \) kg$^{-1}$ in 28 patients anaesthetized with thiopentone, nitrous oxide, oxygen and fentanyl. The results were compared with those previously obtained using a cumulative dose technique in a comparable group of 10 patients. The 50% and 95% blocking doses (ED$_{50}$ and ED$_{95}$) of vecuronium were found to be 23.1 and 39.6 \( \mu g \) kg$^{-1}$, respectively. These were significantly lower than the 30.5 and 56.7 \( \mu g \) kg$^{-1}$ obtained previously using the cumulative dose technique. We recommend the use of single bolus dose method of determining potency for relatively shorter-acting drugs like vecuronium.

The anaesthetic technique and the method of studying neuromuscular transmission were exactly the same as in our previous study using the cumulative dose technique (Ferres et al., 1984). Following premedication with diazepam 10–15 mg by mouth, anaesthesia was induced with thiopentone 4–5 mg kg$^{-1}$ i.v. and maintained with 66% nitrous oxide, and fentanyl 4–5 \( \mu g \) kg$^{-1}$. Additional increments of fentanyl 25–50 \( \mu g \) kg$^{-1}$ or thiopentone 50–75 mg were administered before giving vecuronium if required. The ulnar nerve was stimulated at the wrist with supramaximal stimuli of 0.2 ms duration at 0.1 Hz using surface electrodes, the resultant force of thumb adduction being recorded on a neuromuscular function analyser (Viby-Mogensen, 1982).

Following stabilization of the control twitch height for at least 10 min, patients were randomly allocated to receive vecuronium in doses of 10 \( (n = 4) \), 20 \( (n = 6) \), 30 \( (n = 6) \), 40 \( (n = 6) \) or 50 \( \mu g \) kg$^{-1}$ \( (n = 6) \) as a single bolus. The maximal
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Fig. 1. Dose–response curves using the single bolus and cumulative dose techniques. Each point represents mean±SEM. (The line for cumulative dose technique is based on the data from Ferres and colleagues (1984).)

depression in twitch height obtained in each patient was recorded.

An arc–sine transformation of the data relating to twitch height was carried out, as suggested by Armitage (1971) for responses involving the extremes (0 and 100%) on the dose–response curve. A linear regression analysis was carried out using the method of least squares, and the dose–response curve constructed. This was compared with the curve obtained previously using the cumulative dose technique. The calculated values of ED$_{50}$ and ED$_{95}$ with the two techniques were tested for statistical difference from each other using a Student’s $t$ test.

RESULTS

The patients in the present study were comparable to those in the previously reported study using the cumulative dose method (table I). The dose–response line from the present study and that obtained using the cumulative dose technique (Ferres et al., 1984) are shown in figure 1. The slopes of the two curves did not differ from each other, but the one produced using the single bolus dose method was to the left of that produced using the cumulative dose method, indicating the higher potency of the drug when the single bolus dose method was used. The ED$_{50}$ and ED$_{95}$ of vecuronium were 23.1 and 39.6 µg kg$^{-1}$, respectively, with the single bolus dose technique in comparison with 30.5 and 56.7 µg kg$^{-1}$, respectively, using the cumulative dose method (table I). The differences were significant ($P < 0.05$) for each end point.

The time taken to attain the maximum effect of each bolus dose varied with the size of the dose, ranging from an average of 6.7 min following a 20-µg kg$^{-1}$ dose to 4.5 min following a 50-µg kg$^{-1}$ dose, 10 µg kg$^{-1}$ producing a block of 7% in only one patient.

DISCUSSION

A cumulative dose technique is preferred to a single bolus dose technique for determining the potency of neuromuscular blocking drugs, since the method requires fewer patients. The potency of drugs like pancuronium and tubocurarine is similar with the two methods (Donlon et al., 1980); however, the results from the present study clearly demonstrate that the method of determining potency of relatively shorter-acting agents like vecuronium influences the results, the single bolus dose technique giving a higher potency. The conclusions agree with those of Fisher and his colleagues (1982) who demonstrated similarly that vecuronium was more potent when the single bolus dose method of estimating potency was used. Only the ED$_{50}$ obtained by us can be compared with their findings, since they did not give any figures for ED$_{95}$. The ED$_{50}$ values as obtained by Fisher and co-workers (1982) by both methods are lower than those obtained by us, but they were using halothane anaesthesia throughout, which has been shown to increase the potency of vecuronium (Foldes, Bencini and Newton, 1980). Katz and his colleagues (1982) showed similar

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<th>Table I. ED$<em>{50}$ and ED$</em>{95}$ of vecuronium by cumulative dose and single dose methods. †From Ferres and colleagues (1984). *Significantly different from cumulative dose method (P &lt; 0.05). Figures in parentheses are 95% confidence intervals</th>
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<tbody>
<tr>
<td>Cumulative dose† method</td>
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<tr>
<td>Age (yr) (mean ± SEM)</td>
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<td>Weight (kg) (mean ± SEM)</td>
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<tr>
<td>ED$_{50}$ (µg kg$^{-1}$)</td>
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<td>(24.4–36.7)</td>
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<td>ED$_{95}$ (µg kg$^{-1}$)</td>
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results for atracurium, another relatively shorter acting agent, when they found that a dose of 0.25 mg kg⁻¹ produced a 95% or greater blockade when used as a single bolus in comparison with an average block of only 70% when the same total dose was administered in the form of smaller increments. Our own results with atracurium (Gibson et al., 1985) confirmed these findings.

The main reason for the difference in the results with the two techniques must lie in the shorter duration of action of vecuronium, particularly with the smaller doses used in incremental dose–response studies, significant recovery occurring before the next increment is administered, since this could sometimes be as long as 10–12 min (Fahey et al., 1981; Fisher et al., 1982). In the cumulative method, the next increment of the neuromuscular blocker is administered whenever the three successive twitches are of similar height (Donlon, Ali and Savarese, 1974) following the previous increment. It is possible that the maximum effect of the drug may not be apparent with the low doses of a drug like vecuronium for as long as an average of 6.7 min after a dose of 10 μg kg⁻¹ (Fahey et al., 1981). This was borne out in the present study as well, in which a 20-μg kg⁻¹ bolus produced its maximal effect in over 6.5 min.

In conclusion, the potency of vecuronium is greater when estimated by the single bolus dose technique. Since most anaesthetists administer neuromuscular blocking drugs as a bolus, it is suggested that this technique be used for assessing potency of agents like vecuronium. We further support the suggestion made by Fisher and his colleagues (1982) not to use cumulative dose–response techniques for determining potency of medium- and short-acting agents such as vecuronium and atracurium. If a cumulative dose–response technique is used, it is suggested that a larger initial dose followed by fewer and larger increments be used to minimize the effect of the time factor.

NOTE ADDED IN PROOF: Since the submission of this paper, a similar study, with similar conclusions, has been published (Ørding, H., Skovgaard, L. T., Engbaek, J. and Viby-Mogensen, J. (1985). Dose–response curves for vecuronium during halothane and neurolept anaesthesia: Single bolus versus cumulative method. Acta Anaesthesiol. Scand., 29, 121.)

ACKNOWLEDGEMENT

The authors are grateful to the nursing and theatre staff in the eye theatres at the Royal Victoria Hospital, Belfast.

REFERENCES


