PRIMING WITH ALCURONIUM AND TUBOCURARINE ACCELERATES THE ONSET OF NEUROMUSCULAR BLOCK

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The ideal neuromuscular blocking agent should have a rapid onset of action and a non-depolarizing character [1]. In order to accelerate the rate of onset of action, several techniques have been described, including the administration of a large bolus dose several times that required to achieve full neuromuscular block [2], and preliminary priming with a small subparalytic dose of the drug [3]. For optimum effect using the technique of priming, the first dose should be approximately 15–20% of the intubating dose [4], which may cause symptoms of partial neuromuscular block in a significant proportion of the population [5]. It has been suggested also that the priming dose should be given 6–8 min before the main intubating dose for the greatest effect [4].

Combination of some pairs of non-depolarizing neuromuscular blocking agents exhibits synergism of action [6–8]. It is possible that priming one blocking drug with a different synergistic agent may also accelerate the rate of onset. This has been tested with combinations of pancuronium, tubocurarine and atracurium and the onset of neuromuscular block was increased, but to only a limited extent [9,10]. It was decided, therefore, to examine further this technique of synergistic priming, with a pair of non-depolarizing neuromuscular blocking agents which exhibit strong synergy of action—tubocurarine and alcuronium [6].

PATIENTS AND METHODS

Informed consent was obtained from patients (ASA I or II) in whom the anaesthetic technique of choice would include neuromuscular block. Ethics Committee approval was granted for the study. Patients with a known history of renal, hepatic, neurological or neuromuscular disorder and those taking drugs known to affect neuromuscular transmission were excluded. Each patient was premedicated with diazepam by mouth 1 h before operation. In the anaesthetic room, surface electrodes were placed over the ulnar nerve at the wrist and over the ipsilateral adductor pollicis muscle, after the skin was cleaned with acetone. The electrodes were connected to a Medelec MS6 system and the evoked compound electromyogram (EMG) from the adductor pollicis muscle was displayed and recorded.

Anaesthesia was induced with a sleep dose of thiopentone and the nerve stimulated with trains of four stimuli (0.2 ms duration, supramaximal voltage) at 12-s intervals. The preliminary (priming) dose of blocker was given, and the main intubating dose 3 min later. During this time, anaesthesia was maintained with increments of thiopentone as required and ventilation assisted with 67% nitrous oxide in oxygen, maintaining normocapnia.

The intubating doses of tubocurarine and alcuronium were 0.5 mg kg⁻¹ and 0.25 mg kg⁻¹, respectively; priming doses were 10% of the
intubating doses. Thus six groups were created: an intubating dose of each relaxant preceded by a priming dose of the same drug, the second agent, or normal saline (table 1). Two further groups (7 and 8) were included also, using normal saline as the priming agent and an intubating dose equivalent to the sum of the first and second doses in the previous groups; that is, 110% of the intubating dose. The patients were allocated randomly to the respective groups.

The degree of neuromuscular block was calculated as the percentage change in EMG amplitude of the first response of the train-of-four (T1) from that before administration of any relaxant (T0) and also the train-of-four ratio (amplitude of fourth response/amplitude of first response: T4/T1).

Data from the pairs of control groups (1 and 7; 4 and 8) were analysed using one-way analysis of variance at each time point. The aggregated data from groups 1 and 7 together were compared with those from groups 4 and 8 together. Two-way analysis of variance was carried out at each time point to see if there was any difference between the three agents given first, between the two agents given second, and to determine if the magnitude of any difference between the means was dependent on which drug was given first.

**RESULTS**

There were no significant differences between the groups with respect to mean age, weight and sex ratio (table 11). There was no detectable change in neuromuscular transmission resulting from administration of the priming dose. There was no difference between the mean maximum neuromuscular block reached in each group (table 11). A neuromuscular block of 100% was exceeded only in four patients, two each in groups 3 and 6. There was no significant difference between the two control groups at any time for the change in

**FIG. 1.** Percent reduction in EMG amplitude of first response of train-of-four (T1) with time for tubocurarine as the intubating relaxant. • = Saline—tubocurarine 0.5 mg kg⁻¹; O = saline—tubocurarine 0.55 mg kg⁻¹; ▽ = tubocurarine—tubocurarine; △ = alcuronium—tubocurarine. Significant differences from saline groups (no priming): *P < 0.05; **P < 0.01; †P < 0.025; ‡P < 0.005.
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Fig. 2. Percent reduction in EMG amplitude of first response of train-of-four (T1) with time for alcuronium as the intubating relaxant. • = Saline-alcuronium 0.25 mg kg⁻¹; ◀ = saline-alcuronium 0.275 mg kg⁻¹; ▲ = alcuronium-alcuronium; △ = tubocurarine-alcuronium. Significant differences from saline group (no priming): *P<0.05; **P<0.01; †P<0.025; ††P<0.005.

T1:T0 ratio for those groups in which tubocurarine was used to facilitate intubation (fig. 1). Both of the lines for the two groups in which priming was used (groups 2 and 3) were significantly different from the control lines at the points indicated (fig. 1). Although the line for group 3 (alcuronium before tubocurarine) lies to the left of that for group 2 (tubocurarine before tubocurarine) there was no significant difference between these two groups.

Figure 2 illustrates data for those patients in whom alcuronium facilitated intubation; it resembles figure 1. There was no significant difference between the two control lines at any time. The lines for the two groups in which priming was used (groups 5 and 6) are significantly different from the control lines as indicated on the figure. Although the line for group 6 (tubocurarine before alcuronium) lies markedly to the left of that for group 5 (alcuronium before alcuronium), there was no significant difference.

Comparison of the tubocurarine and alcuronium control groups using the aggregated data of groups 1 and 7 together and groups 4 and 8 together revealed no significant difference at any time between the rates of onset of tubocurarine and alcuronium when given alone.

The changes in mean train-of-four ratio with changes in T1:T0 are shown in figure 3 (control groups 1 and 4: tubocurarine alone and alcur-
nium alone) and figure 4 (groups 3 and 6, in which each agent was primed with the second one). Tubocurarine demonstrated slightly more fade than alcuronium, a difference which was not significant and not present when priming with the second agent had been used.

DISCUSSION

Tubocurarine and alcuronium were chosen because they are known to exhibit synergism of action which is stronger than tubocurarine and pancuronium in vitro [6]. In order to compare equipotent doses, the ED$_{95}$ of each was selected as the intubating dose with a priming dose of 10% of the ED$_{95}$.

Savarese [11] suggested a dose of 0.51 mg kg$^{-1}$ as the ED$_{95}$ for tubocurarine and Shanks [12] an overall mean for all published data of 0.48 mg kg$^{-1}$. A value of 0.50 mg kg$^{-1}$ was therefore chosen for ease of calculation. There are fewer data for alcuronium than for tubocurarine. Shanks [12] suggested an ED$_{95}$ of 0.22 mg kg$^{-1}$ and Lund and Stovner [13] suggested a relative potency of alcuronium and tubocurarine as 1.8:1. A value of 0.25 mg kg$^{-1}$ was chosen, therefore, as an ED$_{95}$ for this study. It is clear from inspection of the mean maximum neuromuscular block reached (table II) that these two doses were near to equivalence.

There is a large margin of safety in neuromuscular transmission such that approximately 75% of receptors have to be occupied by antagonist molecules before failure of transmission begins [14]. After a single bolus dose, receptor occupancy has to increase from zero to more than 75% before depression of T1 is seen. If a small priming dose is administered, sufficient to produce receptor occupancy of just less than 75%, the addition of a second intubating dose has to increase receptor occupancy just above this figure. An additional pharmacokinetic mechanism has been proposed also [15]. Because the concentration of blocking drug at the neuromuscular junction determines neuromuscular block, predosing allows that drug to reach an effective concentration sooner, thereby accelerating the onset of block. Whichever mechanism is operating, onset would be expected to be more rapid, as observed in this study and in previous studies with tubocurarine [4, 16], alcuronium [4, 17], vecuronium [18], atracurium [19, 20] and pancuronium [3, 21].

In addition to the classical postjunctional acetylcholine receptors, other acetylcholine receptor systems exist on the prejunctional region [22] and different neuromuscular blocking drugs are thought to possess a unique spectrum of actions on the whole receptor system. It is likely that synergism between some pairs of non-depolarizing neuromuscular blocking agents appears when two agents with dissimilar activity spectra are combined. The acceleration of neuromuscular block resulting from the priming dose of the second agent in this study was slightly greater than when the relaxant was primed with itself. If a pharmacokinetic effect alone is proposed for priming, one might expect priming with a different agent to be no more effective, or even less effective than priming with itself. This was not observed in the present study. It is interesting to note that the rate of onset of alcuronium was accelerated to a greater extent by tubocurarine than was tubocurarine by alcuronium.

Although no detectable block was found to result from the priming dose in this study, administration of a small dose of a non-depolarizing neuromuscular blocking agent has been shown to cause unpleasant partial paralysis in some patients [5, 23]. Under some circumstances, this might be hazardous [24].

The increase in rate of onset when alcuronium and tubocurarine are primed with each other is marked, 80% neuromuscular block being reached in just over 60 s. With suxamethonium 1 mg kg$^{-1}$ 100% block is reached in approximately 70 s [25]. The time response curve with suxamethonium is steeper, however, and suxamethonium causes a more profound block.

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