PRIMING AND THE ONSET OF NEUROMUSCULAR BLOCKADE WITH ALCURONIUM

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“Priming”, applied to non-depolarizing neuromuscular blocking agents, is the practice of giving a small (priming) portion of a dose some minutes before the balance, and achieving thereby a more rapid onset of action, or a more intense or long-lasting blockade, than if the same total dose had been given undivided (Foldes, 1984). One obvious explanation, for the more rapid onset at least, is that the priming dose occupies the 70–80% of “spare receptors” which must be occupied before any effects of non-depolarizing blockers become apparent (Paton and Waud, 1967).

The term “priming” was coined by Foldes (1984) in a brief report on short intubation times with a range of non-depolarizing blockers, when the priming dose was given 6–8 min before the induction of anaesthesia with the balance given at induction. This practice should possibly be qualified as “pre-induction priming”. Foldes’ report was preceded by that of Gergis and colleagues (1983) on “pre-induction priming” with atracurium, and by ours (Hutton et al., 1983) on “post-induction priming” with alcuronium—that is, the priming dose was given shortly after induction and the balance administered 4 min later.

More recently, Schwartz and co-workers (1985) and Mehta and associates (1985) have published studies which include both pre- and post-induction priming. In an editorial comment, Miller (1985) called for further studies to determine the potential usefulness of priming, and the optimal priming doses and priming intervals.

Pre-induction priming may arguably have some advantage in allowing more rapid tracheal intubation after the induction of anaesthesia. Choice of dose and interval in relation to pre-induction priming has been guided by the clinical use of non-depolarizing blockers to modify the fasciculations produced by suxamethonium, and the priming dose is limited by the requirement not to cause the conscious patient any unpleasant symptoms of pareisis. Post-induction priming has no obvious clinical benefit, but its study allows greater manipulation of priming dose. It may yield insights to the mechanism of priming and these insights may ultimately be of practical use.
Direct application of insights gained from post-induction priming to the context of pre-induction priming would require that the induction of anaesthesia had no effect on the action of neuromuscular blockers, whether primed or unprimed. This is probably not the case, and is the subject of our continuing research. However, for the purposes of this study, a design has been devised in which any effects relating to the induction of anaesthesia should be presented symmetrically to the test and control groups of patients.

**PATIENTS AND METHODS**

The study was approved by the local Hospital Ethical Committee. It concerned only the onset of action of alcuronium until maximal effect was observed. It was carried out in the anaesthetic induction room before surgery and occupied some 10 min more than routine anaesthesia would have done. Neuromuscular monitoring was discontinued, for logistic reasons, before the patient entered the operating room.

**Patients, anaesthesia and monitoring**

Our subjects were 72 fit female patients presenting for elective general, gynaecological or ENT surgery. Their medications consisted only of hypnotics prescribed in hospital. After an explanation of the study, and following consent, they were allocated randomly to eight treatment groups of nine patients each. The average ages and weights in each group are shown in table I. There was no requirement for a particular premedicant: 53 received an oral benzodiazepine, 14 an opiate plus an antisialagogue and five were not premedicated at all. In each treatment group, between five and seven patients received benzodiazepines. Neuromuscular blockade was monitored under anaesthesia by recording, at 10-s intervals, the single twitch response of the adductor pollicis to supramaximal surface stimulation of the ulnar nerve at the wrist, using a Bard Biomedical stimulator (model 750 digital). A Grass FT 03 force transducer on a “handlebar grip” was secured within the patient’s relaxed grasp, and the surface electrodes were attached over the ulnar nerve at the wrist. Induction of anaesthesia was with fentanyl 100–150 |g followed by sufficient thiopentone (over about 30–45 s) to abolish the eyelash reflex. Immediately after the onset of anaesthesia, ulnar nerve stimulation was begun, and the stimulus strength was adjusted to be just supramaximal. This took 30 s or so. A paper record of the output of the transducer was obtained (George Washington Ltd, 40 MD/2).

**Procedure** (table I)

Three total doses of alcuronium were studied: 0.3, 0.2 and 0.15 mg kg$^{-1}$. At the 0.3-mg kg$^{-1}$

| Table I. The eight treatment groups, showing mean (SD) ages and weights of the nine patients in each group. *This mean was significantly less than the control at the 5% level (Wilcoxon Rank sum test) |
|----------------------------------------|--------|--------|--------|--------|
| Total dose 0.3 mg kg$^{-1}$            | Group A| Group B| Group C| Group D|
| Priming                               | 0      | 0.04   | 0.08   | 0.12   |
| Balance                               | 0.3    | 0.26   | 0.22   | 0.18   |
| Age (yr)                              | 40.0 (9.3) | *30.8 (10.2) | 36.8 (10.5) | 51.7 (13.8) |
| Weight (kg)                           | 61.0 (5.8) | 60.7 (6.8) | 58.2 (11.1) | 64.1 (7.9) |
| Total dose 0.2 mg kg$^{-1}$            | Group E| Group F |
| Priming                               | 0      | 0.04   |
| Balance                               | 0.2    | 0.16   |
| Age (yr)                              | 35.9 (9.4) | 34.6 (14.5) |
| Weight (kg)                           | 64.2 (12.5) | 62.3 (13.3) |
| Total dose 0.15 mg kg$^{-1}$           | Group G| Group H |
| Priming                               | 0      | 0.04   |
| Balance                               | 0.15   | 0.11   |
| Age (yr)                              | 35.9 (13.6) | 41.6 (6.4) |
| Weight (kg)                           | 61.3 (7.1) | 61.0 (8.4) |
dose, 36 patients were allocated randomly to four treatment groups (A, B, C and D in table I) to receive priming doses of zero (control), 0.04, 0.08 or 0.12 mg kg\(^{-1}\) immediately after the supramaximal stimulus had been ascertained, with the respective balances (0.3, 0.26, 0.22 and 0.18 mg kg\(^{-1}\)) after a further 4 min. At the 0.2 mg kg\(^{-1}\) dose, 18 patients (groups E and F) were allocated randomly to receive either zero (control) or 0.04 mg kg\(^{-1}\) of alcuronium initially, and 0.2 or 0.16 mg kg\(^{-1}\), respectively, after 4 min. At the 0.15-mg kg\(^{-1}\) dose (groups G and H), a further 18 patients received either zero or 0.04 mg kg\(^{-1}\) initially and 0.15 or 0.11 mg kg\(^{-1}\) after 4 min. The alcuronium was diluted to 1 mg ml\(^{-1}\) and was injected to a fast-running infusion to a forearm vein. The injection took 5–10 s and its start was marked by a sequence of four stimuli given at 0.5-s intervals (a standard "train-of-four").

Thus in each of the eight treatment groups, the design allowed for a "priming" dose to be given initially in the "test" treatment groups (B, C, D, F and H), or no dose at all in the "control" treatment groups (A, E and G), with the balance 4 min later. During the 4 min allowed for any "priming" effect, the patients were generally apnoeic following the fentanyl. They were ventilated gently by hand via a face mask and anaesthesia was maintained with 67% nitrous oxide in oxygen with, occasionally, small supplements of thiopentone if necessary.

Statistical treatment
The characteristics of blockade which were estimated were the latency of onset, the time for the twitch to reach half-way between the initial and final level (T\(_{50}\)), the difference between T\(_{50}\) and latency, and the maximal twitch depression. Their derivation will be described below. Overall differences between the characteristics of the neuromuscular blockade were tested for significance using analyses of variance (ANOVA). The study design required two ANOVA tables for each characteristic—a main 3 × 2 table looking for priming and dose effects in groups A and B, E and F, and G and H, and a subsidiary 4 × 1 table to look for differences between groups A, B, C and D. Individual differences from control were subsequently tested for significance at the 5% level using Wilcoxon Rank Sum Tests.

RESULTS

Effects of the "priming" portions of the dose
In some patients in both control and test groups, increases in stimulus strength were applied at various intervals up to 4 min after the supramaximal stimulus had been determined. There were never any increases in twitch T1 in response to such increases, so that the original determinations of supramaximal stimulus appeared to remain valid.

In the control groups A, E and G, the T1 twitch remained essentially unchanged during the 4-min wait between the determination of the supramaximal stimulus and the administration of the total dose of alcuronium, apart from occasional artefacts created by inadvertent passive movement of the patient’s arm or wrist. The T4/T1 ratio at the end of the 4-min wait was always greater than 95%. (In other situations over much longer periods of recording, the height of the unparalysed twitch can vary, although in no consistent direction.)

In groups B, F and H, the priming doses of alcuronium 0.04 mg kg\(^{-1}\) generally produced no detectable change in T1 during the 4-min wait, and the T4/T1 ratio elicited on giving the balance was generally well maintained. Such small depression as was occasionally produced bore no obvious relationship to the onset characteristics of the neuromuscular blockade which followed the administration of the balance dose.

In groups C and D, the effects of the larger priming doses were more appreciable, although very variable, and the degree of depression was still unrelated to the onset characteristics of the subsequent neuromuscular blockade.

Effects of the "main" portion of the dose
The time of administration of the main portion of the dose (the total dose in the control cases, the balance in the test cases) will be taken as zero time. The twitch height at zero time will be termed "initial twitch height" (h\(_0\)), and the twitch height at maximal effect of the dose will be termed "final twitch" (h\(_f\)). Following the administration of the main portion of the dose, there was a latent period followed by an approximately exponential decline from the initial to the final twitch height. Fractional twitch depression at any time \(t\) expresses the progress of paralysis from the initial towards final level. If \(h_t\) is the twitch height at time \(t\),

\[
\text{Fractional twitch depression} = \frac{h_0 - h_t}{h_0 - h_f}.
\]
The latent period and the decline are shown in figure 1, which is a semilogarithmic plot of the percentage "fractional twitch depression" against time from the administration of the main portion of the dose.

Almost all of the semilogarithmic plots could be described tolerably well by a straight line over the range of fractional twitch depression from 10% to 70%. Clearly, the more rapid the decline, the fewer points there were in this range. The line of best fit for the range was obtained for each plot by linear regression using the filled symbols in the plot in figure 1. These regression lines were used to derive three of the four characteristics of the onset of blockade for the purposes of later comparisons:

(i) Latency. The latency was taken as the time at which the extrapolated regression line intersected the horizontal axis at a fractional twitch depression of zero.

(ii) $T_{50}$. This was the time taken for the twitch to decline to halfway between the initial and final values, and was taken as the time at which the regression line intersected the horizontal dashed line for a fractional twitch depression of 50%. $T_{50}$ was determined by both latency and slope decline.

(iii) $T_{50}$-minus-latency was the time, after the latent period, to half way between initial and final twitch height. It was inversely related to the slope of the semilogarithmic decline.

(iv) Percentage maximal twitch depression. This was the difference between initial and final twitch expressed as a percentage of initial twitch height.

The priming effect

The above four characteristics of neuromuscular blockade were determined for all 72 plots and the average values and standard deviations are tabulated by treatment group in table II.

The analyses of variance identified highly significant effects of dose, highly significant effects of the 0.04-mg kg$^{-1}$ priming dose on all of the onset characteristics of blockade, and an effect, significant at the 5% level, on the maximal twitch depression. This is generally consistent with table II where the asterisks indicate the individual values for primed doses which differ from the corresponding control values at the 5% significance level (Wilcoxon). With the 0.04-mg kg$^{-1}$ priming dose, the time to 50% fractional twitch depression was shorter than control for all three total doses, because of a shorter latency, a more rapid decline, or both. Individual testing failed to identify any significant effects on maximal twitch depression at any total dose, although the figures at the 0.15-mg kg$^{-1}$ total dose suggested that such an effect might be revealed by comparing larger numbers. The larger priming doses did not produce any obvious priming effect. With the
**Table II. The onset characteristics of neuromuscular blockade to maximal effect in the eight treatment groups.**  
*Significantly different from control at the 5% level. Mean values (SD)*

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
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<tbody>
<tr>
<td>Latency (s)</td>
<td>31.9 (9.1)</td>
<td>*22.2 (5.7)</td>
<td>28.7 (5.9)</td>
<td>28.3 (6.3)</td>
</tr>
<tr>
<td>$T_{50}$—latency (s)</td>
<td>19.1 (8.1)</td>
<td>15.3 (5.8)</td>
<td>16.3 (6.9)</td>
<td>*26.2 (7.4)</td>
</tr>
<tr>
<td>$T_{50}$ (s)</td>
<td>50.9 (15.4)</td>
<td>*37.6 (8.3)</td>
<td>45.0 (11.7)</td>
<td>54.5 (8.3)</td>
</tr>
<tr>
<td>% Maximal depression</td>
<td>98.2 (2.4)</td>
<td>99.4 (1.4)</td>
<td>96.1 (3.4)</td>
<td>96.4 (2.7)</td>
</tr>
</tbody>
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<tr>
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<th>Group E</th>
<th>Group F</th>
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<tr>
<td>Latency (s)</td>
<td>36.4 (12.1)</td>
<td>*25.9 (8.1)</td>
</tr>
<tr>
<td>$T_{50}$—latency (s)</td>
<td>43.8 (26.3)</td>
<td>*18.7 (14.0)</td>
</tr>
<tr>
<td>$T_{50}$ (s)</td>
<td>80.2 (34.2)</td>
<td>*44.6 (17.1)</td>
</tr>
<tr>
<td>% Maximal depression</td>
<td>90.1 (6.9)</td>
<td>93.9 (4.4)</td>
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<th>Group G</th>
<th>Group H</th>
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<tbody>
<tr>
<td>Latency (s)</td>
<td>40.5 (9.6)</td>
<td>*25.9 (4.1)</td>
</tr>
<tr>
<td>$T_{50}$—latency (s)</td>
<td>51.2 (27.8)</td>
<td>*22.2 (15.4)</td>
</tr>
<tr>
<td>$T_{50}$ (s)</td>
<td>91.7 (31.6)</td>
<td>*48.2 (16.1)</td>
</tr>
<tr>
<td>% Maximal depression</td>
<td>72.4 (17.5)</td>
<td>85.6 (4.2)</td>
</tr>
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</table>

0.12-mg kg$^{-1}$ priming dose, $T_{50}$—minus-latency was of significantly longer duration than control.

The patients receiving alcuronium 0.04 mg kg$^{-1}$ followed by 0.26 mg kg$^{-1}$ (group B) were significantly younger than the corresponding controls (group A), but no such difference was present at the other doses, and there was no relationship, within the group, between age and any characteristic of neuromuscular blockade.

**DISCUSSION**

*Study design and anaesthetic induction*

A prerequisite for this study was that it should interfere minimally with the working arrangements in busy operating theatres. There was neither time nor space to study post-induction priming under ideal conditions with a stable background of anaesthesia. We were limited to looking for priming effects uncomfortably close to the induction of anaesthesia. Our preliminary studies confirmed our suspicions that the speed of onset and maximal effect of partially paralysing doses of alcuronium can be increased if the dose is given 4 min or so after induction of anaesthesia, compared with giving it immediately after induction. This observation may itself be important, and is being pursued.

For our present purposes in studying priming, it was clear that the main portion of the dose should be presented at the same interval from induction of anaesthesia in both control and test cases. Any spurious effects related to anaesthetic induction should then affect control and test groups equally, and should introduce variability which would tend to obscure real priming effects rather than create artificial ones. Thus we are confident that a real priming effect exists in this study.

Since, in our preliminary studies on interval from induction, the paralysing effect of a paralysing dose of alcuronium seemed to be enhanced by delaying its administration until 4 min after induction, we expected that this would hold also for the priming effect of a priming dose. Accordingly, we have compared, in a separate study, the effects of a regimen giving a priming dose of alcuronium 0.04 mg kg$^{-1}$ 4 min after induction and 0.11 mg kg$^{-1}$ 4 min later with a regimen giving 0.15 mg kg$^{-1}$ 8 min after induction (Pfeiffer and Black, 1985). Contrary to our expectation, the priming effect was very much reduced. This, too, is being studied further.
Characteristics of neuromuscular blockade

We have used the lines of best fit over the linear portion of the semilogarithmic decline (fig. 1) to derive values for latency and T_{60}. We have preferred this to the more obvious approach of measuring latency to the first detectably reduced twitch response, for two reasons. First, detecting the first reduction in twitch height can depend critically on the precision of a single measurement. Second, with a recording interval of 10 s there is a potential error of up to 10 s, depending on whether a response is elicited just before or just after the real onset of paralysing effect. Using the line of best fit uses information from more than one data point and allows more effective interpolation, both for latency and T_{60}, when these times occur in the interval between two elicited responses.

Latency measured to the first detectably reduced response will be weighted somewhat by the fibres which respond soonest. Latency derived as described from the line of best fit will be weighted somewhat by those which respond latest. The difference is immaterial for within-study comparisons, provided that the same measure is used consistently within the study.

Conventions on timing with priming

We have used the same convention as the other workers on priming: time to effect of the main portion of the dose is measured from a "zero time" at the moment of its administration. When a portion of the total dose has been used for priming, that portion has had access to receptors during the priming interval, that is, before zero time. It would not be more correct, for these cases, to add the priming interval to the conventionally measured times to effect, since the total dose will not have been in effect for the total time. The convention which we have followed is reasonable—provided that it is not taken to imply that the priming portion is having no effect whatsoever during the priming interval. Although effects of priming may not be measurable during the priming interval with conventional neuromuscular monitoring they can, nonetheless, become apparent subsequently. Our interest is in how such effects might be brought about.

Mechanisms of priming

Foldes' (1984) rationale for using priming was to occupy the "spare receptors" with the priming dose so that the effects of the balance dose would be more immediately apparent; that is, the latencies and possibly T_{60}-minus-latencies might well be reduced, as in this study. It is quite plausible with saturation kinetics that a very small dose will occupy a large initial fraction of the receptor population, and that increasingly larger doses will be required to complete the receptor occupation. The concept does require that the occupation of the initial fraction of receptors takes an appreciable time when an undivided dose is given, and that this is the time which is saved by priming. This is consistent with the concept of an "access-limited biophase" (Hull, 1982).

An increase in maximal twitch depression is not simply explicable using a minimal hypothesis based on spare receptor occupation. One might reasonably expect that the same number of receptors would ultimately be occupied for a given dose, whether primed or unprimed, so that the maximal twitch depression should be unaffected. However, the results of this study cannot lead to any confident conclusions on this point. The observed effects on maximal twitch depression were certainly less striking than the acceleration of onset of blockade. The analysis of variance suggested an overall effect significant at the 5% level, but this was not confirmed by tests at individual doses. At the 0.2- and 0.3-mg kg^{-1} doses, the control maximal twitch depression was already so complete that it would be difficult to demonstrate an increase. At the 0.15-mg kg^{-1} dose, there was a suggestion of a more complete effect with priming, but the difference was not significant with the number of patients available.

One might expect, further, that the completeness of the occupation of spare receptors by the priming dose might be reflected in its small depressant effects on single twitch or train-of-four, and that these depressant effects ought to be related to the acceleration of the subsequent response to the balance dose. However, this was not the case. Nor did the priming effect increase, as might be expected with the size of the priming dose. Additional complexity is suggested by our unexpected observation (Pfeiffer and Black, 1985) that the priming effect was heavily attenuated by delaying both priming and balance doses by a further 4 min from induction of anaesthesia (see above).

Thus the simple explanation of priming by spare receptor occupancy must either be complemented with subsidiary explanation or replaced by explanations based on more complex processes.
Effects of non-depolarizing neuromuscular blockers on presynaptic terminals are well recognized in pharmacological preparations (Standaert, 1964; Bowman, 1980), as are co-operative or allosteric reactions between multiple receptors controlling ion channels on the postsynaptic membrane (Karlin, 1967; Hull, 1982).

Explanations of most of the clinically observable effects have not, until recently, included such complexities, although the observations of Williams, Webb and Calvey (1980) have forced them into consideration. Depression of first twitch in relation to the unparalysed twitch (percentage T1 depression), and depression of the fourth twitch of a train-of-four in relation to the first (T4/T1 ratio) are two different, although related measures of neuromuscular blockade. The relationship between these two measures is not unique. There are differences for different non-depolarizing blockers. This is “not consistent with the action of non-depolarizing agents at a single site in the region of the neuromuscular junction” (Williams, Webb and Calvey, 1980). In the same vein, Pugh and colleagues (1985) have described two different but related measures of single twitch depression which can be obtained from the depolarization phase of the evoked compound action potential of adductor pollicis: one is the integral of the depolarization and the other is its duration. The relationship between these two measures is different for atracurium than for vecuronium, and this may be a further indication of the complexities in neuromuscular transmission.

The explanation of the priming effect may lie in studies in these directions. The correct explanation, when available, may well explain the supra-additive effects of combinations of neuromuscular blockers (Lebowitz et al., 1980; Foldes et al., 1984), and a better understanding of the recognized mechanisms of neuromuscular blockade may ultimately increase the flexibility with which these agents may be used in clinical practice.

REFERENCES


