NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE IN ANAESTHETIZED MAN

J. P. PAYNE, R. HUGHES AND S. AL AZAWI

SUMMARY

The tetanic and single twitch responses of the adductor pollicis muscle were used to study the neuromuscular effects of neostigmine in 26 patients anaesthetized with thiopentone and nitrous oxide. Neostigmine 2.5 mg i.v. given 5 min after exposure to halothane antagonized non-depolarizing neuromuscular block, whereas a second dose given 2–5 min later depressed the peak tetanic contraction and re-established tetanic fade. In the absence of halothane the second dose of neostigmine had less effect. Recovery of the single twitch was not impaired by the second dose. A single dose of neostigmine 5 mg rapidly antagonized the competitive block of the tetanic response but the subsequent slight depression of the peak contraction and the brief reappearance of fade were less than after 5 mg given in two doses of 2.5 mg. In patients who were not given neuromuscular blocking drugs, one or two injections of neostigmine 2.5 mg caused a substantial reduction in the peak tetanic contraction and severe tetanic fade which persisted for about 20 min; the single twitch was slightly potentiated. The neostigmine block of the tetanic response could be antagonized by gallamine and potentiated by suxamethonium. These findings indicate that neostigmine in clinical doses can produce an acetylcholine-induced block which would be a potential hazard in anaesthetic practice.

Although the potential neuromuscular blocking properties of neostigmine have been known for many years (Briscoe, 1936; Goodman and Gilman, 1956; Blaber and Bowman, 1963), no quantitative assessment of this effect has been described in man. In a previous study we demonstrated that halothane potentiated the neuromuscular block caused by non-depolarizing drugs and that it was reversed by neostigmine (Hughes and Payne, 1979). However, we also found that although the block was antagonized by a first dose of neostigmine, a subsequent dose of the anticholinesterase enhanced the block.

Accordingly, we decided that this interesting observation deserved further investigation and the present work was undertaken to obtain a quantitative assessment of this drug interaction in man.

METHODS

Studies were performed, after informed consent had been obtained, on 26 patients about to undergo elective urological surgery. No premedication was given and anaesthesia was induced with thiopentone 300–600 mg i.v.; some patients were also given halothane 2–4%. Intubation of the trachea was performed without the use of a neuromuscular blocking agent after the larynx had been sprayed with lignocaine 4%. Where appropriate, halothane was then discontinued and anaesthesia maintained with a mixture of nitrous oxide 60–75% in oxygen given by intermittent positive pressure ventilation; supplements of thiopentone 100–200 mg and pethidine 50–150 mg were given as required. Simultaneous recordings of tetanic and single twitch contractions of the adductor pollicis muscles were made as described previously (Sugai, Hughes and Payne, 1975). Each ulnar nerve was stimulated supramaximally at the wrist every 12 s with rectangular pulses of 200 μs duration, one nerve at 50 Hz for 1 s and the other with single pulses.

In one series of experiments halothane 2% was administered after i.v. neuromuscular blocking doses of tubocurarine 0.1–0.24 mg kg⁻¹, dimethyl tubocurarine 0.075–0.1 mg kg⁻¹ and gallamine 1.0–1.6 mg kg⁻¹ when recovery of the tetanic response had reached 50%. After 5 min when the peak height of the tetanic contraction was reduced and tetanic fade was increased by halothane, neostigmine 2.5 mg was given i.v. preceded by atropine 1.2 mg. Two to five minutes later, while the administration of halothane continued, a second dose of neostigmine 2.5 mg...
was given. Groups of three patients were used for each neuromuscular blocking drug studied.

In a second series of experiments halothane was omitted and the first dose of neostigmine was administered when recovery from neuromuscular blockade had reached 50%; a second dose of neostigmine was administered 2 min later. Groups of two patients were used for each neuromuscular blocking drug studied.

Similarly, two patients received a single i.v. dose of neostigmine 5 mg, preceded by atropine 1.2 mg, one during recovery from neuromuscular paralysis by dimethyl tubocurarine 0.075 mg kg\(^{-1}\) and the other after gallamine 1.0 mg kg\(^{-1}\) when paralysis had been enhanced by halothane 2%.

Finally, nine patients, who were not given neuromuscular blocking agents, received up to three i.v. injections of neostigmine 2.5 mg preceded by atropine 1.2 mg. Four of these patients were subsequently given gallamine 10 mg i.v. and two patients received suxamethonium 0.3 mg kg\(^{-1}\).

RESULTS

In each group of three patients simultaneous recordings of the tetanic and twitch responses showed that after tubocurarine, dimethyl tubocurarine and gallamine, administration of halothane 2% caused an immediate increase in tetanic fade with a reduction in the peak height of the tetanic contraction. These effects were readily antagonized by neostigmine 2.5 mg i.v., but reappeared and were often enhanced by a second dose of anticholinesterase given 2–5 min later while the administration of halothane was continued (fig. 1). Recovery of the twitch response was unaffected by halothane; it was usually maximal when the first dose of neostigmine was given, and was not impaired by the second dose. Recordings taken at the same time, but at a faster paper speed, show more clearly the effects on tetanic fade (fig. 2).

Similar effects with neostigmine were obtained during recovery from neuromuscular blockade by tubocurarine, dimethyl tubocurarine and gallamine.
in the absence of halothane. Groups of two patients were used for each drug.

Tetanic fade is defined as the rapid "fall off" of the tetanus from the peak height to a level at which it "holds" until the end of the stimulus. Our method of obtaining a quantitative assessment of this effect has already been described (Hughes and Payne, 1979).

The mean results obtained in the three groups of three patients who also received halothane 2% are summarized in table I. In each patient and for each neuromuscular blocking drug studied, the first dose of neostigmine restored the peak contraction height and abolished the tetanic fade, whereas a second dose of neostigmine given 2-5 min later reduced the peak contraction and re-established the tetanic fade.

Similarly, in those patients who were not given halothane (table II) the first dose of neostigmine was antagonistic. However, the depression of the peak contraction height and the extent of the tetanic fade following a second dose of neostigmine was usually less than in those patients who received halothane 2%.

In one patient, a single dose of neostigmine 5 mg was given after a neuromuscular blocking dose of gallamine 1.0 mg kg\(^{-1}\) in the presence of halothane. Although an immediate antagonism occurred, some tetanic fade (21%) with a slight depression of the peak contraction was evident about 4 min after the administration of neostigmine. Another patient given a single dose of neostigmine 5 mg during recovery from neuromuscular blockade by dimethyl tubocurarine 0.075 mg kg\(^{-1}\) in the absence of halothane showed a similar response (fig. 3); again, the rapid antagonism of the tetanic response was followed by a transient reduction in peak height. The lower tracing recorded at a faster speed shows the brief

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg kg(^{-1})) i.v.</th>
<th>1st dose neostigmine 2.5 mg</th>
<th>2nd dose neostigmine 2.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Peak contraction (% initial)</td>
<td>Tetanic fade (%)</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.1-0.24</td>
<td>170 ± 21.9</td>
<td>0</td>
</tr>
<tr>
<td>Dimethyl tubocurarine</td>
<td>0.075-0.1</td>
<td>169 ± 9.8</td>
<td>0</td>
</tr>
<tr>
<td>Gallamine</td>
<td>1.0-1.6</td>
<td>191 ± 20</td>
<td>0</td>
</tr>
</tbody>
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*Fig. 2. Tracing from an anaesthetized patient recorded at a faster paper speed showing that, after neuromuscular blockade by dimethyl tubocurarine and in the presence of halothane 2%, a first dose of neostigmine 2.5 mg restored the peak height of the tetanic contraction and abolished the fade, whereas following a second dose of neostigmine given 5 min later the peak height was greatly reduced and the tetanic fade was virtually complete.*
TABLE II. Effects on the tetanic responses of the adductor pollicis muscle of two doses of neostigmine 2.5 mg given during recovery from neuromuscular blockade by tubocurarine, dimethyl tubocurarine and gallamine in groups of two anaesthetized patients for each drug. Mean values are quoted with individual results in parentheses.

<table>
<thead>
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<th>Drug</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>i.v.</td>
<td>Peak contraction (% initial)</td>
<td>Tetanic fade (%)</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.1-0.15</td>
<td>169 (166, 171)</td>
<td>0 (94, 95)</td>
</tr>
<tr>
<td>Dimethyl tubocurarine</td>
<td>0.075</td>
<td>143 (136, 150)</td>
<td>0 (46, 84)</td>
</tr>
<tr>
<td>Gallamine</td>
<td>0.75</td>
<td>165 (152, 177)</td>
<td>0 (96, 96)</td>
</tr>
</tbody>
</table>

**Fig. 3.** Tracings from an anaesthetized patient recorded at slow and fast paper speeds showing that a single dose of neostigmine 5 mg preceded by atropine 1.2 mg during recovery from neuromuscular blockade by dimethyl tubocurarine rapidly antagonized the tetanic response, but this was followed by a transient reduction of its peak height with a brief reappearance of some tetanic fade. The single twitch (not illustrated) showed only the initial antagonism. However, in both instances, the blockade produced by a single dose of neostigmine 5 mg was less than that produced by two doses of 2.5 mg.

A final group of nine patients, who were not given neuromuscular blocking drugs, received up to three injections of neostigmine 2.5 mg. In five patients a single injection of neostigmine 2.5 mg was sufficient to block the tetanic response partially. In the remaining four patients a second dose of neostigmine 2.5 mg was required to produce a substantial reduction in the peak height of the tetanic response which persisted for about 20 min. A typical recording is seen in figure 4. The lower tracing recorded at a fast speed shows that the degree of fade was so marked that the tetanic response was virtually converted to a single twitch. The single twitch itself (not shown) was unimpaired and in fact was slightly enhanced. In two of these four patients a third injection of neostigmine was given with a scarcely perceptible additional effect.

A further important observation was that gallamine antagonized the block caused by neostigmine. This
Fig. 5. Tracings from an anaesthetized patient showing neuromuscular block of the tetanic response after two doses of neostigmine 2.5 mg, preceded by atropine 1.2 mg, and the potentiation of the single twitch. Gallamine 10 mg antagonized the neuromuscular block of the tetanic response and reversed the potentiation of the single twitch.

Fig. 6. This recording, taken simultaneously as that shown in figure 7 but at a faster paper speed, shows that the complete tetanic fade which occurred after the two doses of neostigmine 2.5 mg was almost entirely abolished by gallamine 10 mg.

Fig. 7. Recordings from an anaesthetized patient showing that blockade of the tetanic response by two doses of neostigmine 2.5 mg was potentiated by suxamethonium 0.3 mg kg⁻¹; fasciculations occurred on the single twitch.

In contrast, the two doses of gallamine 10 mg progressively reversed the initial potentiation of the single twitch. Figure 6, recorded at faster speed, shows that the complete tetanic fade which occurred after the two doses of neostigmine 2.5 mg was almost entirely abolished by gallamine 10 mg. Finally, two patients in this group were given suxamethonium 0.3 mg kg⁻¹ after neuromuscular block had been established with neostigmine. In both instances the block of the tetanic response was potentiated by suxamethonium (fig. 7) and in each case the subsequent recovery was slow. Fasciculations preceded the block on the single twitch which recovered more slowly than normal.

**DISCUSSION**

These studies in anaesthetized man have substantiated the early work of Briscoe (1936, 1937) who showed in cats that neostigmine and physostigmine rapidly depressed the muscle responses to high rates of stimulation and that these muscle responses became twitch-like in character. Furthermore, Briscoe (1938) also reported that these effects of anticholinesterase drugs could be abolished by curare and our observation that gallamine will reverse neostigmine block confirms her claim.

In our studies neostigmine was given to one group of patients in whom the recovery from neuromuscular block by non-depolarizing drugs had been reversed by exposure to halothane. In these patients paralysis of the tetanic responses of the adductor pollicis muscle was antagonized by a first dose of neostigmine 2.5 mg, whereas a second dose, given a few minutes
later, reduced the peak height of the tetanic contraction and produced tetanic fade. The study was repeated without halothane when a second dose of neostigmine was usually less effective than in those patients who were also receiving halothane. This difference is not surprising because we have demonstrated previously that halothane itself, in the presence of a competitive blocking agent, will depress the peak tetanic contraction and increase tetanic fade (Hughes and Payne, 1979).

The question then arose whether or not a single dose of neostigmine 5 mg would produce a similar effect as the same amount in two doses of 2.5 mg when given during recovery from blockade by competitive agents and in the presence or absence of halothane. In both instances, after the immediate antagonism by neostigmine 5 mg, there was a transient reduction in the peak height of the tetanic contraction and a brief reappearance of tetanic fade. However, these effects were substantially less than those produced by 5 mg given in two doses of 2.5 mg.

Since the neuromuscular paralysing action of neostigmine in the presence of a competitive blocking agent was more marked when given in divided doses, it is possible that the tetanic response had fully recovered after the first dose of neostigmine 2.5 mg, so that the second dose was acting on normal unblocked muscle. When this hypothesis was tested in patients who were not given neuromuscular blocking drugs, one or two doses of neostigmine 2.5 mg produced a substantial reduction in the peak height of the tetanic contraction which persisted for about 20 min. The tetanic fade was so marked that this response had now virtually become a single twitch. Furthermore, we found that the neostigmine block could be antagonized by a small dose of gallamine and potentiated by suxamethonium, the action of which was also prolonged. These findings provide evidence that neostigmine, in sufficient dosage, will produce an acetylcholine-induced block of the tetanic response in anaesthetized man. The preserved acetylcholine will accumulate at the muscle end-plate and produce a depolarization block.

Tetanic fade produced by anticholinesterases is associated with a marked inhibition of acetylcholinesterase (Barnes and Duff, 1953). The end-plate potentials are prolonged and during high frequency nerve stimulation they summate and block the neuromuscular function by a persistent depolarization of the postsynaptic membrane. It is worth noting that anticholinesterase drugs also have a facilitatory action on the motor nerve terminal (Riker and Standaert, 1966) which would further increase the acetylcholine available at the muscle end-plate. Furthermore, it is likely that such prejunctional events would be more evident when the motor nerve terminals are fully activated and when the acetylcholine reserves are fully mobilized as during tetanic stimulation. It is also possible that an initial excessive release of acetylcholine produced by an anticholinesterase drug would rapidly exhaust the available transmitter which may in part account for the transmission failure (Blaber and Bowman, 1963). No doubt each of these factors contributed to our observation that neostigmine depressed the peak tetanic contraction and caused severe tetanic fade in anaesthetized man.

In contrast, it was intriguing that the responses of the single twitch were in fact potentiated by one or two doses of neostigmine 2.5 mg and that gallamine restored the single twitches to their initial contraction height. This feature illustrates the genuine differences between the tetanic and single twitch responses. The potentiation of the single twitch response by neostigmine may be explained by the fact that anticholinesterase drugs at low frequencies of stimulation produce a short burst of muscle action potentials (repetitive firing) so that the muscle now responds as if stimulated at a higher frequency and the twitch tension increases (Brown, Dale and Felding, 1936; Brown, 1937). The increased availability of acetylcholine at the muscle end-plate, mainly as a result of inhibition of acetylcholinesterase and partly as a result of an increased release of the transmitter from the motor nerve terminals, would augment and prolong the end-plate potentials and lead to repetitive firing of the muscle fibres as described by Eccles, Katz and Kuffler (1942). However, the amount of acetylcholine available, unlike that after high frequency tetanic stimulation, is insufficient to produce a depolarizing neuromuscular block. Nevertheless, it must be emphasized that tetanic stimulation provides the more physiological response since breathing and contractions of skeletal muscles are activated by tetanic trains of stimuli rather than by single pulses.

It is not immediately clear why gallamine should antagonize the neuromuscular blocking action of neostigmine, but the fact that the fade in the tetanic response was so rapidly reversed by gallamine might imply that the drug was competing with the excess acetylcholine for the appropriate receptors and this interpretation is supported, if the earlier argument is accepted, by the restoration to control height of the intensified twitch response, and the enhancement...
of the neostigmine block by suxamethonium gives further substance to this explanation.

It may be concluded from our results that neostigmine, in clinical doses, could be a potential hazard in anaesthetic practice. Obviously, the critical factors are the total dose of neostigmine administered and the degree of recovery achieved when the drug is given to reverse paralysis. Clearly, if recovery of the tetanic response has reached about 50%, then a single 2.5-mg dose should be sufficient to provide adequate reversal. If a larger dose of neostigmine is required for complete antagonism of a deeper block, then a single dose of 5 mg may be preferable to two doses of 2.5 mg.

However, when full recovery has been achieved, a further dose of neostigmine 2.5 mg could be hazardous because a prolonged depolarizing block with apnoea could ensue. Moreover, it is possible that instances of residual curarization after apparent inadequate reversal may have been attributable to overdosage with neostigmine.

ACKNOWLEDGEMENTS

We are indebted to Miss V. A. Bishop, S.R.N., Mr D. Knox, B.TECH. and Mr A. J. Harman for skilled technical assistance, to our surgical and nursing colleagues for their tolerance and patience and to our volunteers without whom this study would not have been possible.

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BLOCAGE NEUROMUSCULAIRE APRES ADMINISTRATION DE NEOSTIGMINE CHEZ LES ANESTHESIES

RESUME

Les réactions tétaniques et de contraction unique du muscle adducteur du pouce ont servi à l'étude des effets neuromusculaires de la neostigmine sur 26 patients anesthésiés à l'aide de thiopentone et de protoxyde d'azote. L'administration intraveineuse de 2,5 mg de neostigmine après exposition à l'halothane a été à l'encontre du blocage neuromusculaire non dépolarisant, alors qu'une seconde dose administrée entre 2 et 5 min plus tard a déprimé la contraction tétanique de crête et rétabli le "fading" tétanique. Sans halothane, la seconde dose de neostigmine a eu moins d'effet. La récupération à la suite de la contraction unique n'a pas été affectée par la seconde dose. Une seule dose de 5 mg de neostigmine s'est rapidement opposée au blocage compétitif de la réaction tétanique, mais la légère répression ultérieure de la contraction de crête et la brève réapparition de "fading" ont été moins prononcées qu'après l'administration de 5 mg en deux doses de 2,5 mg. Chez les patients n'ayant pas reçu d'agents de blocage neuromusculaire, une ou deux injections de 2,5 mg de neostigmine ont considérablement réduit la contraction tétanique de crête mais causé un "fading" tétanique grave qui a duré pendant environ 20 min ; la contraction unique a été légèrement activée. Le blocage de la réaction tétanique par la neostigmine peut être opposé par la gallamine et activé par le suxaméthonium. Les résultats de ces études font ressortir que la néostigmine administrée en doses cliniques peut être à l'origine d'un blocage provoqué par l'acétylcholine, lequel pourrait présenter un risque éventuel en anesthésie.

NEUROMUSKULÄRE BLOCKIERUNG DURCH NEOSTIGMIN BEI NARKOTISIERTEN MENSCHEN

ZUSAMMENFASSUNG

Die tetanische und die Einzel-Zuckreaktionen des Adductor pollicis-Muskel wurden zum Studium der neuromuskulären Effekte von Neostigmin bei 26 mit Thiopenton und Stickoxyd narkotisierten Patienten verwendet. Neostigmin (2,5 mg) wird intravenös nach Halothan verabreicht und hatte eine Gegenwirkung auf die nicht-depolarisierende neuromuskuläre Blockierung, wogegen eine 2-5 min später verabreichte Dosis die tetanische Spitzeneaktion unterdrückte und ein tetanisches Absinken bewirkte. Bei
Abwesenheit von Halothan war die zweite Neostigmin-Dosis weniger wirksam, und Wiederherstellung der Einzelzuckung wurde dadurch nicht beeinträchtigt. Eine Dosis von 5 mg Neostigmin brachte eine schnelle Gegenwirkung gegen die Blockierung der tetanischen Reaktion, aber die folgende leichte Unterdrückung der Spitzenkontraktion und das kurze Wiederauftreten des tetanischen Absinkens waren geringer als nach einer Verabreichung von 5 mg in zwei Einzeldosen zu 2,5 mg. Bei Patienten, die keine Drogen zur neuromuskulären Blockierung erhalten hatten, bewirkten eine oder zwei Injektionen von Neostigmin (2,5 mg) eine wesentliche Verringerung der tetanischen Spitzenreaktion und schweres tetanisches Absinken auf etwa 20 min; die Einzelzuckung war leicht verstärkt. Die Neostigmin-Blockierung der tetanischen Reaktion konnte durch Gallamin aufgehoben und durch Suxamethonium verstärkt werden. Diese Resultate zeigen an, dass Neostigmin in klinischen Dosierungen durch Acetylcholin bewirkte Blockierung hervorrufen kann, die eine potentielle Gefahr in der Narkosepraxis bedeuten kann.

BLOQUEO NEUROMUSCULAR POR NEOSTIGMINA EN HOMBRE ANESTESIADO

SUMARIO
Se usaron las respuestas contraccional única y tetánica del músculo aductor del pulgar para estudiar los efectos neuromusculares de la neostigmina en 26 pacientes anestesiados mediante tiopentona y óxido nitroso. Con 2,5 mg i.v. de neostigmina administrados después de la exposición al halotano, se antagonizó al bloqueo neuromuscular no-depolarizante, mientras que mediante una segunda dosis administrada 2–5 min después, se deprimió la contracción tetánica tope y se restableció la debilitación tetánica. Al no usarse halotano con la segunda dosis, ésta tuvo efectos menores. La recuperación de la contracción única no fue afectada negativamente por la segunda dosis. Una dosis única de 5 mg de neostigmina antagonizó rápidamente el bloqueo competitivo de la respuesta tetánica, pero la ligera depresión consecutiva de la contracción tope y la breve reaparición de la debilitación fueron menos fuertes que después de la administración de 5 mg en dos dosis de 2,5 mg cada una. En los pacientes a quienes no se administró substancias bloqueadoras neuromusculares, una o dos inyecciones de 2,5 mg de neostigmina causaron una reducción substancial de la contracción tetánica tope y una debilitación tetánica severa que duró por 20 min aproximadamente; aumentó la potencia de la contracción única de manera débil. Se podía antagonizar al bloqueo de la respuesta tetánica por neostigmina mediante galamin y aumentarlo con suxametonio. Estos resultados indican que la neostigmina en dosis clínicas puede producir un bloqueo inducido por acetilcolina, lo que constituiría un riesgo potencial en la anestesia.