Effects of cholinesterase inhibitors on the neuromuscular blocking action of suxamethonium†

J. B. Valdrighi, N. W. Fleming, B. K. Smith, G. L. Baker and D. A. White

SUMMARY
Prolonged neuromuscular block occurs when suxamethonium is given after neostigmine or pyridostigmine; however, studies of edrophonium and suxamethonium have yielded conflicting results. We have studied, therefore, interactions between suxamethonium and all three anticholinesterases in rats anaesthetized with pentobarbitone. After recovery from an initial bolus of suxamethonium, saline, edrophonium, pyridostigmine or neostigmine was administered and a second dose of suxamethonium was then given. All three anticholinesterases prolonged the duration of neuromuscular block (90% suppression to 50% twitch recovery) to 127(SEM 9)% 127(10)% and 138(11)% of baseline for edrophonium, pyridostigmine and neostigmine, respectively. Recovery index (25% to 75% twitch recovery) was increased also to 125(9)% 149(10)% and 185(15)% of baseline, respectively for the three drugs. (Br. J. Anaesth. 1994; 72: 237-239)

KEY WORDS

Case reports and clinical studies have suggested that suxamethonium administered after neostigmine or pyridostigmine has a prolonged duration of action [1,2], while studies investigating interactions with edrophonium have produced less consistent results [3,4]. Because of the confounding variables present in previous studies, inconsistent findings with regard to edrophonium and the absence of a study comparing all three cholinesterase inhibitors, we have developed an in vivo rat model to investigate specifically the interactions between suxamethonium and the three cholinesterase inhibitors in common clinical use.

METHODS AND RESULTS
After obtaining university Animal Use and Care Committee approval, we studied 40 male Sprague-Dawley rats (300-400 g) anaesthetized with i.p. pentobarbitone 80-120 mg kg⁻¹. Tracheotomy was performed and the lungs ventilated mechanically with 100% oxygen (Model 680 ventilator, Harvard Apparatus Co. Inc., Dover, MA). The external jugular vein and carotid artery were cannulated for administration of drugs and arterial blood sampling. The sciatic nerve was isolated, ligated proximally and a bipolar stimulating electrode placed distal to the ligature. The gastrocnemius muscle was isolated from the foot by transecting the calcaneus and the animal was then secured in a Brown-Scheuster myograph (Harvard Apparatus Co. Inc.). A silk suture connected the achilles tendon to a force transducer (Grass model FT-03, Grass Instrument Co., Quincy, MA). The sciatic nerve was stimulated supramaximally (Grass model S-88 stimulator, 0.1 ms duration square wave, 0.2 Hz). Muscle length was adjusted to produce maximal twitch tension. The analogue signal from each contraction was digitized and analysed in real time.

After 30 min of equilibration, suxamethonium 0.5 mg kg⁻¹ i.v. was administered. Thirty minutes after complete recovery of twitch tension, the same volume (1.0 ml kg⁻¹) of normal saline, edrophonium 1.0 mg kg⁻¹, pyridostigmine 0.24 mg kg⁻¹ or neostigmine 0.06 mg kg⁻¹ was given i.v. (10 rats received each). Five minutes later, a second dose of suxamethonium 0.5 mg kg⁻¹ was given.

Neuromuscular block after each suxamethonium bolus was analysed for onset time (10% to 90% twitch suppression), duration of action (90% suppression to 50% twitch recovery) and recovery index (25% to 75% twitch recovery) (table I). Onset time was measured from 10% twitch suppression instead of time of injection because variability caused by the rate of injection and catheter deadspace was much greater than the change in neuromuscular response. Within each treatment group, responses before and after treatment were compared by paired t test. Comparison between groups was by analysis of variance (Dunnett’s test) of data normalized to the initial response. *P < 0.05 was considered to be significant. All values are expressed as mean (SEM).

There were no measured differences among any of the treatment groups in the response to the initial dose of suxamethonium. The onset time for the second dose of suxamethonium was shorter in all groups. Comparisons between groups demonstrated

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that the onset time after either pyridostigmine or neostigmine was significantly shorter than that after saline. The duration of action of suxamethonium was not altered after saline, but was prolonged after the administration of any of the three cholinesterase inhibitors. The effects of neostigmine on duration of action were significantly greater than those of edrophonium or pyridostigmine. Similarly, the recovery index was prolonged following treatment with any of the cholinesterase inhibitors and the effects of neostigmine were significantly greater than those of edrophonium or pyridostigmine.

**COMMENT**

When suxamethonium is required after a cholinesterase inhibitor, the consequent decreased metabolism may result in prolonged neuromuscular block. This interaction has been reported for pyridostigmine and neostigmine [1, 2]. In contrast, it has been suggested that edrophonium is less likely to prolong the effects of suxamethonium, but previous studies have produced conflicting results and contained confounding variables that limit extrapolations to other clinical situations [3, 4].

Mirakhur studied plasma cholinesterase activity in 15 patients in whom neuromuscular block produced by atracurium was antagonized by edrophonium 0.5 or 1.0 mg kg"-1 [3]. In contrast with a previous study [5] in which either pyridostigmine 0.25 mg kg"-1 or neostigmine 0.05 mg kg"-1 was used to antagonize the effects of pancuronium, no change in enzyme activity was observed. It was suggested, therefore, that edrophonium should not prolong the effects of suxamethonium. Sohn, Cronnelly and Sharma [4] studied six patients in whom neuromuscular block produced by pancuronium was antagonized by edrophonium 0.5 mg kg"-1 and a second bolus of suxamethonium administered 5 min later. The second block was of 1.6-fold greater duration than that produced by suxamethonium given after induction of general anaesthesia. Plasma cholinesterase activity was decreased by 53% 1 min after administration of edrophonium and returned to 89% of baseline activity within 15 min. These results were compared with those of previous clinical studies [2] and it was suggested that, while edrophonium does prolong the effects of suxamethonium, it has less effect than pyridostigmine or neostigmine.

No study has examined the effects of all three cholinesterase inhibitors using the same design. Differences in background anaesthetics, anaesthetic adjuncts, drug dosages and timing are all critical. Even with apparently normal neuromuscular function, a significant number of nicotinic cholinergic receptors may still be occupied. The shorter onset time for the second dose of suxamethonium in our saline treatment group is an example of the need to control for variables which may produce a subclinical receptor block. Additionally, caution is required when studies of cholinesterase inhibitor effects on plasma cholinesterase activity are used to predict interactions with suxamethonium. These compounds have direct effects at the neuromuscular junction [6], and some of the variability in measurements of the inhibitory effects of edrophonium on plasma cholinesterase activity may reflect difficulty in assaying the transient electrostatic bonds formed by edrophonium at the active site of cholinesterase enzymes compared with the covalent bonds formed by pyridostigmine or neostigmine.

With this rat model and drug administration design, we found that all three cholinesterase inhibitors prolonged the duration of action of suxamethonium to a small, but comparable, extent. The model allowed specific study of these drug interactions without the genetic variability or multiple anaesthetic drugs associated with clinical studies; however, its limitations must be considered. Rat plasma has about 12.5% of the butyrylcholinesterase activity of human plasma [6]. If the rat is dependent upon plasma cholinesterase to metabolize suxamethonium, then it should be more sensitive to its effects. Indeed, a 0.5-mg kg"-1 dose of suxamethonium produced neuromuscular block having a duration similar to that produced by a 1.5-mg kg"-1 dose in humans. Further validation of this model was provided by our own pilot dose–response studies in which the minimally effective doses of cholinesterase inhibitor required to antagonize neuromuscular block produced by vecuronium were found to be similar (on an mg kg"-1 basis) to those used in humans.

In summary, there were no clinically significant differences among the cholinesterase inhibitors in their prolongation of the effect of suxamethonium in this rat model. Furthermore, the duration of neuromuscular block was not prolonged to a clinically

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**TABLE 1. Summary of experimental results (mean (SEM); 10 animals in each treatment group). P < 0.05 compared with:**

* before treatment (paired t test); † saline treatment group (Dunnett's test)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Onset time (s)</th>
<th>Duration of action (min)</th>
<th>Recovery index (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td>Saline</td>
<td>94 (17.8)</td>
<td>92 (16.6)</td>
<td>15.0 (1.1)</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>92 (16.6)</td>
<td>65 (10.9)</td>
<td>16.6 (1.3)</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>65 (10.9)</td>
<td>17 (2.3)†</td>
<td>15.6 (2.6)</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>73 (10.0)</td>
<td>14 (2.4)†</td>
<td>15.7 (1.8)</td>
</tr>
</tbody>
</table>

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significant extent. Studies reporting greater effects may reflect the confounding influences of co-administered medications, differences in experimental procedures or a decreased sensitivity of our model. Further study is required to confirm clinical inferences.

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REFERENCES