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Title : INHALATION ANESTHETIC-RELAXANT INTERACTIONS IN VITRO

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Introduction. Augmentation of the neuromuscular (NM) effect of d-tubocurarine by several inhalation anesthetics and that of d-Tc and succinylcholine (SCh) by halothane and isoflurane had been previously investigated on the lumbrical muscle of the guinea-pig¹ and on the rat phrenic nerve-diaphragm preparation² respectively. In the present study the observation of the interaction of inhalation anesthetics has been extended to pancuronium and to its demethylated monoquaternary analog, ORG-NC45.

Methods. Rat phrenic nerve-hemidiaphragm preparations were suspended in organ baths filled with modified Krebs' solution containing the same concentrations of ionized calcium [Ca²⁺] (1.1 mM) and magnesium [Mg²⁺] (0.8 mM) as human or rat plasma. The bath was aerated with 95% O₂-5% CO₂ and its temperature was kept at 37°C. To approximate physiological conditions the hemidiaphragms were indirectly stimulated with 0.1 sec trains of 50 Hz supramaximal impulses of 0.2 msec duration every 20 sec. The tetanic tension was recorded with an FT03 transducer on a Grass polygraph. After equilibration of the preparations 0.25 nmol/ml d-Tc, 1.25 nmol/ml pancuronium, 2.5 nmol/ml ORG-NC45, or 4.0 nmol/ml SCh was added to the bath. After steady state NM block had developed 0.5, 1.0 and 1.5 MAC concentrations of halothane, enflurane or isoflurane were added sequentially to the 95% O₂-5% CO₂ mixture. The gas chromatographically controlled concentrations of anesthetics were only increased when the tetanic tension became stable after exposure to the previous concentration. The standard deviations of the indicated concentrations varied by 0.02 to 0.07 MAC.

Results. The data presented in table 1 indicate that all concentrations of the 3 inhalation agents investigated caused a highly significant, concentration dependent increase of the depression of tetanic tension caused by the 4 relaxants. The effects of comparable concentrations of halothane and isoflurane were about the same. Enflurane, however, was significantly more potent than the other 2 inhalation agents. After removal of the inhalation agents from the gas mixture, tetanic tensions returned to about 65% to 92% of control. The addition of 0.25 µg/ml neostigmine to the bath at this time caused no further improvement. 4 µg/ml 4-aminopyridine, however, alone or after neostigmine consistently increased tetanic tension to above control values.

Discussion. The results of this study indicate that the about 20% NM block pro-

duced by low concentrations of the 4 relaxants could be increased to about 70 to 90% (table 1) by aeration of the bath with clinically employed concentrations (0.5 to 1.5 MAC) of halogenated inhalation anesthetics. In spite of the different experimental approach our findings on the relative ability of the 3 inhalation agents (halothane = isoflurane < ethrane) to increase the NM effects of the 4 relaxants was the same as that reported by Waud¹ for d-Tc. It is of interest that in contrast to the *in vitro* situation *in vivo*, isoflurane increases the NM effect of d-Tc in man³ or that of pancuronium or ORG-NC45 in rat (Unpublished Observations, 1980) more than halothane.

References.

1. Waud BE: Decrease in dose requirement of d-tubocurarine by volatile anesthetics. *Anesthesiology* 51:298-302, 1979
2. Vitez TS, Miller RD, Eger EI II, et al: Comparison *in vitro* of isoflurane and halothane potentiation of d-tubocurarine and succinylcholine neuromuscular blockades. *Anesthesiology* 41:53-56, 1974
3. Miller RD, Eger EI II, Way WL, et al: Comparative neuromuscular effects of forane and halothane alone and in combination with d-tubocurarine in man. *Anesthesiology* 35: 38-42, 1974

Table 1. Augmentation of the Neuromuscular Effect of Relaxants by Inhalation Agents

Relaxant (µM)	Inhal. Anesth.	Neuromuscular Block (%) With The Indicated Concentrations (MAC) of Anesthetics			
		0	0.7	1.0	1.5
d-Tc	Haloth.	21.1	49.6	75.7	93.9
	Enflur.	18.5	67.1	93.4	—
	Isoflur.	20.6	54.5	78.6	94.5
Pancur.	Haloth.	22.7	30.7	51.4	79.7
	Enflur.	19.5	67.0	98.0	—
	Isoflur.	23.3	53.1	73.5	93.5
NC45	Haloth.	18.2	29.8	56.3	75.8
	Enflur.	19.1	59.1	90.4	—
	Isoflur.	21.0	43.6	59.9	68.9
SCh	Haloth.	77.8	29.2	63.4	87.9
	Enflur.	18.5	51.3	88.8	—
	Isoflur.	16.9	26.4	51.6	87.9

¹Mean of 4 experiments; SEM not shown for lack of space. Inhalation anesthetics caused a concentration dependent significant (p < 0.05 to 0.001 paired t test) increase of NM block of all relaxants.