ANTAGONISM OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE OR EDROPHONIUM

B. A. ASTLEY, R. HUGHES AND J. P. PAYNE

It has been reported that edrophonium, in relatively large doses, induces a more rapid antagonism of the neuromuscular blockade produced by pancuronium (Bevan, 1979), atracurium (Baird and Kerr, 1983; Jones, Pearce and Williams, 1984) and alcuronium (Harper, Bradshaw and Healy, 1984) than does neostigmine. However, since effective recovery is related to the degree of blockade immediately before antagonism (Katz, 1967), the present study was undertaken to determine whether edrophonium produces a more rapid antagonism of the partial or complete neuromuscular blockade induced by atracurium than does neostigmine, and whether antagonism is equally persistent after either anticholinesterase.

PATIENTS AND METHODS

Studies were performed on 22 patients about to undergo urological surgery. Informed consent was obtained from all patients and the studies were approved by the Ethics Committee of the St Peter’s Hospital, London. In addition, a further group of nine patients who were allowed to recover spontaneously from the effects of atracurium, and who had also given their informed consent, acted as a control group.

No premedication was given and anaesthesia was induced with thiopentone 500–600 mg i.v. In

SUMMARY

Antagonism of atracurium-induced neuromuscular blockade by neostigmine or edrophonium has been studied using the tetanic (50 Hz) and train-of-four (2 Hz) or single twitch responses of the adductor pollicis muscle in 22 anaesthetized patients. A further nine patients not given an anticholinesterase acted as a control group. In two groups (six patients for each anticholinesterase) in whom antagonism was attempted at 95–98% blockade of the tetanic response, recovery of the tetanic response after two or three doses of edrophonium 0.75 mg kg⁻¹ i.v. was not statistically different from that in the control group; recovery after two doses of neostigmine 2.5 mg i.v. was significantly faster (P < 0.001).

Recovery of the single twitch response after antagonism with edrophonium, although longer than that with neostigmine (P < 0.01), was significantly shorter than in the control group (P < 0.05). When edrophonium is given at the commencement of recovery, the initial rapid antagonism of tetanic block is not sustained, whereas antagonism by neostigmine is more persistent and the recovery phase is significantly shortened. In a further two groups of patients (n = 5) given atracurium 0.3 mg kg⁻¹ i.v., antagonism was not attempted until the peak height of the tetanic contraction had reached approximately 50% of the control value. It was found that recovery of the tetanic and train-of-four responses was significantly faster (P < 0.05–0.001) after antagonism with edrophonium 0.75 mg kg⁻¹ i.v. than with neostigmine 2.5 mg i.v. (approx. 0.04 mg kg⁻¹). The train-of-four response recovered more slowly than did the tetanic response after both agents (P < 0.05–0.01).
12 patients tracheal intubation was achieved during the administration of 2–4% halothane inspired concentration, without the use of a neuromuscular blocking agent. Anaesthesia was then maintained with 60–66% nitrous oxide and 0.5% halothane in oxygen. Ventilation was controlled. In a further 10 patients, the trachea was intubated after the administration of atracurium 0.3 mg kg\(^{-1}\) i.v. In all patients, recordings of the tetanic contraction of the adductor pollicis were obtained by stimulating the ulnar nerve supramaximally at the wrist every 12 s with tetanic bursts of 50 Hz for 1 s. Simultaneous recordings were obtained of either the responses of the adductor pollicis muscle to single twitch (in 12 patients) or train-of-four stimulation (in 10 patients) of the ulnar nerve. Arterial pressure was measured via an indwelling polyethylene cannula placed in a radial artery. The electrocardiogram was recorded from non-conventional chest leads.

The first 12 patients, who were given halothane, were divided into two groups of six. In both groups atracurium in the dose range 0.15–0.3 mg kg\(^{-1}\) i.v. was used to produce 100% blockade of the tetanic response. As soon as signs of recovery of the peak tetanic contraction appeared, the patients were pretreated with atropine 1.2 mg and blockade was antagonized, in one group with two doses of neostigmine 2.5 mg i.v. and in the other with two or three doses of edrophonium 0.75 mg kg\(^{-1}\) i.v. given at 2.5-min intervals. All drugs were administered through a cannula in a large forearm vein and were flushed into the circulation with a fast flowing infusion.

The remaining 10 patients were divided into two groups (n = 5), and atracurium 0.3 mg kg\(^{-1}\) i.v. was given to both groups before intubation. When recovery of the peak height of the tetanic contraction had reached approximately 50% of its initial value, all the patients were pretreated with atropine as before. In one group residual blockade was antagonized with neostigmine 2.5 mg i.v. (approx. 0.04 mg kg\(^{-1}\)); in the other, with edrophonium 0.75 mg kg\(^{-1}\) i.v.

The results were analysed statistically using paired and unpaired t tests on log-transformed data.

### RESULTS

The results obtained when 95–98% blockade induced by atracurium was antagonized with neostigmine and edrophonium in the two groups of six patients are set out in Table I. The mean recovery time of the tetanic response for those patients given neostigmine was significantly faster than that in the control group of patients in whom neuromuscular blockade was not antagonized. Recovery after edrophonium was not significantly different from control. In contrast, the mean recovery time of the single twitch response after antagonism with edrophonium, although longer than recovery with neostigmine, was significantly shorter than recovery in the control group of patients (P < 0.05). Examples of these responses are shown in Figure 1, which illustrates recordings of the tetanic and single twitch contractions of the adductor pollicis muscle from two patients given atracurium 0.3 mg kg\(^{-1}\) and 0.2 mg kg\(^{-1}\), respectively. Neostigmine or edrophonium was administered at the commencement of recovery of the tetanic response. In the patient given two doses of neostigmine 2.5 mg, recovery of the tetanic and single twitch responses was complete in about 10 min, whereas in the patient given two doses of edrophonium 0.75 mg kg\(^{-1}\) the initial rapid antagonism of the blockade of the tetanic response was not sustained. However, antagonism of the single twitch response was almost as effective as that by neostigmine.

A quantitative comparison of the antagonism of atracurium-induced neuromuscular blockade with neostigmine or edrophonium, given when recovery of the peak height of the tetanic contraction had reached approximately 50% of its initial height, is presented in Table II. Differences in the percentage recovery between the neostigmine and edrophonium groups at reversal were not

### Table I. Antagonism of 95–98% atracurium-induced blockade

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<tr>
<th>No. patients</th>
<th>Time to 95% recovery (min)</th>
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<tbody>
<tr>
<td></td>
<td>Tetanic response</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>6</td>
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<td></td>
<td>***</td>
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<tr>
<td>Control</td>
<td>9</td>
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Significant differences: **P < 0.01; ***P < 0.001.
significant. These results show that recovery of both the tetanic and train-of-four responses from blockade by atracurium was significantly faster after antagonism with edrophonium than with neostigmine. Observations were continued for up to 15 min after the administration of edrophonium and there was no evidence of residual curarization. Tracings of the tetanic and train-of-four contractions of the adductor pollicis muscles from two anaesthetized patients who were given atracurium 0.3 mg kg\(^{-1}\) i.v. are shown in figure 2. In one patient residual neuromuscular blockade was
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![Diagram showing recordings of tetanic and train-of-four responses of adductor pollicis muscles.]

**Fig. 2.** Recordings of the tetanic and train-of-four responses of the adductor pollicis muscles from two anaesthetized patients given atracurium 0.3 mg kg⁻¹ i.v. Antagonism from approximately 50% neuromuscular blockade was more rapid with edrophonium 0.75 mg kg⁻¹ i.v. than with neostigmine 2.5 mg i.v.

antagonized with neostigmine 2.5 mg and in the other with edrophonium 0.75 mg kg⁻¹. It is evident from these recordings that recovery of the tetanic responses was more rapid after antagonism with edrophonium than with neostigmine. Recovery of the train-of-four responses followed a similar pattern.

**DISCUSSION**

In this study we have shown that the time taken to achieve 95% recovery of the tetanic response, when edrophonium was given at the commencement of recovery from atracurium-induced blockade, was not significantly different from that in a control group of patients who were not given an anticholinesterase. Furthermore, the rate of recovery after edrophonium was not appreciably increased after the administration of subsequent doses of the anticholinesterase. In contrast, recovery after neostigmine was significantly faster than in the control group. Bevan (1979) reported a similar pattern of recovery of the train-of-four response when edrophonium was administered as soon as muscle activity began to return after blockade by pancuronium. Recovery reached a plateau within 2 min and the subsequent recovery was slow. In another study, Harper, Bradshaw and Healy (1984) administered edrophonium when less than four responses of the train-of-four were present during recovery from alcuronium-induced neuromuscular blockade. They reported that in the first 1–2 min the train-of-four ratio was greater than in those patients given neostigmine, but during the following 5–35 min the initial rapid antagonism by edrophonium was not sustained and the ratio became less than that in the neostigmine group of patients.
If, however, recovery of the peak height of the tetanic contraction of the adductor pollicis muscle had reached approximately 50% of the pre-dose response then a large dose of edrophonium 0.75 mg kg⁻¹ i.v. would effectively antagonize the neuromuscular blocking action. Furthermore, recovery of both the tetanic and train-of-four responses was significantly faster after edrophonium than after neostigmine and there was no evidence of recurarization. These findings are in agreement with other reports of rapid antagonism of the blockade produced by pancuronium, alcuronium and atracurium by large doses of edrophonium 0.5–1 mg kg⁻¹ i.v. (Bevan, 1979; Kopman, 1979; Harper, Bradshaw and Healy, 1984; Jones, Pearce and Williams, 1984). In the present study we found it curious that recovery of the train-of-four response was significantly slower than that of the tetanic contraction after the administration of neostigmine and edrophonium. It would seem likely that relatively more acetylcholine should be available for receptor occupancy to antagonize neuromuscular block during train-of-four stimulation at 2 Hz because the decline in the output of the transmitter should be less than during repeated tetanic stimulation at 50 Hz, especially since we have no evidence to suggest that tetanic stimulation enhances recovery. Indeed, it has been a consistent finding of our studies that the tetanic response always recovers more slowly than the single twitch from competitive neuromuscular blockade. In the present study that pattern was followed.

In contrast to the tetanic response, the time taken for recovery of the single twitch response after antagonism with edrophonium was significantly shorter than that in the control group who were not given an anticholinesterase. However, it was significantly longer than after neostigmine. Other workers have reported that the first response of the train-of-four, regarded as a single twitch, recovered more rapidly than the fourth response and the train-of-four ratio (Bevan, 1979; Harper, Bradshaw and Healy, 1984; Jones, Pearce and Williams, 1984). Reliance on the return of the single twitch to the control value could be misleading, since a significant degree of residual receptor occupancy, as indicated by marked tetanic or train-of-four fade, may still be present (Ali et al., 1981; Payne and Hughes, 1981).

It is widely believed that tetanic or train-of-four fade is essentially a prejunctional effect, whereas the suppression of the single twitch occurs predominantly as the result of postjunctional receptor occupancy (Hubbard and Wilson, 1973; Bowman, 1980). Consequently, the single twitch recovers more rapidly than the tetanic and train-of-four responses during antagonism of atracurium-induced blockade with edrophonium because during high frequency stimulation the depletion in acetylcholine stores and reduced mobilization of the transmitter would favour longer receptor occupancy by the neuromuscular blocking drug.

The rapidity with which edrophonium acts may be related to its smaller molecular weight (166) compared with that of neostigmine (223) and a more rapid diffusion to its site of action than that achieved by neostigmine (Harper, Bradshaw and Healy, 1984). Another factor is that anticholinesterase drugs, in addition to their postsynaptic action in conserving the released acetylcholine, may also act presynaptically to increase the output of the transmitter from the motor nerve terminals. In this respect it has been claimed that edrophonium is particularly effective (Blaber, 1972). Thus, the rapid initial antagonism of competitive neuromuscular blockade by edrophonium may be associated with a rapid release of acetylcholine from the motor nerve terminal. The fact that the initial rapid antagonism by edrophonium is not maintained when the anticholinesterase is given at the commencement of recovery from neuromuscular blockade may be a result of transmission failure, because acetylcholine stores may be so rapidly depleted that mobilization cannot be maintained. It is also possible that the duration of action of edrophonium, even at relatively high doses, may be too short to sustain recovery from complete blockade. The anti-curare effect of edrophonium wanes if it is administered during complete neuromuscular blockade, because it is rapidly redistributed and excreted (Doughty and Wylie, 1952). However, if edrophonium is administered when spontaneous recovery from neuromuscular blockade is well established, it is unlikely that paralysis will recur because the plasma concentration of the blocking agent would be too low (Matteo, Spector and Horowitz, 1974; Mcleod, Watson and Rawlins, 1976).

It has been suggested by Jones, Pearce and Williams (1984) that a train-of-four ratio of 50% provides a reasonable level of recovery for the safe antagonism of residual atracurium-induced blockade with appropriately large doses of edrophonium. In support of that view, we found that
approximately 50% recovery of the peak tetanic contraction was an adequate value for effective antagonism by edrophonium. However, neostigmine should be used in preference to edrophonium when antagonism is required at the beginning of recovery, particularly that associated with the neuromuscular blockade induced by the longer acting competitive blocking agents, because the antagonism by neostigmine is more persistent and the recovery phase is significantly shortened. The determination of the extent of neuromuscular blockade and the effectiveness of the antagonist may require the use of a peripheral nerve stimulator.

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REFERENCES


