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 Title : HALOTHANE-ISOFURANE-RELAXANT INTERACTIONS IN VIVO
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Introduction. It has been reported that halogenated inhalation anesthetics (anesthetics) increase the neuromuscular (NM) potency of d-tubocurarine (d-Tc) in man.¹⁻³ In this study the interaction of halogenated anesthetics with pancuronium and its recently synthesized, demethylated monoquaternary derivative, ORG-NC45 (NC45) was investigated in rats.

Methods. Male Sprague-Dawley rats anesthetized with i.p. pentobarbital and urethane were tracheostomized and mechanically ventilated with O₂, or O₂ containing various concentrations of anesthetics. Jugular veins and a carotid artery were cannulated for drug administration and recording of i.a. BP. Platinum electrodes were placed on the sciatic nerves in the gluteal region, the tibialis anterior muscles were dissected and their tendons were attached to FT03 transducers. One sciatic nerve was stimulated with supra-maximal stimuli of 0.2 msec duration at 0.1 Hz ("twitch" side) and the other with 0.1 sec trains of 50 Hz supramaximal stimuli of 0.2 msec duration every 20 sec ("tetanus" side). Optimal resting tension was applied to the muscles and their stimulated tension output was recorded on a Grass polygraph. When the preparations became stable, a 10 to 15% steady state NM block was produced on the "tetanus" side by the continuous i.v. infusion of pancuronium or NC45. Subsequently increasing concentrations of anesthetics were added to the inhaled O₂. Anesthetic concentrations, monitored by gaschromatography, were increased when the tension output became stabilized after the previous concentration on both the "tetanic" and "twitch" side. When the "tetanic" tension had decreased to <10% the animals were again ventilated with O₂ and when the tension output became stabilized on both sides, the infusion of the relaxant was discontinued.

Results. The anesthetics, dose dependently, increased the NM effects of pancuronium and NC 45 (Table 1). The NM block, with or without ventilation with anesthetics, was consistently greater on the "tetanus" than on the "twitch" side (p <0.05 to <0.001; paired t test). The potentiating effect of isoflurane was greater than that of halothane. After discontinuation of the anesthetics recovery of the tension output was more rapid and complete on the "twitch" (90 to 100% of control) than on the "tetanus" (55 to 65% of control) side. When the infusion of the relaxants had also been discontinued tension output returned to or above control on both the "twitch" and "tetanus" side.

Discussion. In agreement with human

studies with d-Tc and pancuronium, the NM effects of pancuronium and NC45 were found to be increased more by isoflurane than halothane. Pilot studies with enflurane in rats revealed that the potentiating effect of enflurane is even greater. These findings indicate that it should be possible to obtain surgical relaxation during isoflurane or enflurane anesthesia with doses of nondepolarizing relaxants that would have no significant effect on NM transmission after excretion of the inhalation agents.

References.

1. Katz RL, Gissen AJ: Neuromuscular and electromyographic effects of halothane and its interaction with d-tubocurarine in man. *Anesthesiology* 28:564-567, 1967
2. Lebowitz MH, Blitt CD, Walts LF: Depression of twitch response to stimulation of the ulnar nerve during ethrane anesthesia in man. *Anesthesiology* 33:52-57, 1970
3. Fogdall RP, Miller RD: Neuromuscular effects of enflurane, alone and combined with d-tubocurarine, pancuronium, and succinylcholine, in man. *Anesthesiology* 42:173-178, 1975

Table 1. Augmentation of the Neuromuscular Blocking Effect of Pancuronium and ORG-NC45 by Halothane and Isoflurane In Vivo

Relax- and Stimulus	Type of Anesthetics	Tension (% of Control) During Ventilation with O ₂ Containing the Indicated Concentrations (MAC) of				
		0	0.7	1.0	1.5	2.0
Halothane						
Pancur.	Twitch	102.5 ¹	98.9	96.2	79.8	11.3
	Tetanus	87.9*	64.0**	51.6***	32.0**	5.0*
NC45	Twitch	107.2	105.7	100.4	73.7	15.5
	Tetanus	90.6**	60.9***	47.2**	30.9*	6.2
Isoflurane						
Pancur.	Twitch	107.7	87.6	60.7	18.6	—
	Tetanus	86.1**	43.1**	24.1*	5.9	—
NC45	Twitch	105.3	92.5	52.4	16.2	—
	Tetanus	88.4*	43.9**	22.4*	9.3	—

¹Mean of 4 experiments; SEM not shown for lack of space.

*, ** and *** indicate differences at the p <0.05, <0.01 and <0.001 levels respectively (paired t test) between the "twitch" and "tetanus" side.