EFFECT OF HYPOCARBIA AND HYPERCARBIA ON THE ANTAGONISM OF PANCURONIUM-INDUCED NEUROMUSCULAR BLOCKADE WITH NEOSTIGMINE IN MAN

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SUMMARY

The effects of variations in carbon dioxide concentration on the antagonism of pancuronium-induced neuromuscular block by neostigmine were studied in 21 patients, normocarbia \( (P_{\text{CO}_2} = 5.4\% \text{, } P_{\text{aCO}_2} = 4.93 \text{ kPa, } n = 7) \), hypocarbia \( (P_{\text{CO}_2} = 3.6\% \text{, } P_{\text{aCO}_2} = 3.30 \text{ kPa, } n = 7) \) and hypercarbia \( (P_{\text{CO}_2} = 7.5\% \text{, } P_{\text{aCO}_2} = 7.13 \text{ kPa, } n = 7) \). Mechanical and electromyographic responses to ulnar nerve stimulation (0.1 Hz and 2 Hz) were recorded. A 90% block during nitrous oxide in oxygen anaesthesia was maintained by incremental single injections of pancuronium and reversed with neostigmine 0.035 mg kg\(^{-1}\) with atropine 0.0175 mg kg\(^{-1}\). The recovery of twitch tension up to 50% was similar in all groups but thereafter slower in the hypercarbia group. The recovery times from 25% to 75% twitch tension correlated with \( P_{\text{aCO}_2} \) \((r = 0.55, P < 0.05)\). A residual block of about 10% was seen in hypercarbic patients. However, the recovery of e.m.g. amplitude and train-of-four ratios was similar in all groups. Thus, the impaired recovery of twitch tension seems to be the result of depressed contractility rather than failure of neuromuscular transmission.

Residual neuromuscular blockade is considered to contribute significantly to morbidity and possibly even mortality following operation (Cascorbi and Gravenstein, 1974). Factors which impair recovery from neuromuscular blockade include alterations in pH, and metabolic acidosis has been claimed to cause a state of neostigmine-resistant curarization (Feldman, 1979). It has been shown that blockade by tubocurarine and pancuronium cannot be antagonized fully in the presence of hypercarbia (Miller et al., 1975; Miller and Roderick, 1978). In addition, hypercarbia can attenuate the twitch response to nerve stimulation during blockade with tubocurarine (Katz and Wolf, 1964) and impede recovery from blockade with pancuronium (Norman, Katz and Seed, 1970). However, the role of these factors in association with the degree of hypercarbia likely to be encountered in clinical practice during the reversal of blockade does not seem to have been established in man. Therefore the recovery of neuromuscular transmission during the reversal of blockade with neostigmine was studied under conditions of moderate hypercarbia and moderate hypocarbia.

PATIENTS AND METHODS

Twenty-one patients (23–59 yr) in good general health and undergoing varicose vein surgery lasting less than 1 h participated in the study. Consent for the study was obtained from each patient. They were matched by sex, age, weight and height into three groups of seven patients (table I). Each patient was premedicated with oxycodone 1.4 mg per 10 kg i.m., promethazine 25–50 mg i.m. and atropine sulphate 0.1 mg per 10 kg i.m. 30 min before the induction of anaesthesia. Fentanyl 0.05–0.1 mg was administered i.v. and followed by thiopentone 200–400 mg i.v. Tracheal intubation was facilitated with suxamethonium 0.7 mg kg\(^{-1}\) and, after full recovery of twitch tension, pancuronium 0.05 mg kg\(^{-1}\) i.v. was given as an initial single injection and in incremental doses to achieve and maintain a twitch suppression of about 90%. The lungs were ventilated mechanically with nitrous oxide in oxygen with an average oxygen concen-
dration of 30% as measured with a polarographic sensor. Fentanyl was administered in doses of 0.05-0.1 mg to provide analgesia when required.

The minute ventilation was adjusted to produce end-tidal carbon dioxide concentrations of about 3.5, 5.5 or 7.5% by varying the respiratory rates, the tidal volumes remaining constant. At the end of the operation the 90 ± 2% neuromuscular blockade was reversed with neostigmine 0.035 mg kg⁻¹ combined with atropine 0.0175 mg kg⁻¹ i.v. A sample for blood-gas analysis was drawn from the radial artery just before the administration of the neostigmine. During reversal ventilation remained unchanged.

The ulnar nerve was stimulated through steel needle electrodes near the wrist with 0.1 Hz supramaximal square-wave stimuli of 0.1 ms duration. In addition, train-of-four stimuli at 2 Hz were given after recovery of the twitch height to a plateau—a state of no change of twitch height over 2 min. Mechanical myographic (m.m.g.) responses (the isometric tension produced by thumb adduction) were measured with a force transducer and the corresponding electromyogram (e.m.g.) was recorded through a 0.35-mm x 15-mm (27-gauge) needle electrode located in the adductor pollicis muscle. The calibration of the force and e.m.g. measurements was performed for each patient after induction of anaesthesia (thiopentone-fentanyl-nitrous oxide) and before the administration of suxamethonium.

For statistical comparisons Student's t test, Mann-Whitney test and linear regression analysis were used. P < 0.05 was considered significant.

RESULTS

Mean $\text{Pa}_{\text{CO}_2}$ and pH values for the three groups of patients are shown in table II. The normocarbic group differed significantly from its hypocarbic and hypercarbic counterparts. The pH values correlated well with the corresponding carbon dioxide values, and no metabolic compensation was observed during anaesthesia. The amount of pancuronium administered to maintain 90% twitch suppression was slightly greater ($P<0.2$) in the hypocarbic group than in the normocarbic or hypercarbic groups (table II). The duration of 10% twitch tension was comparable in all groups (table II).

The initial recovery to 50% twitch tension took about 3 min in all groups (fig. 1). Thereafter, recovery was slower in the hypercarbic group. In the normocarbic and hypocarbic groups the recovery was similar up to 90% twitch tension at 9 min, and from which point it seemed slightly faster in the hypocarbic group, but no statistical significance was reached.

The recovery time from 25% to 75% twitch tension correlated with arterial $\text{P}_{\text{CO}_2}$ ($r = 0.55$, $P < 0.05$) although the scatter was wide (fig. 2). The means of the peak recovery values of twitch tension, e.m.g. amplitude and the corresponding train-of-four ratios achieved in the three groups are summarized in figure 3. Twitch tension recovered to slightly more than its initial value in the hypocarbic and normocarbic groups, but in

<table>
<thead>
<tr>
<th>Group</th>
<th>End-tidal CO₂</th>
<th>$\text{Pa}_{\text{CO}_2}$ (kPa)</th>
<th>pH</th>
<th>Total pancuronium (µg kg⁻¹ min⁻¹)</th>
<th>Duration of 10% twitch tension (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normocarbia</td>
<td>5.4</td>
<td>4.94 ± 0.15</td>
<td>7.41 ± 0.01</td>
<td>1.83 ± 0.26</td>
<td>40.6 ± 4.1</td>
</tr>
<tr>
<td>Hypocarbia</td>
<td>3.6</td>
<td>3.30 ± 0.17</td>
<td>7.55 ± 0.02</td>
<td>2.18 ± 0.23</td>
<td>37.4 ± 4.9</td>
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<tr>
<td>Hypercarbia</td>
<td>7.5</td>
<td>7.13 ± 0.20</td>
<td>7.28 ± 0.01</td>
<td>1.80 ± 0.16</td>
<td>42.6 ± 3.8</td>
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the hypercarbic group a 10% residual effect persisted ($P<0.001$). The mechanical myograph train-of-four ratios were similar in all groups and amounted to about 60%. The recovery of e.m.g. amplitude (0.1 Hz) seemed to be better in the hypercarbic group (mean $96.4 \pm 3.0\%$) than in the normocarbic group ($83.4 \pm 5.7\%$, $P<0.05$), and was intermediate in hypocarbia ($89.1 \pm 7.2\%$). There were no significant differences between the e.m.g. train-of-four ratios during reversal (2 Hz) ($79.9 \pm 3.1\%$ in hypercarbia, $68.4 \pm 11.1\%$ in normocarbia and $61.0 \pm 10.1\%$ in hypocarbia).

**DISCUSSION**

Hypercarbia has been shown to attenuate the twitch response to nerve stimulation during blockade with tubocurarine in man (Katz and Wolf, 1964). This has not been as clearly demonstrated with pancuronium and could be a result of the different ionization behaviour of these two drugs at physiological pH (Feldman, 1979). Norman, Katz and Seed (1970) showed that spontaneous recovery from pancuronium blockade was slower when hypercarbia was induced in previously hyperventilated patients and that the recovery was faster with overventilation after hypercarbia. Crul-Sluijter and Crul (1974) found that pancuronium blockade was potentiated by metabolic and respiratory acidosis in cats in vivo and in the rat phrenic nerve-diaaphragm preparation in vitro. Based on their findings in cats, Miller and Roderick (1978)
concluded that hypercarbia prevents the antagonism of pancuronium by neostigmine.

The contribution of these slight changes in the stimulation-evoked responses to overall clinical blockade is probably insignificant during the maintenance of anaesthesia. However, during recovery from blockade and anaesthesia, hypercarbia could precipitate a vicious circle of residual neuromuscular blockade, progressive hypventilation and increasing carbon dioxide tension. The impairment of the response to neostigmine in the presence of hypercarbia could be of even more importance.

In this study moderately hyperventilated patients showed a tendency to consume more pancuronium than their hypoventilated or normoventilated counterparts, although the trend was small, when the myoneural blocking drug was administered in such a way as to maintain constant twitch depression. Since increasing the amounts of blocker is known to decrease the recovery of twitch height, the more rapid recovery of twitch tension in hyperventilated patients than in hypoventilated patients might have been more pronounced had the doses of pancuronium been identical.

The decrease in the mechanical twitch response following neostigmine in the hypoventilated patients was not seen in the measurements of e.m.g. amplitude. This finding was interpreted as evidence for the direct depressant effects of carbon dioxide tension on contractility. E.m.g. amplitude has been claimed to be a better indicator of actual neuromuscular blockade than measurements of twitch tension (Lee and Katz, 1980).

A train-of-four ratio greater than 70% is thought to correlate with clinical tests of the adequacy of reversal (Ali and Savarese, 1976). Using electromyography, a train-of-four ratio of 75% correlates with adequate clinical recovery (Ali and Savarese, 1976). The similarity of the train-of-four ratios after recovery in the present patient groups suggested that hypercarbia did not induce failure of neuromuscular transmission but rather affected contractility. This is supported by the fact that none of our patients showed signs of residual muscle weakness by the standard clinical criteria, which suggests that the depression of contractility brought about by clinically acceptable hypercarbia is well tolerated in the presence of intact neuromuscular transmission.

The mechanism of the decrease in twitch tension in hypercarbia is not clear, but seems also to apply to heart muscle. A decrease of about 30% in the isometric contraction force of the isolated papillary muscle of a cat's heart related to Pco2 has been demonstrated when the concentration of carbon dioxide was increased from 4.7% to 9.8% (Foex, 1980). Secondary changes in extracellular pH or ions might be mediators of the effect.

In conclusion, clinically relevant moderate hypercarbia impaired the recovery of twitch tension in anaesthetized patients after neostigmine had been used to antagonize pancuronium blockade. However, no impairment of recovery was demonstrated in e.m.g. or in train-of-four ratios which probably reflect better the functioning of the neuromuscular junction. Thus the hypercarbia-induced decrease in twitch tension seemed to be the result of depressed contractility rather than of neuromuscular blockade. Since proper functioning of the neuromuscular junction probably contributes more to restitution of adequate muscle tone than slight changes in contractility, the clinical significance of moderate hypercarbia is questionable.

REFERENCES
CO₂ AND PANCURONIUM NEUROMUSCULAR BLOCK

EFFET DE L’HYPOCARBIE ET DE L’HYPERCARBIE SUR L’ANTAGONISME PAR LA NEOSTIGMINE D’UN BLOCAGE NEUROMUSCULAIRE PROVOQUE PAR LE PANCURONIUM CHEZ L’HOMME

RESUME
Les effets des variations dans la concentration de gaz carbonique sur l’antagonisme par la neostigmine d’un blocage neuromusculaire provoqué par le pancuronium ont fait l’objet d’une étude portant sur 21 patients et couvrant: normocarbie (PE′CO₂, 5,4%, Paco₂, 4,93 kPa, n = 7) hypocarbie (PE′CO₂, 3,6%, Paco₂, 3,30 kPa, n = 7) et hypercarbie (PE′CO₂, 7,5%, Paco₂, 7,13 kPa, n = 7). Nous avons enregistré les réactions mécaniques et électromyographiques à la stimulation du nerf ulnaire (0,1 Hz et 2 Hz). Un blocage à 90% pendant une anesthésie au protoxyde d’azote dans l’oxygène a été maintenu à l’aide d’injections croissantes de pancuronium, puis inversé à l’aide de néostigmine à raison de 0,035 mg kg⁻¹ et d’atropine administrée à raison de 0,0175 mg kg⁻¹. La récupération de la tension de la contraction jusqu’à 50% a été similaire dans tous les groupes, mais au-delà de ce chiffre elle a été plus lente dans le groupe hypercarbie. Les temps nécessaires à la récupération compris entre 25% et 75% de la tension de la contraction ont été en corrélation avec la Paco₂ (r = 0.55, P<0.05). Un blocage résiduel d’environ 10% a été constaté chez les patients du groupe hypercarbie. Quoi qu’il en soit, la récupération de l’amplitude de l’é.m.g et des rapports de la chaîne de quatre a été similaire dans tous les groupes. Ainsi, l’altération de la récupération de la tension de la contraction semble être le résultat d’une contractilité déprimée plutôt que d’une défaillance de la transmission neuromusculaire.

DIE AUSWIRKUNG VON HYPOKAPNIE UND HYPERKAPNIE AUF DIE BEKämpFUNG EINER MIT PANCURONIUM INDUIZIERTEN NEUROMUSKULÄREN BLOCKADE MITTELS NEOSTIGMIN

ZUSAMMENFASSUNG
Die Auswirkungen von Änderungen der Kohlendioxidkonzentrationen auf die Bekämpfung von einem pancuronium-induzierten neuromuskulären Blockade mittels Neostigmin wurden bei 21 Patienten studiert: Normokapnie (PE′CO₂, 5,4%, Paco₂, 4,93 kPa, n = 7), Hypokapnie (PE′CO₂, 3,6%, Paco₂, 3,30 kPa, n = 7) und Hyperkapnie (PE′CO₂, 7,5%, Paco₂, 7,13 kPa, n = 7). Die mechanische und elektromyographische Reaktionen auf Reizungen des Nervus ulnaris (0,1 und 2 Hz) wurden ermittelt. Eine 90% Blockade während einer Anästhesie mit Lachgas in Sauерstoff wurde mittels gestufter einzelner Injektion von Pancuronium aufrechterhalten und mittels Neostigmin 0,035 mg kg⁻¹ und Atropin 0,0175 mg kg⁻¹ umgekehrt. Die Erholung der Zuckungsspannung bis zu 50% war bei allen Gruppen ähnlich, aber ging danach bei der Hyperkapnie-gruppe langsamer vor sich. Die Erholungszeiten von 75% zu 50% Zuckungsspannung zeigten eine Korrelation zu Paco₂ (r = 0.55, P<0.05) Eine Restblockade von 10% wurde bei Hyperkapnie Patienten beobachtet. Die Erholung der emg-Amplitude und Viererzugverhältnisse war jedoch bei allen Gruppen ähnlich. Die beeinträchtigte Erholung der Zuckungsspannung scheint eher das Ergebnis von herabgedrückter Contractualität als das Ergebnis eines Versagens von neuromuskulärer Übertragung zu sein.

EFFECTO DE LA HIPERCARBIA Y DE LA HIPOCARBIA EN EL CONTRARRESTO MEDIANTE NEOSTIGMINA DEL BLOQUEO NEUROMUSCULAR INDUCIDO POR PANCURONIO

SUMARIO
Se estudiaron en 21 pacientes con normocarbia (PE′CO₂ al 5,4%, Paco₂, 4,93 kPa, n = 7) hypocarbica (PE′CO₂ al 3,6%, Paco₂, 3,30 kPa, n = 7), e hipercarbica (PE′CO₂ al 7,5%, Paco₂, 7,13 kPa, n = 7), los efectos de las variaciones en la concentración de dióxido de carbono al contrarrestar, mediante neostigmina, el bloqueo neuromuscular inducido por pancuronio. Se registraron los resultados de las respuestas mecánicas y electromiográficas a la estimulación del nervio cubital (0,1 Hz y 2 Hz). Se mantuvo un bloqueo del 90% durante la anestesia con óxido nitroso en oxígeno, incrementando las inyecciones unitarias de pancuronio y contrarrestandolas y con 0,035 mg kg⁻¹ de neostigmina con 0,0175 mg kg⁻¹ de atropina. La recuperación de hasta el 50% de la tensión de contracción fue similar en todos los grupos pero más lenta posteriormente en el grupo con hipercarbica. Los tiempos de recuperación correspondientes a la tensión de contracción de entre el 25% y el 75% vinieron correlacionados con Paco₂ (r = 0,55 P<0,05). En los pacientes hiperárbicos se contempló un bloqueo residual de aproximadamente el 10%. No obstante, la recuperación de los regímenes de amplitud y de los tres de cuatro impulsos fue similar en todos los grupos. De este modo, parece que la dificultad en la recuperación de la tensión de contracción es consecuencia de contractabilidad deprimida y no de fallo alguno en la transmisión neuromuscular.