THE EFFECTS OF DIFFERENT LEVELS OF VENTILATION
ON THE ACTION OF PANCURONIUM IN MAN

BY

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SUMMARY

The effect of changes of Pco₂ on the duration of action of pancuronium was studied. No significant difference was found between the recovery times of a group of 16 patients with a mean Pco₂ of 38.1 mm Hg, and another group of 16 with a mean Pco₂ of 23.8 mm Hg.

The effect of carbon dioxide on the neuromuscular blocking effect of the non-depolarizing muscle relaxants tubocurarine and gallamine has been known for some time. Kalow (1954) noted that the action of tubocurarine on an isolated muscle preparation was increased by lowering the pH. Payne (1958) found that in the anaesthetized cat the activity of tubocurarine was increased with a reduction of pH. Baraka (1964) and Katz and Wolf (1964) noted a delay in recovery from tubocurarine of patients with an acidosis. Waltz, Lebowitz and Dillon (1967), however, found no significant difference in the response of patients to tubocurarine whether ventilation was controlled (mean PaCO₂ 18.9 mm Hg) or assisted (mean PaCO₂ 49.2 mm Hg). Both Baraka (1967) and Waltz, Lebowitz and Dillon (1967) showed that the action of gallamine was antagonized by carbon dioxide.

More recently Norman, Katz and Seed (1970) investigated the action of pancuronium during anaesthesia and showed that in five out of six patients a sudden increase in carbon dioxide tension from an average stabilized level of 24 to 65 mm Hg led to a definite slowing of the rate of recovery of neuromuscular transmission.

The results of a study designed to determine whether changes of carbon dioxide tension, such as are commonly found during anaesthesia, alter the activity of pancuronium are reported.

METHODS

The study was carried out on 45 adult patients undergoing major surgery and who had no history of neurological or muscular disorders. Informed consent was obtained in all cases. Most patients were premedicated with pethidine 50–100 mg and atropine 0.6 mg or pethidine 25–50 mg with promethazine 25 mg. Some patients received only chlordiazepoxide 20–30 mg. Anaesthesia was induced with thiopentone 200–350 mg and maintained with nitrous oxide, oxygen and halothane. After intubation the patients were submitted to intermittent positive pressure ventilation. Halothane (0.5–1.5 per cent) was added as necessary, using a Fluotec Mark IV vaporizer outside the circuit. In some patients anaesthesia was supplemented with an intravenous injection of pethidine. Suxamethonium was not given to any patient, intubation being achieved under halothane after the pharynx and larynx had been sprayed with lignocaine solution (4 per cent). Pancuronium 0.05 mg/kg was given after base line measurements of the force of thumb abduction had been taken.

The patients were randomly allocated to one of two groups. In the first group the end-tidal carbon dioxide tension was maintained near the normal value of 40 mm Hg, by adjustment of ventilation and addition of carbon dioxide to the inspired gases if necessary. Patients in the second group were hyperventilated to achieve a carbon dioxide tension of 22–24 mm Hg. Alveolar Pco₂ was monitored continuously using an end-tidal sampler coupled to an infra-red carbon dioxide analyzer (Grubb Parsons Ltd), the output of which was recorded on a Servoscribe pen recorder (RE511). The mean partial pressure for each period under study was calculated.

Neuromuscular transmission was studied using the method described by Tyrrell (1969). The

ulnar nerve at the wrist was stimulated percutaneously by a supramaximal stimulus consisting of a square wave impulse of duration 110 msec and a frequency of 0.33 Hz delivered by a stimulator of our own design. The resulting thumb adduction (largely due to the activity of the adductor pollicis) was recorded using a Statham UC3 (gold cell) universal transducer coupled with a Statham UL 4–5 load cell (B and K Instruments Ltd, London) mounted in a handlebar grip to which the patient's hand was firmly strapped. The output from the transducer was displayed (after amplification) on a Tektronic type 564 storage oscilloscope and permanent records were taken with a polaroid camera (Tektronic C30).

Measurements lasting 1 minute were taken every 2½ minutes. The stimulator was turned off between measurements in order that the stimulation applied should be kept to a minimum, because it has been demonstrated that recovery from neuromuscular block is hastened by repeated stimulation of the nerve (Feldman and Tyrrell, 1970).

The intensity of the neuromuscular action was measured as the height of the twitch response, and the intensity of the block expressed as the percentage of this height compared with the height of the original twitch response. The recovery time was measured as the time taken after injection of the drug for the twitch to recover to 10, 20, 30, 40, and 50 per cent of the original twitch height.

**RESULTS**

Complete sets of measurements were obtained in 16 patients in the normocarbic group and 16 in the hypocarbic group. At no stage during recovery was there a significant difference between the two groups (tables I and II, fig. 1). The mean time taken to achieve 50 per cent recovery for the normocarbic group was 60.8 (SD 19.1) min, compared with 56.7 (SD 14.9) min for the hypocarbic group.

To assess the effect of variation in anaesthetic technique the results from patients who had or had not been given pethidine supplements (10–60 mg) during anaesthesia were compared. The group

**Table I**

| Case No. | 7  | 9  | 12 | 16 | 18 | 21 | 24 | 26 | 29 | 30 | 32 | 33 | 37 | 38 | 39 | 44 | Mean | SD |
|----------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|-----|
| PCO₂ (mmHg) | 37.7 | 39.9 | 35.4 | 39.3 | 37.3 | 39.5 | 37.0 | 38.8 | 37.1 | 40.5 | 38.6 | 36.1 | 39.5 | 37.6 | 38.2 | 36.8 | 38.1 |

**Table II**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>8</th>
<th>10</th>
<th>13</th>
<th>15</th>
<th>19</th>
<th>22</th>
<th>25</th>
<th>23</th>
<th>27</th>
<th>28</th>
<th>31</th>
<th>35</th>
<th>36</th>
<th>40</th>
<th>41</th>
<th>45</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCO₂ (mmHg)</td>
<td>27.4</td>
<td>24.3</td>
<td>22.8</td>
<td>28.5</td>
<td>20.6</td>
<td>23.4</td>
<td>23.8</td>
<td>24.2</td>
<td>23.3</td>
<td>23.1</td>
<td>26.3</td>
<td>23.2</td>
<td>22.1</td>
<td>23.1</td>
<td>22.2</td>
<td>21.3</td>
<td>23.75</td>
<td>2.08</td>
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receiving pethidine were given less halothane. There was no significant difference between the two groups in the time taken to achieve any level of neuromuscular recovery.

Table IV shows the 50 per cent recovery times for patients above and below 50 years of age. There was no significant difference between the two groups in the time taken to achieve any level of neuromuscular recovery (table III).

| TABLE IV |
| Comparison of time required to achieve 50 per cent recovery of original twitch height in patients above or below 50 years of age. |

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of patients</th>
<th>Recovery time to 50% (min)</th>
<th>SD</th>
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<tr>
<td>&gt;50</td>
<td>18</td>
<td>59.4</td>
<td>15.0</td>
</tr>
<tr>
<td>&lt;50</td>
<td>14</td>
<td>57.9</td>
<td>19.9</td>
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**DISCUSSION**

There are several mechanisms by which the action of muscle relaxants may be affected by changes in pH. Kalow (1954) pointed out that the tubocurarine molecule has two ionizable groups with pKb values near the biological range. A change in pH of the blood would, therefore, affect the degree of ionization of the drug with both groups undergoing further ionization as the pH is raised.
The pKb of pancuronium was measured using automatic titration equipment (Radiometer type SBR2) and found to be in excess of 13. This agrees with the level reported by Dr A. Simm (personal communication). With such a high pKb, changes of pH within the physiological range would not produce significant changes of ionization of the drug.

Gallamine does not contain ionizable groups. Payne (1958) has suggested that the altered effects of gallamine may be due to changes in drug plasma protein binding. Little is known about the protein binding properties of pancuronium but the results of this study suggest that the binding of this agent to plasma protein is not affected by such changes in carbon dioxide tension, and thus of pH, as are found in clinical anaesthesia.

Norman, Katz and Seed (1970) using the same dose of 0.05 mg/kg in a group of four patients found a mean duration to 50 per cent recovery of 36.8 min, with a range of 29–44 min. This is considerably less than our mean time of 58.8 min (range 30–97 min) to achieve the same degree of recovery. There is no obvious explanation for this difference as the anaesthetic techniques are similar in both studies.

The measured range of recovery times to 50 per cent of the initial twitch is large, confirming a general clinical impression of variation of action of this drug. No explanation for this wide range was found in the analysis of the effect of pethidine and halothane or of the effect of patient’s age on the recovery times. All studies of the duration of action of muscle relaxants show a considerable degree of spread in the recovery times (Walts, Lebowitz and Dillon, 1967; Katz, 1967). The large spread seen in the present study may in part be explained as a factor in the long recovery times seen with the chosen dose of pancuronium.

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REFERENCES


