THE INFLUENCE OF CHANGES IN ACID-BASE BALANCE ON NEUROMUSCULAR BLOCKADE IN CATS

BY

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SUMMARY

During inhalation of carbon dioxide, the tetanic contractions of indirectly stimulated gastrocnemius muscles of anaesthetized cats were increased whereas the single twitches were often slightly decreased. Hyperventilation or an infusion of hydrochloric acid slightly reduced the tetanic responses of the muscles; the neuromuscular effects of an infusion of sodium carbonate were trivial. Blockade by tubocurarine was significantly increased by respiratory and metabolic acidosis and was slightly reduced by respiratory and metabolic alkalosis; these effects have been attributed to changes in the ionization of the phenolic hydroxyl groups. Corresponding disturbances in acid-base balance had opposite but often significant effects on paralysis by gallamine and to a lesser extent on that by dimethyltubocurarine; such effects could be related to variations in protein binding and in the ionization of the receptors. Similarly, blockade by suxamethonium was significantly reduced by respiratory acidosis and slightly increased by respiratory alkalosis but usually was unaffected by metabolically induced changes in pH.

There have been numerous reports that in cats, rabbits and man inhalation of carbon dioxide enhanced the activity of tubocurarine but sometimes reduced that of dimethyltubocurarine, gallamine, suxamethonium and decamethonium, whereas hyperventilation produced opposite effects (Payne, 1958, 1959; Gamstorp and Vinnars, 1961b, 1963; Johansen and Osgood, 1962; Baraka, 1964, 1967). In rabbits and cats an infusion of acid intensified paralysis by tubocurarine but alkali was antagonistic (Gamstorp and Vinnars, 1961b; Katz, Ngai and Papper, 1963); additionally, Katz and his co-workers found that an infusion of alkali potentiated blockade by dimethyltubocurarine, gallamine and suxamethonium in cats.

However, these reports are by no means consistent and the following results are at variance with the general observations: paralysis by tubocurarine in cats was increased when the blood pH was raised and reduced when it was lowered (Payne, 1960); the action of dimethyltubocurarine in rabbits was not influenced by changes in pH or carbon dioxide tension (Gamstorp and Vinnars, 1961b); blockade by suxamethonium was enhanced by respiratory acidosis in rabbits and man (Gamstorp and Vinnars, 1963; Baraka, 1967) but was not significantly influenced by respiratory alkalosis or by metabolic acidosis or alkalosis in rabbits (Gamstorp and Vinnars, 1963). These inconsistencies may be attributable to differences in species and experimental techniques and a more detailed evaluation seems desirable in some instances.

The present experiments, carried out under controlled conditions using groups of anaesthetized cats, were designed to measure and correlate the effects of changes in acid-base balance on neuromuscular blockade by tubocurarine, dimethyltubocurarine, gallamine and suxamethonium.

METHODS

Cats of either sex, weighing between 2.1 and 3.2 kg, were anaesthetized and prepared as described previously (Hughes, 1970). The contractions of both gastrocnemius muscles were recorded in response to supramaximal stimulation of the sciatic nerves every 10 sec, one with single shocks, the other with tetanic bursts of
30 shocks/sec. The left brachial artery was cannulated for sampling of blood for acid-base measurements and the right subclavian vein for infusion of acid or alkali. The lungs were ventilated 18 times per minute with at least 50 per cent pure oxygen using a Starling Ideal pump (Palmer) with the tidal volume set between 30 and 60 ml, depending on the weight of the cat used. Blood pressure was recorded from the carotid artery and rectal temperature was monitored in some experiments.

The pH and PCO₂ of the arterial blood was measured by the method described by Siggaard-Andersen and associates (1960) and Siggaard-Andersen (1962); the apparatus was manufactured by Radiometer (Copenhagen). In some experiments, the Eschweiler Combi-Analyser was used with an Ingold electrode for determining pH and with the Lubbers stabilized electrode for PO₂; PCO₂ was measured using a Severinghaus electrode and the Beckman physiological gas analyzer. Respiratory acidosis was induced by ventilating the lungs with 10 or 20 per cent carbon dioxide in oxygen for 15–30 min; respiratory alkalosis was caused by increasing the tidal volume by 2.5–3-fold for a similar period. Metabolic acidosis was produced by infusing 5.7–7.7 m.equiv of 0.75 N-hydrochloric acid in 15–30 min; the tidal volume was increased by 10–20 per cent to maintain the PCO₂ as near to control level as possible. Metabolic alkalosis was induced by infusion of 11–14 m.equiv of N-sodium carbonate in 15–30 min.

An aortic catheter was implanted in an anaesthetized cat using procedures analogous to those described by Hughes (1967) and the animal was allowed to recover. Arterial blood was sampled frequently to determine normal values of pH and PCO₂.

Experimental procedure.

A preliminary dose of the neuromuscular blocking agent under test was administered in divided amounts (Payne, 1958). The total dose sought was that which produced about 35 per cent paralysis of the right gastrocnemius muscle stimulated indirectly with single shocks. The concentration of drug was adjusted so that the desired depth of blockade was usually achieved by two injections of 0.5 ml/kg. Each injection was given in 10 sec, at intervals of 2 min for tubocurarine and dimethyltubocurarine and of 1 min for gallamine and suxamethonium. Subsequent doses of tubocurarine were administered after 60–75 min, of dimethyltubocurarine after 75–90 min, of gallamine after 45–60 min and of suxamethonium after 30–45 min. Such periods were necessary between doses to avoid cumulative effects and to allow sufficient time to produce the required changes in acid-base balance.

After completion of the preliminary tests the required dose of the drug was given and a blood sample was collected within 2 min for determination of pH, PCO₂ and occasionally PO₂. The induction of acidosis or alkalosis was commenced after recovery from blockade and 15–30 min prior to the next dose, and blood samples were taken every 5 min until the desired change in Pco₂ or pH had been achieved. The standard dose of the paralyzing agent was then administered and the blood sampled for analysis. Following respiratory induced changes, the Pco₂ and pH returned to almost normal during the prescribed period before a second control dose of the drug was given. However, after metabolic acidosis it was necessary, at intervals, to infuse 1–2 m.equiv of N-sodium carbonate to restore the pH to control level. Subsequent to metabolic alkalosis, 1–2 m.equiv of 0.75 N-hydrochloric acid were frequently infused to restore the pH to normal before a second control dose of the drug was administered. It was often possible in the same cat to study the effects of both acidosis and alkalosis.

Statistical analyses.

The results were assessed by t-tests applied to differences observed in experimental variables during treatments and significance, where established, is indicated in the tables.

RESULTS

Preliminary experiments.

In an unanaesthetized cat with an indwelling aortic catheter, the mean pH and PCO₂ of the arterial blood, sampled over 35 days, were 7.42, SD ± 0.23 units, and 31.0 ± 2.56 mm Hg respectively.

Initial tests were carried out in four anaesthe-
Records from two cats, chloralose anaesthesia.

(a) 3.4 kg; an intravenous dose of 0.2 mg/kg tubocurarine lowered blood pressure and diminished the tetanic contractions of the gastrocnemius muscle stimulated with 30 shocks/sec every 10 sec and reduced the single twitches of the contralateral muscle. Inhalation of 10 per cent carbon dioxide elevated blood pressure and accelerated recovery; the $P_{co_2}$ of the arterial blood was raised while the pH was lowered.

(b) 4.7 kg; an intravenous dose of 0.5 mg/kg gallamine abolished the tetanic and twitch responses of the gastrocnemius muscles. Infusion of 4.7 m.equiv of sodium carbonate antagonized paralysis; the pH of the arterial blood was raised.

Cardiovascular and neuromuscular effects prior to drug administration.

Inhalation of 10 or 20 per cent carbon dioxide accelerated recovery from tubocurarine (fig. 1a) and an infusion of 4.7 m.equiv of sodium carbonate reduced blockade after gallamine (fig. 1b) in each of two cats. As these results were contrary to known effects (see introduction), in subsequent experiments the desired change in acid-base balance was induced before the blocking agent was administered.
INFLUENCE OF CHANGES IN ACID-BASE BALANCE

Records from a cat, 2.9 kg; chloralose anaesthesia.

(a) Control dose of 0.03 mg/kg suxamethonium i.v. depressed the tetanic contractions of the gastrocnemius muscle stimulated with 30 shocks/sec every 10 sec and reduced the single twitches of the contralateral muscle.

(b) Inhalation of 20 per cent carbon dioxide elevated blood pressure, reduced heart rate and increased the tetanic responses of the gastrocnemius muscle; the Pco₂ of the arterial blood was raised while the pH was lowered.

(c) Respiratory acidosis antagonized paralysis by 0.03 mg/kg suxamethonium i.v.

(d) Further control dose of 0.03 mg/kg suxamethonium i.v. after return of Pco₂ and pH to near control levels. A period of 35 min was allowed between doses.

Cardia (c.10 per cent) (tables I–IV). The Pco₂ was reduced to about 15 mm Hg and the pH elevated to approximately 7.6 units (P<0.01). The responses of the tetanically stimulated muscles were often slightly decreased (8 per cent, SE±3 per cent), but the twitch responses of the contralateral muscles were usually unaffected.

An infusion of 5.7–7.7 m.equiv of hydrochloric acid reduced the pH to about 7.0 and often lowered blood pressure (by 5–50 mm Hg) and heart rate (c.19 per cent) (tables I–IV). The responses of the tetanically stimulated muscles were usually slightly reduced (5 per cent, SE±2 per cent) whereas the twitch responses of the contralateral muscles were often unimpaired. An infusion of 11–14 m.equiv of sodium carbonate raised the pH to a mean of 7.6 and sometimes elevated blood pressure (5–40 mm Hg) and heart rate (c.10 per cent). The responses of the muscles stimulated tetanically or by single shocks were scarcely changed.

Tubocurarine.

Respiratory acidosis, induced in two cats by ventilation with 10 per cent carbon dioxide, and
in another two cats by 20 per cent of the gas, enhanced paralysis of the single twitches and delayed recovery (table I); these effects were significant at the 5 per cent level (P<0.05). Neuromuscular blockade by tubocurarine was also potentiated in two other experiments but both cats died in cardiovascular collapse before further control doses of the drug could be administered. Respiratory alkalosis, induced by hyperventilation, slightly antagonized paralysis of the twitch responses and shortened recovery in each of three cats but the treatment had no effect in a fourth cat; recovery in subsequent control tests was significantly longer (P<0.01) than that during alkalosis. In another cat blockade was also slightly antagonized but only one control dose was given. A test in a sixth cat was abandoned because the animal became progressively more sensitive to subsequent doses of tubocurarine. Effects on tetanic responses could not be evaluated because paralysis was often complete but differences in recovery times followed those of the twitch responses and sometimes achieved significance (table I).

Metabolic acidosis, caused by infusion of hydrochloric acid, significantly intensified and prolonged paralysis (P<0.05) of the single twitches in each of four cats (table I). Metabolic alkalosis, produced by infusion of sodium carbonate, moderately antagonized paralysis of the twitches and hastened recovery while blockade in a fourth cat was unchanged; paralysis in subsequent control tests was significantly deeper (P<0.01) than that during alkalosis. Effects on blockade of the tetani were minimal but differences in recovery times were similar to those occurring in the muscles stimulated by single shocks.

Dimethyltubocurarine.

Mild respiratory acidosis induced by 10 per cent carbon dioxide did not modify paralysis in two cats. However, 20 per cent carbon dioxide slightly reduced blockade of the twitch responses to single shocks and slightly speeded recovery in another four cats (table II); in a fifth cat paralysis was potentiated (c.25 per cent) and the recovery time was increased nearly threefold. Blockade of the twitch responses was increased (P<0.05) and recovery was moderately pro-

longed by respiratory alkalosis in four cats. Control doses of the drug often produced deeper blockade following alkalosis despite the fact that the pH and Pco₂ of the arterial blood had returned to near initial levels. Effects on paralysis of tetanically stimulated muscles were minimized because paralysis was almost complete but changes in recovery times followed those of the muscles stimulated by single shocks (table II).

Metabolic acidosis slightly diminished the paralyzing action of dimethyltubocurarine and slightly shortened its effect on the muscle twitches in each of four cats (table II). During metabolic alkalosis in four cats, blockade of the twitch responses was slightly increased and prolonged; recovery in subsequent control tests was significantly shorter (P<0.05) than that during alkalosis. Paralysis of the tetanic responses were virtually unaltered but differences in recovery times corresponded to those of the single twitches.

Gallamine.

Respiratory acidosis, caused by inhalation of 10 per cent carbon dioxide, did not alter blockade in two cats. In four other cats, ventilation with 20 per cent carbon dioxide significantly antagonized paralysis (P<0.01) and accelerated recovery (P<0.05) in the muscles stimulated with single shocks (table III). Similar effects were observed in a fifth cat but no control test was carried out after acidosis; in a sixth cat, paralysis of the muscle stimulated by single shocks was enhanced (66 per cent) and the recovery time was increased nearly threefold. During respiratory alkalosis, blockade of the twitch responses was significantly intensified (P<0.01) and prolonged (P<0.05) in four cats. The effect in a fifth cat was similar but the animal died in cardiovascular collapse before a second control dose could be given; in a sixth cat, paralysis became progressively deeper during the period of the experiment. Effects on tetanic responses could not be assessed because blockade was usually complete but differences in the recovery times followed those of the single twitches and were often significant (table III).

Metabolic acidosis slightly reduced paralysis of the single twitches by gallamine and slightly hastened recovery in three out of four cats but
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Effects of respiratory and metabolic acidosis and alkalosis on mean carotid blood pressure and on neuromuscular paralysis by tubeocurarine in groups of four anaesthetized cats. Both gastrocnemius muscles were stimulated indirectly every 10 sec, one with single shocks, the other with 30 shocks/sec for 1 sec. An interval of 60-75 min was allowed between controls and treatments. Arterial blood was sampled for pH and Pco₂ measurements within 2 min of each dose. Mean values and ranges are quoted. Asterisks denote differences in values between controls and treatments significant at the 1 per cent (**) and 5 per cent (*) levels.

### TABLE I

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tubocurarine, standard dose i.v. (mg/kg)</th>
<th>Procedure</th>
<th>pH</th>
<th>Pco₂ (mm Hg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Paralysis (%)</th>
<th>Recovery time (min)</th>
<th>Paralysis (%)</th>
<th>Recovery time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis, inhalation of 10% CO₂ (2 cats)</td>
<td>0.14 (0.08-0.20)</td>
<td>Precontrol</td>
<td>7.32**</td>
<td>35.9*</td>
<td>114</td>
<td>42*</td>
<td>(15-75)</td>
<td>23*</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-control</td>
<td>7.24-7.36</td>
<td>29.5-47</td>
<td>75-120</td>
<td>34</td>
<td>(15-67)</td>
<td>24*</td>
<td>(86-100)</td>
</tr>
<tr>
<td>Respiratory alkalosis, hyper-ventilation 3-fold</td>
<td>0.16 (0.10-0.18)</td>
<td>Precontrol</td>
<td>7.32-7.36</td>
<td>31.5-44</td>
<td>90-130</td>
<td>36</td>
<td>(15-67)</td>
<td>31*</td>
<td>(86-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-control</td>
<td>7.24-7.50</td>
<td>30.5-40</td>
<td>80-135</td>
<td>36</td>
<td>(15-67)</td>
<td>31*</td>
<td>(86-100)</td>
</tr>
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</table>

### TABLE II

Effects of respiratory and metabolic acidosis and alkalosis on mean carotid blood pressure and on neuromuscular paralysis by dimethyl-tubocurarine in groups of four anaesthetized cats. An interval of 75-90 min was allowed between controls and treatments. Other details are given in legend to table I.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dimethyl-tubocurarine, standard dose i.v. (mg/kg)</th>
<th>Procedure</th>
<th>pH</th>
<th>Pco₂ (mm Hg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Paralysis (%)</th>
<th>Recovery time (min)</th>
<th>Paralysis (%)</th>
<th>Recovery time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis, inhalation of 20% CO₂</td>
<td>0.012 (0.006-0.020)</td>
<td>Precontrol</td>
<td>7.30-7.53</td>
<td>35.5-40</td>
<td>100-160</td>
<td>37</td>
<td>(15-60)</td>
<td>24*</td>
<td>(86-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-control</td>
<td>7.27-7.52</td>
<td>31.5-40</td>
<td>80-135</td>
<td>37</td>
<td>(15-75)</td>
<td>24*</td>
<td>(86-100)</td>
</tr>
<tr>
<td>Respiratory alkalosis, hyperventilation 3-fold</td>
<td>0.012 (0.010-0.018)</td>
<td>Precontrol</td>
<td>7.30-7.53</td>
<td>35.5-40</td>
<td>100-160</td>
<td>37</td>
<td>(15-60)</td>
<td>24*</td>
<td>(86-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-control</td>
<td>7.27-7.52</td>
<td>31.5-40</td>
<td>80-135</td>
<td>37</td>
<td>(15-75)</td>
<td>24*</td>
<td>(86-100)</td>
</tr>
</tbody>
</table>

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Effects of respiratory and metabolic acidosis and alkalosis on mean carotid blood pressure and on neuromuscular paralysis by gallamine in groups of four anaesthetized cats. An interval of 45-60 min was allowed between controls and treatments. Other details are given in legend to Table I.

**Table III**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gallamine, standard dose i.v. (mg/kg)</th>
<th>Procedure</th>
<th>pH</th>
<th>Pco₂ (mm Hg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Paralysis (%)</th>
<th>Recovery time (min)</th>
<th>Paralysis (%)</th>
<th>Recovery time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis, inhalation of 20% CO₂</td>
<td>0.64 (0.50-0.80)</td>
<td>Precontrol</td>
<td>7.40**</td>
<td>31.9**</td>
<td>139</td>
<td>26**</td>
<td>15</td>
<td>99</td>
<td>30</td>
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<td>Acidosis</td>
<td>6.89</td>
<td>170</td>
<td>148</td>
<td>4</td>
<td>4</td>
<td>93</td>
<td>27</td>
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<td></td>
<td></td>
<td>Post-control</td>
<td>7.39**</td>
<td>31.9**</td>
<td>108</td>
<td>20**</td>
<td>13*</td>
<td>98</td>
<td>37*</td>
</tr>
<tr>
<td>Respiratory alkalosis, hyperventilation, 2.5-3-fold</td>
<td>0.90 (0.50-1.7)</td>
<td>Precontrol</td>
<td>7.41*</td>
<td>34.0**</td>
<td>123</td>
<td>20**</td>
<td>11*</td>
<td>97</td>
<td>34*</td>
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<td></td>
<td></td>
<td>Alkalosis</td>
<td>7.62</td>
<td>13.3</td>
<td>110</td>
<td>38</td>
<td>15</td>
<td>99</td>
<td>43</td>
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<tr>
<td></td>
<td></td>
<td>Post-control</td>
<td>7.37**</td>
<td>30.6**</td>
<td>135</td>
<td>19**</td>
<td>10</td>
<td>97</td>
<td>34*</td>
</tr>
<tr>
<td>Metabolic acidosis, infusion of 5.7 m.eqquiv HCl (3.5-7.2)</td>
<td>0.76 (0.50-1.05)</td>
<td>Precontrol</td>
<td>7.33**</td>
<td>39.5</td>
<td>135</td>
<td>26</td>
<td>16</td>
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<tr>
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<td>Acidosis</td>
<td>7.04</td>
<td>37.1</td>
<td>100</td>
<td>21</td>
<td>14</td>
<td>99</td>
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<td></td>
<td>Post-control</td>
<td>7.19</td>
<td>35.6</td>
<td>111</td>
<td>17</td>
<td>10</td>
<td>97</td>
<td>14-44</td>
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<tr>
<td>Metabolic alkalosis, infusion of 14 m.eqquiv Na₂CO₃ (10-21)</td>
<td>0.80 (0.25-1.05)</td>
<td>Precontrol</td>
<td>7.27**</td>
<td>41.7</td>
<td>128</td>
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<td>12*</td>
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<td>Alkalosis</td>
<td>7.60</td>
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<td>Post-control</td>
<td>7.31**</td>
<td>39.5</td>
<td>141</td>
<td>38*</td>
<td>18</td>
<td>99</td>
<td>37*</td>
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</table>

**Table IV**

Effects of respiratory and metabolic acidosis and alkalosis on mean carotid blood pressure and on neuromuscular paralysis by succinycholine in groups of four and six anaesthetized cats respectively. An interval of 30-45 min was allowed between controls and treatments. Other details are given in legend to Table I.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Succinycholine, standard dose i.v. (mg/kg)</th>
<th>Procedure</th>
<th>pH</th>
<th>Pco₂ (mm Hg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Paralysis (%)</th>
<th>Recovery time (min)</th>
<th>Paralysis (%)</th>
<th>Recovery time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory acidosis, inhalation of 20% CO₂</td>
<td>0.07 (0.03-0.15)</td>
<td>Precontrol</td>
<td>7.17**</td>
<td>35.4**</td>
<td>114</td>
<td>30</td>
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<td>92</td>
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<td>141</td>
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<td>7.27**</td>
<td>37.5**</td>
<td>96**</td>
<td>38*</td>
<td>5.5*</td>
<td>93</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory alkalosis, hyperventilation, 3-fold</td>
<td>0.04 (0.02-0.07)</td>
<td>Precontrol</td>
<td>7.33**</td>
<td>36.1**</td>
<td>110</td>
<td>43</td>
<td>7.5</td>
<td>94</td>
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<td>Metabolic acidosis, infusion of 7.7 m.eqquiv HCl (4.0-10)</td>
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<td>120</td>
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<td>9</td>
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<tr>
<td>Metabolic alkalosis, infusion of 11 m.eqquiv Na₂CO₃ (9.0-17)</td>
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<td>Precontrol</td>
<td>7.32**</td>
<td>39.3</td>
<td>119</td>
<td>69</td>
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<td>Alkalosis</td>
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<td>36.3</td>
<td>127</td>
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<td>10</td>
<td>78-88</td>
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INFLUENCE OF CHANGES IN ACID-BASE BALANCE

in the fourth cat the course of action of the drug was similar to that in both control tests (table III). Paralysis in a fifth cat became progressively deeper with each subsequent dose. Blockade of the muscles stimulated by single shocks was significantly potentiated and prolonged (P<0.05) in each of four cats during metabolic alkalosis. Control doses of the drug often caused deeper blockade following alkalosis but the mean pH was only 0.04 units above the initial level. The tetanically stimulated muscles were completely paralyzed but changes in recovery times sometimes achieved significance (table III).

Suxamethonium.

Mild respiratory acidosis, induced by 10 per cent carbon dioxide, did not modify paralysis in one of two cats but caused some reduction (25 per cent) in the second cat. In three out of another four cats, ventilation with 20 per cent carbon dioxide antagonized blockade of the twitch responses and speeded recovery (fig. 2) but in the fourth cat this treatment had no effect; mean changes were significant at the 5 per cent level (table IV). Paralysis and recovery of the tetanic contractions were virtually unaltered. In each of four cats, respiratory alkalosis enhanced and slightly prolonged paralysis of the muscles stimulated by single shocks. A similar action occurred in a fifth cat but no control test was carried out following acidosis. Effects on blockade of the tetanic responses were minimal but recovery was delayed.

Paralysis was unaffected by metabolic acidosis in four out of six cats, in a fifth cat it was slightly reduced and in the sixth cat it was slightly increased. Blockade by suxamethonium often became less intense during the course of these tests and was significantly deeper (P<0.05) in the initial controls of the tetanus. These results were combined and the mean effects are shown in table IV. Metabolic alkalosis did not modify blockade of the twitch responses in four out of six cats; paralysis was slightly antagonized in the remaining two cats but the recovery times were similar to those recorded in both control tests. It was curious that the slight reduction in block of the tetanic responses, observed during alkalosis in three out of the six cats, achieved significance (P<0.05).

DISCUSSION

When changes in acid-base balance were induced during recovery from neuromuscular blockade in cats the results differed from those in which the blocking drug was given after the changes had been induced. Thus, inhalation of 10 per cent carbon dioxide enhanced recovery from paralysis by tubocurarine and a rapid infusion of sodium carbonate antagonized the action of gallamine. The observed effect of carbon dioxide may have been related to the rapid rise in blood pressure and presumably blood flow, particularly as the tetanic responses were affected more than the single twitch responses; reinforcement of neuromuscular transmission by sodium ions (Del Castillo and Katz, 1956; Bowman, Rand and West, 1968) might account for the apparent effect of sodium carbonate.

Cardiovascular and neuromuscular effects.

The responses of the gastrocnemius muscles of cats to indirect tetanic stimulation were usually slightly increased when blood pressure was elevated during inhalation of carbon dioxide and were slightly reduced when blood pressure was lowered by hyperventilation or by infusion of hydrochloric acid. A possible explanation is that the tetanic contraction is directly dependent upon muscle blood flow. Alternatively, carbon dioxide might act indirectly by releasing adrenaline (Sechzer et al., 1960), small amounts of which may increase muscle tension (Bowman and Zaimis, 1958).

Responses of the gastrocnemius muscles to single shocks were often slightly reduced by carbon dioxide; such an effect was also observed in cats by Payne (1958) and in man by Baraka (1964) and could be accountable to the known depressant effect of carbon dioxide on nerve excitability (Lehmann, 1937; Lorente de Nó, 1946). Gamstorp and Vinnars (1961a) found in rabbits that if the nerve stimulus was increased during inhalation of carbon dioxide no constant change in the electrical responses of the gastrocnemius muscle occurred. However, in the present experiments and those of Baraka (1964) using myographic recordings, increasing the strength and duration of the stimulatory pulse did not prevent the depression of the muscle responses.
Effects of changes in acid-base balance on neuromuscular blockade.

In keeping with the results of other workers in cats, rabbits and man (Payne, 1958, 1959; Gamstorp and Vinnars, 1961b; Johansen and Osgood, 1962; Baraka, 1964), it was found that paralysis by tubocurarine in cats was significantly increased during inhalation of carbon dioxide and slightly reduced during hyperventilation. Similar changes in pH, induced by hydrochloric acid or by sodium carbonate, had corresponding effects on blockade as reported by Gamstorp and Vinnars (1961b) in rabbits. In contrast, Payne (1960) found that the activity of tubocurarine in cats was reduced during metabolic acidosis and increased during metabolic alkalosis and considered that carbon dioxide had a specific effect on the drug differing from that of pH. The present findings support those of Kalow (1954) who demonstrated on the isolated frog rectus preparation that the potency of tubocurarine was increased when the pH was lowered to 6.7 and reduced when it was elevated to 8.7. Such effects have been attributed to a decrease and an increase respectively in the ionic state of the two phenolic hydroxyl groups. However, Katz, Ngai and Papper (1963) argued that the small changes in ionization produced experimentally by changes in pH of 0.4 units were insufficient to account for the modified activity of tubocurarine.

Baraka (1964) found that the plasma level of tubocurarine was low and recovery was rapid during respiratory alkalae mia in man. It was suggested that the introduction of anionic charges, as a result of increased ionization of the phenolic hydroxyl groups, would decrease the attachment of the drug molecules to the negatively charged cholinergic receptors; secondly, that the extracellular concentration of tubocurarine was lowered by its passage into cells resulting in a rapid recovery and that the liver was a probable site of disappearance. Conversely, during respiratory acidemia the high plasma level of the drug was associated with marked enhancement of blockade. Following Baraka’s suggested hypothesis, the reduced ionization of the phenolic hydroxyl groups would increase their attachment to the receptors and impede intracellular penetration by the cationic quaternary ammonium molecule, thus maintaining a high extracellular concentration at the endplate.

Paralysis by dimethyltubocurarine in cats was slightly reduced during respiratory and metabolic acidosis and was slightly increased during respiratory and metabolic alkalosis; the changes were not usually significant. Payne (1959, 1960) also has demonstrated in cats such effects of carbon dioxide and changes in pH, and Katz, Ngai and Papper (1963) have shown in the same species that sodium carbonate potentiated the action of the drug. Although Gamstorp and Vinnars (1961b) found that the action of dimethyltubocurarine was not influenced by changes in pH or carbon dioxide tension, they were recording electrical responses in rabbits. Disturbances in acid-base balance had corresponding but often significant effects on blockade by gallamine in cats. Antagonism by carbon dioxide has previously been demonstrated by Payne (1959), Johansen and Osgood (1962) in cats and by Baraka (1967) in man, and potentiation with metabolic alkalosis by Katz, Ngai and Papper (1963) in cats. In dimethyltubocurarine the phenolic hydroxyl groups of tubocurarine have been replaced by methoxy groups and, like gallamine, it does not possess ionizable groups other than the quaternary ammonium groups which are completely ionized within the physiological range. Baraka (1967) suggested that carbon dioxide antagonized gallamine by acting as a physiological anticholinesterase (Gesell, Mason and Brassfield, 1944) but Payne (1958) discounted this possibility because the action of tubocurarine was enhanced by carbon dioxide.

In the present experiments in cats, blockade by succinylcholine was significantly antagonized by respiratory acidosis and slightly potentiated by respiratory alkalosis but was not usually modified by metabolic acidosis or alkalosis. Payne (1958) and Johansen and Osgood (1962), also found that carbon dioxide reduced the effect of the drug in cats. However, Gamstorp and Vinnars (1963), using electrical rather than mechanical responses, reported that paralysis produced in rabbits was enhanced by severe respiratory acidosis but was not significantly influenced by respiratory alkalosis, metabolic acidosis or by alkalosis. These authors suggested that the effect of respiratory acidosis could be attributed to decreased enzymatic hydrolysis of succinylcholine at lowered pH (Augustinsson, 1948; Fraser, 1954). Baraka (1967) attributed a similar but small effect in man.
to the same mechanism. Sodium carbonate deepened blockade when given to cats during recovery from paralysis by suxamethonium, according to Katz, Ngai and Papper (1963), who suggested that this was due to the neuromuscular effects of increases in sodium concentration rather than to variations in pH. The diversity of these experimental results illustrates that changes in the action of depolarizing drugs are more difficult to evaluate since their effect varies in different muscles and in different species and is often weakened after repeated injections (Paton and Zaimis, 1951; Zaimis, 1953; Payne and Holmdahl, 1959).

Possible mechanisms of action.

Changes in paralysis produced by agents other than tubocurarine, with the procedures presently employed, may be related to the following factors.

(1) Blood pressure was considerably elevated during inhalation of carbon dioxide and substantially lowered during hyperventilation. Statistical analysis revealed that there were negative correlations, often significant at the 1 per cent level, between mean blood pressure at the time of drug administration and the ensuing intensity and duration of paralysis produced by dimethyltubocurarine and gallamine. That is, high blood pressure and presumably elevated blood flow was associated with reduced blockade and shorter recovery, and low blood pressure with a more intense and prolonged paralysis. In contrast, when changes in pH were induced by infusion of acid or alkali, the corresponding moderate decrease or increase in blood pressure was positively correlated with the depth and recovery of blockade by dimethyltubocurarine and gallamine. Moreover, the cardiovascular effects of these drugs were small and independent of previous treatments. Thus, it was unlikely that variations in blood pressure and flow could be mainly responsible for the observed changes in activity of these drugs. However, such factors could have been contributory in the case of suxamethonium, since in all situations where a change in sensitivity was observed, this was inversely related to resting blood pressure.

(2) The activity of a drug is inversely proportional to that fraction bound to protein and alterations in plasma pH modify the ability of plasma proteins to take up certain drugs (Goldstein, 1949), and Payne (1958) has suggested that a reduction in pH may limit the effect of the quaternary ammonium drugs in this way.

(3) Changes in ionization could also occur at the receptors when pH is altered (Payne, 1958). A rise in pH might produce more anionic receptors and increase the attachment of the cationic quaternary ammonium group while a fall in pH would have the opposite effect. Such a mechanism could explain why the action of these agents was usually potentiated during alkalosis and antagonized during acidosis.

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