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The Effects of Hypercarbia and Hypocarbia on Pancuronium and Vecuronium Neuromuscular Blockades in Anesthetized Humans

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To determine the effects of hypercarbia and hypocarbia on a pancuronium or vecuronium neuromuscular blockade, 54 patients were anesthetized with halothane and 60% nitrous oxide in oxygen. In 30 patients, end-tidal P_{CO_2} was maintained at either 25 mmHg (3.5 kPa, N = 10), 41 mmHg (5.5 kPa, N = 10), or 56 mmHg (7.5 kPa, N = 10). Five patients in each group then were given pancuronium or vecuronium 0.022 mg/kg iv. Neither maximal depressions of twitch tension nor recovery indexes (time for spontaneous recovery of twitch tension from 25 to 75% of control) were altered by hypercarbia or hypocarbia. The remaining 24 patients were divided into three equal groups. Either pancuronium (N = 8) or vecuronium (N = 8) was administered iv as continuous infusion at a rate sufficient to produce a 50% depression of twitch tension. In the remaining eight patients, no muscle relaxant was given. After twitch tension was stable, half of the patients in each group had hypercarbia induced, which depressed twitch tension in all three groups. The patients who received vecuronium had a significantly larger decrease in twitch tension than those who received pancuronium or no muscle relaxant. Conversely, in the remaining patients, hypocarbia produced a significant increase in twitch tension. There was no difference in the magnitude of the increases in twitch tension among the three groups. The authors conclude that pre-muscle relaxant administration-induced hypercarbia or hypocarbia has no effect on a subsequent neuromuscular blockade from pancuronium or vecuronium. Conversely, hypercarbia decreases and hypocarbia increases twitch tension when no muscle relaxant is given and during a partial pancuronium or vecuronium neuromuscular blockade. Vecuronium was affected by hypercarbia more than the other two groups. The authors propose that when larger doses of vecuronium are given, hypercarbia may increase the danger of residual neuromuscular blockade. (Key words: Neuromuscular relaxants: pancuronium, vecuronium; Acid-base equilibrium: acidosis, respiratory; alkalosis, respiratory.)

VECURONIUM (ORG NC45) is a new nondepolarizing muscle relaxant with little or no cumulative effect, no apparent cardiovascular actions and a shorter duration of action than its homologue pancuronium.[1] Vecuronium is unstable in alkaline solutions, deacetylating to hydroxy metabolites by spontaneous alkaline hydrolysis.[2] Because the metabolites of vecuronium have reduced neuromuscular blocking properties,[3] acid-base changes may change not only the rate of vecuronium hydrolysis but also its potency and duration of neuromuscular blockade. In animals, Funk *et al.*[4] found that vecuronium-induced paralysis is enhanced by respiratory or metabolic acidosis but only slightly reduced with respiratory or metabolic alkalosis. The influence of changes in acid-base on a vecuronium blockade has not been studied in humans.

Although the influence of acid-base balance on pancuronium neuromuscular blockade has been studied extensively in animals, only two studies in humans evaluated respiratory acid-base changes, and they produced contradictory results.[5,6] Norman *et al.*[5] found that respiratory acidosis delayed and respiratory alkalosis hastened the rate of recovery from a pancuronium neuromuscular blockade. Conversely, Dann[6] found that changes in end-tidal P_{CO_2} ranging from a mean of 23.8 mmHg to 38.1 mmHg had no effect on the duration of a pancuronium neuromuscular blockade. This study was undertaken to determine the effect of hypercarbia and hypocarbia on pancuronium and vecuronium neuromuscular blockades in humans.

Methods

Fifty-four adult surgical patients of either sex, ASA class I or II, were studied during otolaryngologic surgery. Informed consent was granted by each patient for participation in the study, which was approved by the University of Leiden's Medical Ethics Committee. Their mean age was 28.0 ± 9.9 yr (±SD) and mean weight 69.8 ± 13.0 kg.

One to two hours after administration of 10 mg diazepam po, anesthesia was induced with 2–4 mg/kg thiopental and continued with increasing concentrations of halothane in 60% nitrous oxide and oxygen. All patients had radial artery catheters inserted, from which all blood samples were obtained for analysis of arterial blood gases. Endotracheal intubation was accomplished without administration of muscle relaxants but with topical spraying with lidocaine into the trachea prior to intubation. Ventilation was controlled, and esophageal temperature was

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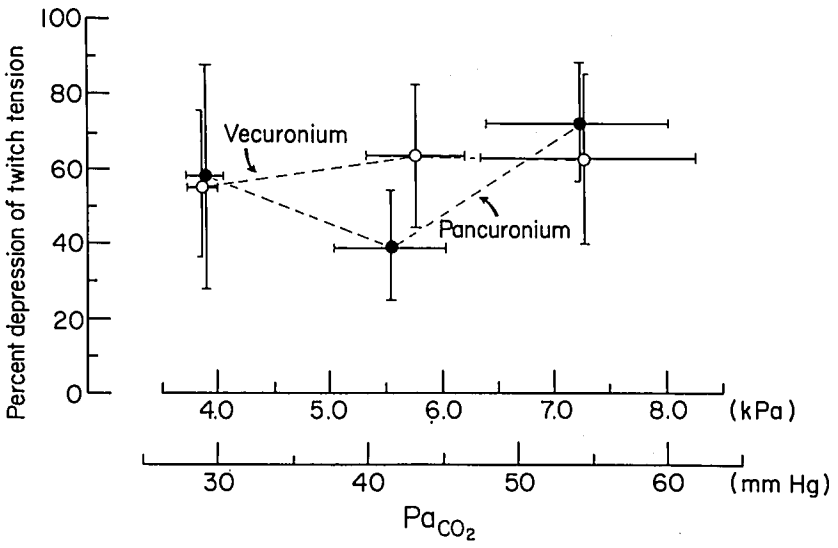

FIG. 1. The relationship between percentage of depression of control twitch tension from vecuronium or pancuronium and Pa_{CO_2}. Each point represents the mean ± SD for five patients. The lines connecting points are added to aid interpretation. (O = vecuronium data, ● = pancuronium data.)

kept within 35.0–36.0°C. Halothane end-tidal concentration was maintained at 0.4–0.6% (measured by hydrogen flame ionization technique)[7,8] for the duration of the study. Small doses of fentanyl (50–100 μg) were administered iv if anesthesia required augmentation.

A Grass S-88 stimulator was used to apply supramaximal square wave pulses of 0.15 ms duration and 0.15 Hz to thin-walled 23-gauge needle electrodes placed 2–3 cm apart near the ulnar nerve at the wrist. The resultant thumb adduction was measured by a force displacement transducer (Gould Stratham UC-3 with a 9-kg load cell) and recorded on a polygraph. Control twitch tension was established immediately after induction of anesthesia and before any muscle relaxants were administered.

In Part I, ventilation was adjusted and 5–10% CO_2 added if necessary to the inspired gases to achieve and maintain for the duration of the study an end-tidal P_{CO_2} (measured with a Datascope 500-CO_2 Analyzer®) of either 25 mmHg (3.5 kPa), 41 mmHg (5.5 kPa), or 56 mmHg (7.5 kPa). At each end-tidal P_{CO_2}, 10 patients were studied (each patient studied once). Following analysis of arterial blood gases, five patients in each P_{CO_2} group were given pancuronium 0.022 mg/kg and the other five vecuronium 0.022 mg/kg. If the maximum effect of this single iv bolus dose did not depress twitch tension to less than 15% of control, a small subsequent dose of the same muscle relaxant was given so that twitch tension was reduced to 0–15% of control. Spontaneous recovery of twitch tension was allowed to occur, and then a second analysis of arterial blood gases was performed.

In Part II ventilation was adjusted to achieve an end-tidal P_{CO_2} of 41 mmHg. Twenty-four patients were divided randomly into groups of eight. In the first group of patients, a continuous infusion of pancuronium was administered and adjusted to produce a constant 50% of control twitch tension as determined by at least 30 min of unchanging infusion rate and twitch tension. In the second group, vecuronium was used instead of pancuronium. In the third group, no muscle relaxant was administered. Then, half the patients of each group were hyperventilated for 30 min. In the other half, ventilation was reduced and 5–10% CO_2 added to the inspired gases for 30 min. Analyses of arterial blood gases were made just prior to and at the termination of each period of hypo- or hypercarbia.

Only Pa_{CO_2} and pH_a values were used for analysis of the data. Spontaneous recovery from neuromuscular blockade was measured with the recovery index: the time for the increase from 25% to 75% control twitch tension. The data groups in Part I and Part II were compared by analysis of variance. Statistically significant differences were assumed at $P < 0.05$.

Results

The simultaneous Pa_{CO_2} and pH_a measurements had a high correlation ($r = -0.94$), and mean base excess was −1.0 ± 3.4 mEq/l (±SD). Evaluating the data by using either Pa_{CO_2} or pH_a as the independent variable produced no significant changes in results.

PART I

Neither maximal depressions of twitch tension nor recovery indexes (*i.e.*, the time for spontaneous recovery of twitch tension from 25% to 75% of control) were altered significantly by changes in Pa_{CO_2} (figs. 1,2). The mean (±SD) reductions of twitch tension from pancuronium and vecuronium during hypocarbia and hypercarbia were similar (fig. 1). At each Pa_{CO_2} level, the re-

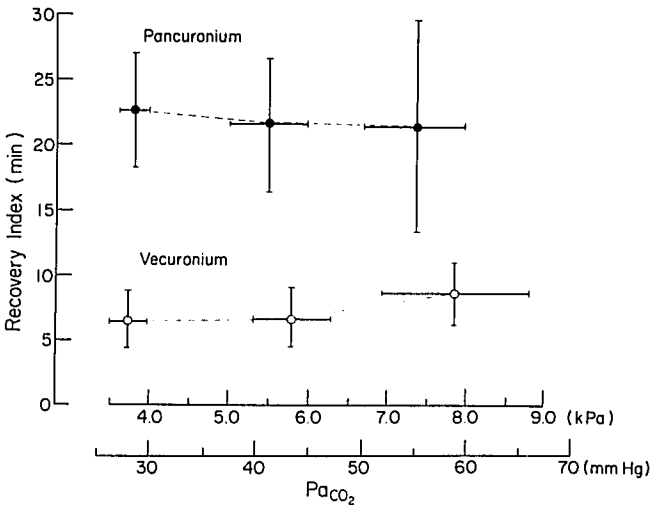

FIG. 2. The relationship between recovery index (time for spontaneous recovery of twitch tension from 25 to 75 percent of control) and Pa_{CO_2} for vecuronium and pancuronium. Each point represents the mean ± SD for five patients. The lines connecting points are added to aid interpretation.

covery index of pancuronium was significantly longer than that of vecuronium (fig. 2). The approximate ratio of recovery indexes of pancuronium to vecuronium was 3.0.

PART II

Hypercarbia consistently induced a significant depression of twitch tension in all three groups (figs. 3–5). A measure of this effect is the absolute value of the ratio:

$$\frac{\text{Change in twitch tension (per cent of control)}}{\text{Change in } Pa_{CO_2} \text{ (in kPa, 1kPa = 7.5 mmHg)}}$$

In Group 1 (pancuronium), Group 2 (vecuronium), and Group 3 (no neuromuscular blockers), the mean ratios (±SD) were 2.7 ± 1.2, 7.7 ± 2.8, and 2.6 ± 1.0, respectively. The ratios of Group 2 (vecuronium) were significantly greater than those from Groups 1 and 3. The ratios from Groups 1 and 3 were not significantly different.

In contrast to hypercarbia, hypocarbia consistently induced a significant increase in twitch tension in all three groups (figs. 3–5). The mean ratios for Groups 1, 2, and 3 were 7.3 ± 5.6, 6.6 ± 2.8, and 7.9 ± 6.1, respectively. The differences between the increases in twitch tension of the three groups were not statistically significant.

The mean infusion rates (±SD) of pancuronium and vecuronium were 0.016 ± 0.006, and 0.034 ± 0.007 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively.

Discussion

The differences in results between Parts I and II of this study probably reflect differences in experimental designs. In Part I first the Pa_{CO_2} was altered and then muscle relaxant dose–response relationships and recovery times were determined. Because the Pa_{CO_2} was established prior to determining control twitch tension and was unchanged for the duration of each study, acute changes in Pa_{CO_2} probably did not contribute to the results. Also, because each patient was studied only once, patient-to-patient variability in muscle relaxant response probably contributed to the variability of the data. With large data variability, Part I of the study could not detect minor influences of alterations in Pa_{CO_2} on pancuronium or vecuronium twitch tension. In the experimental design of Part II, the sequence of muscle relaxant and Pa_{CO_2} changes were reversed; first the muscle relaxant effect was established as a steady state and then Pa_{CO_2} was

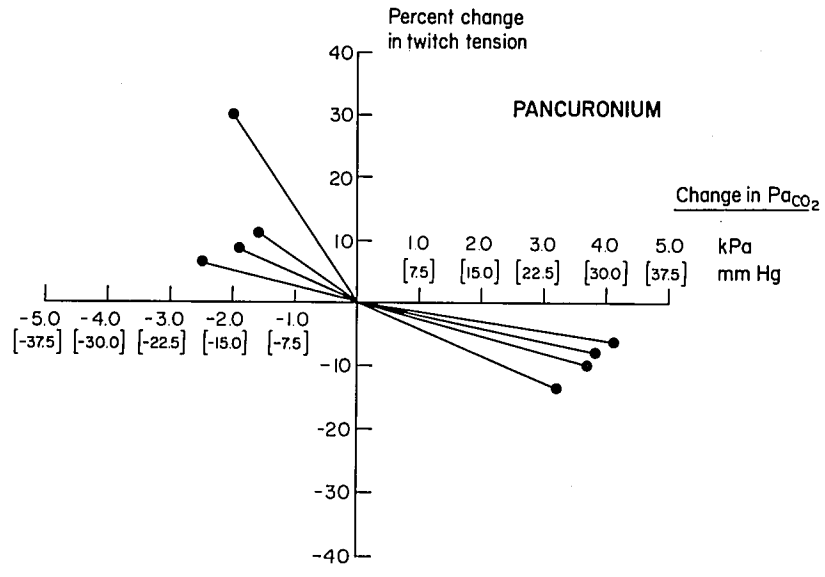

FIG. 3. The relationships between acute changes in Pa_{CO_2} and subsequent changes in twitch tension in patients receiving pancuronium. Each point represents the data for one patient.

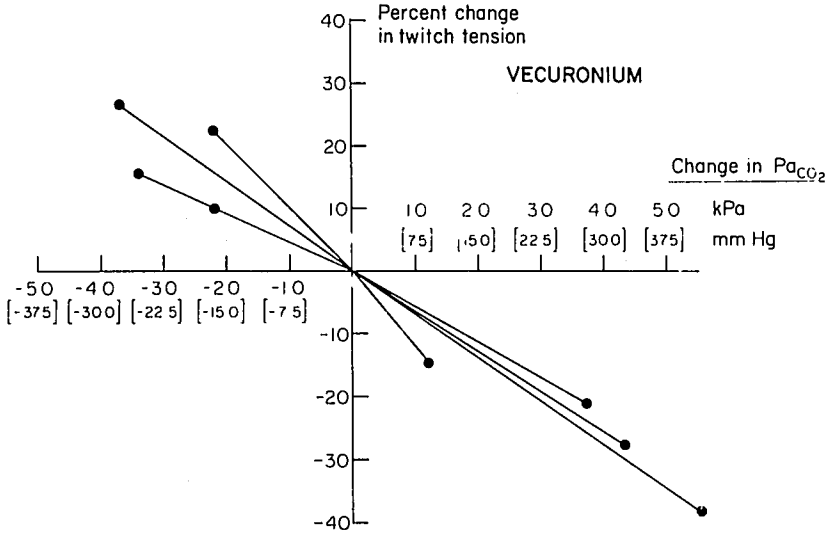

FIG. 4. The relationships between acute changes in Pa_{CO_2} and subsequent changes in twitch tension in patients receiving vecuronium. Each point represents the data for one patient.

changed. Though a cumbersome technique for obtaining dose–response data and recovery times, this design allowed measurement of the effects of acute changes in Pa_{CO_2} and eliminated patient-to-patient muscle-relaxant dose–response variability by using each patient as his or her own control. Thus, Part II of the study eliminated an extraneous source of data variability and measured the more subtle influence of changes in Pa_{CO_2} on twitch tension.

The results of both parts of our study are consistent if the experimental design is taken into account. Part I provides evidence that predetermined changes in Pa_{CO_2} have little effect on pancuronium and vecuronium dose–response relationships and recovery indexes. Also, the recovery index for pancuronium is about three times longer than that of vecuronium. Part II reveals three findings. First, acutely induced hypocarbia or hypercarbia alone causes an increase and decrease (respectively) of control twitch tension. Secondly, acute hypocarbia induced increases in twitch tension during a partial pancuronium or vecuronium neuromuscular blockade. Lastly, acute hypercarbia induced significantly greater decreases in twitch tension during a partial vecuronium neuromuscular blockade than during the similar twitch depressions observed during a pancuronium partial neuromuscular blockade and when no muscle relaxants were given.

These findings may confirm the results and perhaps clarify the varying conclusions of previous investigators. Katz and Wolf[9] reported changes similar to ours in control twitch tension (without muscle relaxants) from changes in ventilation. Norman et al.[5] described a marked slowing of the rate of spontaneous recovery from pancuronium neuromuscular blockade from increasing Pa_{CO_2}. However, these authors did not measure the effect of increas-

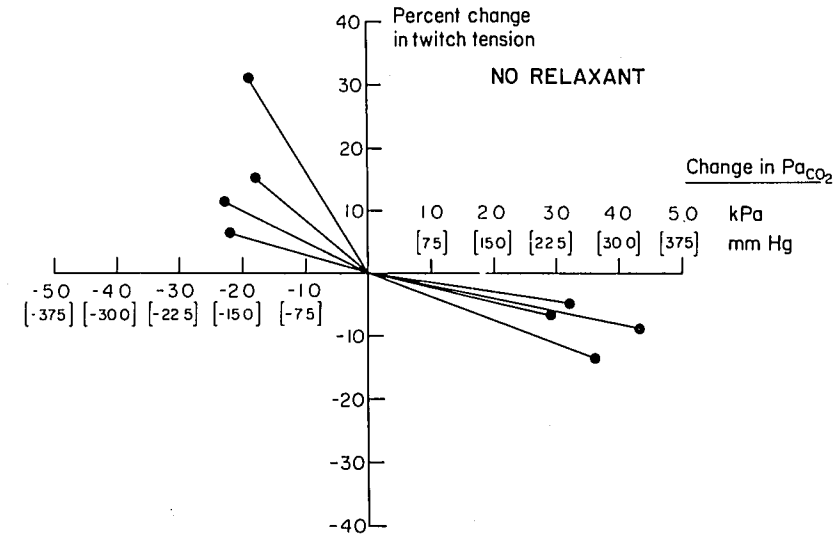

FIG. 5. The relationships between acute changes in Pa_{CO_2} and subsequent changes in twitch tension in patients receiving no muscle relaxant. Each point represents the data for one patient.

ing Pa_{CO_2} on control twitch tension, and according to our data, their large increase in Pa_{CO_2} (about 5.5 kPa or 41 mmHg) by itself should have depressed twitch force significantly. The finding of Dann[6] of similar recovery times of pancuronium neuromuscular blockades during normo- and hypocarbia is in agreement with our results. The animal study of Funk *et al.*[4] revealed enhancement with respiratory acidosis and a smaller insignificant antagonism of a vecuronium neuromuscular blockade with respiratory alkalosis. These findings are similar to our results.

Other aspects of our results concur with previously reported characteristics of pancuronium and vecuronium's clinical pharmacology. The relatively large variability of pancuronium dose–response and recovery index has been described by previous investigators.[5,6,10] The potency ratio between the mean neuromuscular blockades of vecuronium and pancuronium during normocarbia of 1.6 agrees with previously published potency ratios for these drugs by Fahey *et al.*[1] of 1.5 and Krieg *et al.*[11] of 1.7. Interestingly, the ratio between pancuronium and vecuronium recovery indexes of 3.0 is similar to the inverse of the ratio of the two drugs' plasma clearances.[12]

Our results do not allow us to distinguish the relative importance of the different pharmacologic and physiologic influences of changes in Pa_{CO_2} including whether the hypercarbic potentiation of vecuronium neuromuscular blockade is due to a change in the rate of vecuronium metabolism (by alkaline hydrolysis).[13–19] However, the authors consider the neuromuscular junction not to be the site of the main effect of hypercarbia on twitch tension. The Pa_{CO_2} changes had a similar effect on twitch tension in patients with partial pancuronium neuromuscular blockade (Part II, Group 1) and those who received no muscle relaxants (Part II, Group 3). If the main effect of altering Pa_{CO_2} were at the neuromuscular junction it would be unlikely to depress twitch force similarly in patients whose neuromuscular function was already markedly decreased (to approximately 50% of control twitch tension) and in patients whose neuromuscular function was virtually intact.

Our findings may explain some of the effects of changes in Pa_{CO_2} and possibly predict potentially dangerous interactions between changes in ventilation and muscle relaxant effects. Twitch tension is altered by changes in Pa_{CO_2} alone; therefore, significant increases in Pa_{CO_2} may depress skeletal muscle function slightly in an anesthetized patient. This may interact with other factors tending to augment hypoventilation (*e.g.*, partial neuromuscular blockade or neuromuscular disease like myasthenia gravis). Though we observed no alteration in pancuronium effect beyond that attributable to changes in Pa_{CO_2} alone, there was a marked potentiation of a vecuronium neuromuscular blockade by hypercarbia. Because vecuronium has a medium duration of action, its enhancement by hypercarbia may not be commonly of clinical significance. But when larger doses of vecuronium are given, producing a longer duration of effect,[1] hypercarbic-induced enhancement of vecuronium effect might increase the danger of residual neuromuscular blockade.

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