Title: THE INFLUENCE OF RESPIRATORY AND METABOLIC ACID-BASE CHANGES ON THE NEUROMUSCULAR EFFECTS OF NONDEPOLARIZING MUSCLE RELAXANTS

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Introduction. A discrepancy has been reported between respiratory and metabolic acid-base changes in terms of their influences on the neuromuscular (NM) effects of nondepolarizing muscle relaxants. In this study, the influence of changes in CO_2 and bicarbonate (HCO_3) concentration on the NM block produced by d-tubocurarine (dTc), vecuronium, metocurine or pancuronium was investigated in vitro.

Method. The experiments were carried out using the phrenic nerve-hemidiaphragm preparations of male Sprague-Dawley rats. The hemidiaphragms were suspended in organ baths, filled with modified Krebs' solution[1] containing 25 mM HCO_3, aerated with 95% O_2-5% CO_2, temperature 37°C. The preparation was stimulated indirectly every 10 sec with supramaximal impulses of 0.2 msec duration and elicited twitch tension was quantitated and continuously recorded. After stable twitch tension was obtained, either respiratory or metabolic acid-base changes were induced by varying CO_2 concentration of the aerating gases (2.5% or 9%) or by replacing the fluid in the bath with the modified Krebs' solution of different HCO_3 concentration (13.5 mM or 50 mM), respectively. Electrolytes composition and pH of the solutions used are shown in Table 1 and 2. About a 50% NM block was then produced by preselected dose of dTc (0.65 μM), vecuronium (4.45 μM), metocurine (0.17 μM) or pancuronium (0.31 μM), and its response to changes in CO_2 (from 2.5% to 9%, or from 9% to 2.5%) or changes in HCO_3 (from 13.5 mM to 50 mM, or from 50 mM to 13.5 mM) was observed. Statistical analyses were performed using Student's t-test for paired data, and differences were considered significant if $p<0.05$.

Results. As shown in Table 3, with the change in CO_2 from 2.5% to 9%, dTc- or vecuronium-induced NM block increased, while metocurine- or pancuronium-induced block decreased (The change in metocurine-induced block was not statistically significant). With the change in CO_2 from 9% to 2.5%, dTc- or vecuronium-induced block decreased, while metocurine- or pancuronium-induced block increased. Likewise, with the change in HCO_3 from 50 mM to 13.5 mM, dTc- or vecuronium-induced block increased, while metocurine- or pancuronium-induced block decreased. With the change in HCO_3 from 13.5 mM to 50 mM, dTc- or vecuronium-induced block decreased, while metocurine- or pancuronium-induced block increased.

Discussion. The results of this study demonstrate that CO_2- and HCO_3-induced acid-base changes act similarly on the NM effects of dTc, vecuronium, metocurine and pancuronium in rats. The NM effects of dTc and vecuronium were greater at a lower pH than at a higher pH. In contrast, those of metocurine and pancuronium were greater at a higher pH than at a lower pH. These findings give support to the assumption[2] that a basis for above observations may be attributed to the difference in chemical structure of these muscle relaxants, that is, the mono-quaternary nature of dTc and vecuronium versus the bisquaternary structures of the other compounds.

References.

1. Foldes FF: The significance of physiological Ca^{2+} and Mg^{2+} for in vitro experiments on synaptic transmission. Life Sci 28: 1585-1590, 1981

2. Ono K, Ohta Y, Morita K, Kosaka F: The influence of respiratory-induced acid-base changes on the action of non-depolarizing muscle relaxants in rats. ANESTHESIOLOGY (In press)

Table 1. Electrolyte composition of the modified Krebs' solutions.

	Concentration of Electrolyte(mM)		
Na	138.0	138.0	138.0
K	5.9	5.9	5.9
Ca	1.4	1.4	1.4
Mg	0.9	0.9	0.9
Cl	134.2	122.7	97.7
H_2PO_4	1.2	1.2	1.2
SO_4	1.2	1.2	1.2
HCO_3	13.5	25.0	50.0
Glucose	11.5	11.5	11.5

Table 2. pH of the modified Krebs' solutions.

Concentration of HCO_3(mM)	Concentration of CO_2	pH of Solution
25.0	5.0%	7.41±0.02*
25.0	2.5%	7.64±0.04
25.0	9.0%	7.17±0.04
13.5	5.0%	7.13±0.04
50.0	5.0%	7.68±0.03

* Mean±SEM, n=10

Table 3. The effect of CO_2-or HCO_3-induced acid-base changes on the partial neuromuscular block produced by dTc, vecuronium, metocurine or pancuronium.

	% Change in Neuromuscular Block			
	CO_2-induced		HCO_3-induced	
	2.5%→9.0%	9.0%→2.5%	50mM→13.5mM	13.5mM→50mM
dTc	+26.1±1.3	-12.1±2.4	+21.8±2.2	-15.0±1.4
Vec	+24.4±1.5	-20.9±2.1	+31.0±3.8	-16.2±2.9
Met	- 2.9±1.2†	+ 4.3±0.8	-14.7±3.7	+11.7±2.7
Pan	- 8.2±1.6	+ 9.9±1.5	-25.5±2.8	+30.7±2.7

dTc: d-tubocurarine, Vec: vecuronium, Met: metocurine, Pan: pancuronium.
Each value is mean±SEM, n=5.
All values except for † are statistically significant at the $p<0.05$ level(paired Student's t test).