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INFLUENCE OF "PRIMING" ON THE POTENCY OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

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SUMMARY

Dose–response curves have been constructed to determine the ED_{50} and ED_{95} (doses required to produce a 50% and a 95% block, respectively) following administration of a small "priming" dose of atracurium 50 μg kg^{-1}, vecuronium 10 μg kg^{-1} or pancuronium 10 μg kg^{-1}. The myoneural blockers were administered subsequently as a single bolus. The results were compared with previously published work on these drugs, in which no priming dose had been administered. The respective ED_{50} and ED_{95} values in the primed and control groups were 122 and 126 μg kg^{-1} and 208 and 226 μg kg^{-1}, respectively, for atracurium; 26 and 23 μg kg^{-1} and 42 and 39 μg kg^{-1}, respectively, for vecuronium; and 31 and 30 μg kg^{-1} and 56 and 60 μg kg^{-1}, respectively, for pancuronium. The values showed no significant differences between the respective primed and control groups. Contrary to previous suggestions, our results show no enhancement of blockade when these drugs were administered in divided doses.

It has been suggested that the onset of action of non-depolarizing neuromuscular blocking drugs can be accelerated by "priming"—the administration of the agent in divided doses (Foldes, 1984; Doherty et al. 1985; Mehta et al., 1985; Schwarz et al., 1985; Black et al., 1986). In addition, it has been argued that the block produced by the administration of these drugs in divided doses may be more intense than when the same total dose is given as a single bolus (Foldes, 1984; Doherty et al., 1985; Schwarz et al., 1985; Black et al., 1986). However, at present there is no evidence to support the possible potentiation of effect in association with priming. This point has been investigated, in the present study, by constructing dose–response curves for atracurium, vecuronium and pancuronium after priming, and then comparing the results with those obtained previously in control (non-primed) groups (Gibson et al., 1985a, b; Gibson and Mirakhur, 1987).

PATIENTS AND METHODS

Seventy-eight adult patients (ASA grades I and II) undergoing elective surgery requiring the use of neuromuscular blockade were included in the study. The informed consent of the patients and the approval of the regional ethics committee were obtained. Patients were premedicated with diazepam 10–15 mg by mouth and anaesthetized with thiopentone 5–6 mg kg^{-1}, nitrous oxide in oxygen and fentanyl 4–5 μg kg^{-1}. Further smaller increments of fentanyl were given, as required. Ventilation was adjusted to maintain the end-tidal carbon dioxide concentration between 4.5 and 5.0%.

The ulnar nerve was stimulated percutaneously at the wrist using a peripheral nerve stimulator (Myotest) delivering supramaximal square wave stimuli of 0.2 ms duration at a frequency of 0.1 Hz. The resultant force of contraction of adductor pollicis was measured and recorded using a force displacement transducer and a neuromuscular

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function analyser (Myograph 2000). A preload of 300 g was applied throughout the study.

Following stabilization of the control twitch height for about 10 min patients were randomly allocated to receive atracurium, vecuronium or pancuronium. A priming dose of atracurium 50 $\mu g\ kg^{-1}$, vecuronium 10 $\mu g\ kg^{-1}$ or pancuronium 10 $\mu g\ kg^{-1}$ was administered. Four minutes later patients were given a single dose of atracurium 50, 100, 150 or 200 $\mu g\ kg^{-1}$, vecuronium 10, 20, 30 or 40 $\mu g\ kg^{-1}$, or pancuronium 10, 20, 30, 40 or 50 $\mu g\ kg^{-1}$ to obtain dose–response data using a single dose method as described previously (Gibson et al., 1985a, b; Gibson and Mirakhur, 1987). The size of the increments of neuromuscular blocker was the same as in our previous studies of dose–response relationships in the absence of the priming doses. There were six patients in each of the subgroups. The maximum degree of blockade attained and the time taken to achieve this were recorded in each patient. The same drug was administered to each patient both for priming and, subsequently, as the main dose. The data were subject to arc–sine transformation as described by Armitage (1971) for responses involving the extreme end-points (0 and 100%) on the dose–response curves. Dose–response curves were constructed following regression analysis. The data were compared (using a *t* test) with our previously published results on potency estimates for each of the three drugs (Gibson et al., 1985a, b; Gibson and Mirakhur, 1987). These earlier studies had been carried out using exactly the same methodology, with the exception of administration of the priming doses.

TABLE I. *Physical characteristics*

	n	Age (yr ± SEM)	Weight (kg ± SEM)
Atracurium			
Primed group	24	48 ± 6.44	71 ± 5.49
Control group (Gibson et al., 1985a)	28	40 ± 6.68	65 ± 4.74
Vecuronium			
Primed group	24	44 ± 5.98	72 ± 6.54
Control group (Gibson et al., 1985b)	30	38 ± 3.12	67 ± 3.84
Pancuronium			
Primed group	30	48 ± 5.95	74 ± 5.54
Control group (Gibson and Mirakhur, 1987)	36	44 ± 5.52	66 ± 4.34

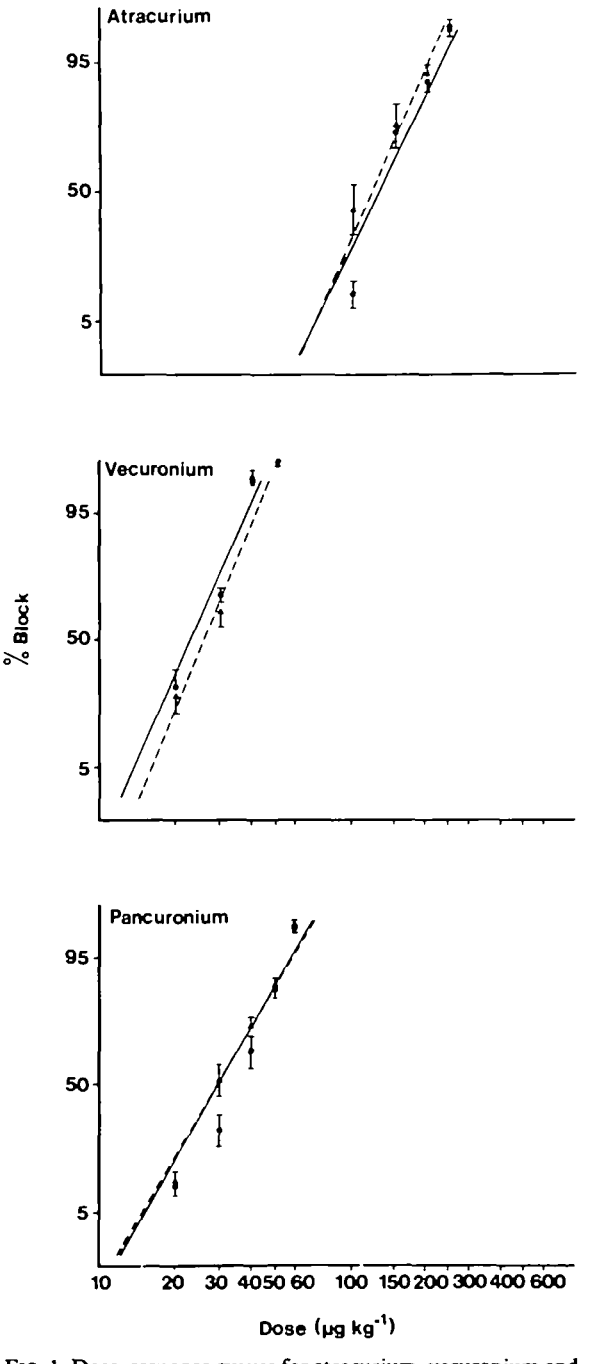

FIG. 1. Dose–response curves for atracurium, vecuronium and pancuronium in the primed (▲——▲) and control (non-primed, ●——●) groups. Data for control groups from Gibson and colleagues (1985a) for atracurium; Gibson and colleagues (1985b) for vecuronium; and Gibson and Mirakhur (1987) for pancuronium. Doses on the *x*-axis are on log-scale and responses following arc–sine transformation are on the *y*-axis.

TABLE II. *ED_{50} and ED_{95} values in the primed and control groups*

	ED_{50} (μg kg^{-1}) (95% confidence intervals)	ED_{95} (μg kg^{-1}) (95% confidence intervals)
Atracurium		
Primed group	122 (117–127)	208 (203–213)
Control group (Gibson et al., 1985a)	126 (115–137)	226 (207–246)
Vecuronium		
Primed group	26 (22–30)	42 (38–46)
Control group (Gibson et al., 1985b)	23 (20–26)	40 (36–43)
Pancuronium		
Primed group	31 (27–34)	56 (48–64)
Control group (Gibson and Mirakhur, 1987)	30 (24–36)	60 (48–72)

TABLE III. *Average maximum blockade following administration of various doses of the neuromuscular blockers in the primed and control groups.* n = 6 *for each subgroup except the vecuronium control group given 10 μg kg^{-1}, where* n = 4*). Data for control groups from: *Gibson et al. (1985a); †Gibson et al. (1985b); ‡Gibson and Mirakhur (1987). Ns = Not significant*

	Maximum block (% ± SEM)			Time taken to attain maximum block (min ± SEM)		
	Primed group	Control group	*P*	Primed group	Control group	*P*
Atracurium*						
50 μg kg^{-1}	—	—		—	—	
50+ 50 μg kg^{-1}	41 ± 10.11	16 ± 5.7	< 0.05	4.3 ± 1.37	6.6 ± 0.97	< 0.02
50 + 100 μg kg^{-1}	72 ± 13.08	70 ± 8.0	ns	6.3 ± 0.53	6.2 ± 0.69	ns
50 + 150 μg kg^{-1}	92 ± 2.29	88 ± 3.3	ns	5.5 ± 0.78	5.9 ± 0.43	ns
50 + 200 μg kg^{-1}	98 ± 1.36	98 ± 1.3	ns	4.8 ± 0.75	5.9 ± 0.86	ns
Vecuronium†						
10 μg kg^{-1}	—	—		—	—	
10 + 10 μg kg^{-1}	28 ± 10.28	31 ± 10.16	ns	2.9 ± 0.53	6.7 ± 0.48	< 0.001
10 + 20 μg kg^{-1}	62 ± 12.18	68 ± 8.0	ns	4.1 ± 0.47	6.1 ± 0.89	ns
10 + 30 μg kg^{-1}	96 ± 3.83	98 ± 1.02	ns	4.3 ± 0.64	4.9 ± 0.92	ns
10 + 40 μg kg^{-1}	98 ± 1.16	99 ± 0.49	ns	3.9 ± 0.55	4.5 ± 0.19	ns
Pancuronium‡						
10 μg kg^{-1}	—	2 ± 1.16	ns	—	7.9 ± 0.36	
10 + 10 μg kg^{-1}	13 ± 5.30	12 ± 5.96	ns	3.8 ± 0.31	7.8 ± 0.30	< 0.001
10 + 20 μg kg^{-1}	51 ± 9.99	32 ± 10.57	ns	4.9 ± 0.34	7.4 ± 0.81	< 0.02
10 + 30 μg kg^{-1}	76 ± 5.63	65 ± 11.59	ns	5.4 ± 0.28	8.5 ± 1.55	ns
10 + 40 μg kg^{-1}	89 ± 4.60	88 ± 6.08	ns	6.6 ± 0.74	8.4 ± 1.71	ns
10 + 50 μg kg^{-1}	99 ± 1.00	98 ± 1.67	ns	5.8 ± 1.49	6.1 ± 1.51	ns

RESULTS

The groups were comparable in their physical characteristics (table I), and these were similar to those of the patients in our previous studies in which the dose–responses were studied without priming.

The dose–response curves for atracurium, vecuronium and pancuronium are shown in figure 1. These did not differ significantly in their slopes, and the lines for primed and control groups were almost superimposed for each of the myoneural blockers. The actual calculated ED_{50} and ED_{95} values (doses producing 50% and 95% blockade, respectively) are given in table II, those for the control groups being from our previously published data. The calculated ED_{95} for the primed and the control groups were 208 and 226 μg kg^{-1}, respectively, for atracurium; 42 and 40 μg kg^{-1},

respectively, for vecuronium and 56 and 60 μg kg^{-1}, respectively, for pancuronium. These were not significantly different from each other, nor were the respective ED_{50} as given in table II.

The average maximum degree of blockade produced by each increment, and the times taken to achieve maximum blockade—whether given as a bolus or in divided doses—are shown in table III. It is clear that there were very few significant differences between the primed and the control groups in the degree of neuromuscular block produced, or the time to achieve blockade.

DISCUSSION

It has been suggested by Foldes (1984), Doherty and co-workers (1985) and Schwarz and colleagues (1985) that the degree of blockade produced by the administration of a given dose of vecuronium or pancuronium in divided doses produced a more intense degree of block than when the same dose was given as a single bolus. More recently, the same has been suggested by Black and colleagues (1986) in relation to alcuronium. However, the results from the present study demonstrate that the administration of any particular dose of atracurium, vecuronium or pancuronium produced the same degree of blockade whether given as a single bolus or in divided doses. It is difficult to find an explanation for potentiation with the use of myoneural blocking drugs in divided doses, on the basis of recently published work which compares the cumulative and single dose techniques. All show a significantly greater degree of blockade when atracurium or vecuronium were administered as a single bolus (Fisher et al., 1982; Katz et al., 1982; Gibson et al., 1985a, b) or, in the case of pancuronium, no difference (Gibson and Mirakhur, 1987). Obviously, the technique of priming is somewhat akin to a cumulative technique. A possible reason for the claims made by other workers for more intense blockade could be the use of relatively larger doses of neuromuscular blocking agents which produce close to complete blockade, under which circumstances it would be difficult to detect any differences in the degree of block produced. In addition, others have used different doses in primed and in control subjects (Taboada, Rupp and Miller, 1986). Although some of the previously published studies had shown some advantage of priming in terms of an acceleration in the onset of blockade, more recent studies, in which the same neuromuscular blocker has been administered for priming and for subsequent use, have failed to confirm these results (Ramsey et al., 1985; Weinberg, Stirt and Longnecker, 1985; Donati et al., 1986; Ramsey, Morell and Gerr, 1986; Brady et al., 1987). However, accelerated onset or potentiation of blockade may be expected, and has been observed, when different drugs are used for priming and subsequent administration; for example, tubocurarine or metocurine for priming and pancuronium or vecuronium for subsequent administration (Donati et al., 1986; Ramsey, Morell and Gerr, 1986). This is the result perhaps of the use of potentiating combinations of drugs based on their relatively different pre- and post-junctional effects.

It is not within the remit of this study to comment on the usefulness of priming technique, but it is likely that the only benefit is some improvement in the intubating conditions with the use of atracurium and vecuronium—as has been reported previously (Schwarz et al., 1985; Mirakhur et al., 1986). However, with doses of atracurium and vecuronium in the order of 0.5 and 0.1 mg kg^{-1}, respectively, one can intubate the trachea in the absence of a complete block (Mirakhur et al., 1983, 1985); thus this would not be a very discriminating technique with which to show the differences resulting from priming.

In conclusion, the results from the present study show that the administration of the same neuromuscular blocking drug in divided doses (the "priming" technique) is not associated with an increase in potency.

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