Title : IN VIVO MUSCLE RELAXANT-LOCAL ANESTHETIC INTERACTIONS

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Introduction. Neuromuscular (n.m.) blocking agents and local anesthetics mutually increase the n.m. blocking action of one another, in the rat phrenic nerve-hemidiaphragm preparation.[1] In the present study the in vivo interaction of these compounds at the n.m. junction of rats was investigated.

Methods. Sprague-Dawley rats anesthetized with i.p. pentobarbital and urethane were tracheostomized and mechanically ventilated with O_2. Both jugular veins and a carotid artery were cannulated for the injection of drugs and recording of intra-arterial (i. a.) B.P. respectively. The tendon of the tibialis anterior muscle was attached to a Grass FTO3C transducer. A resting tension of 25 g was applied to the muscle which was indirectly stimulated with supramaximal impulses of 0.2 msec duration at 0.1 Hz. Isometric twitch tension, H.R. and B.P. were continuously recorded on a Grass polygraph. After stabilization of the twitch, steady state >90% block was produced with fractional i.v. doses of d-tubocurarine (d-Tc), succinylcholine (SCh), procaine (proc.), procaine methobromide (proc. meth.), or lidocaine methobromide (lido.meth.). Doses of lidocaine (lido.) that produced about 30% n.m. block caused profound bradycardia, hypotension, and death. In other experiments >90% block was produced with d-Tc or SCh during continuous i.v. infusion of subeffective doses of local anesthetics, or with local anesthetics during infusion of subeffective doses of d-Tc or SCh.

Results. The findings presented in table 1 indicate that the continuous infusion of subeffective doses of proc. and lido. and their quaternized analogs significantly decreased the ED50 of d-Tc. Proc. and proc. meth. had no effect, lido. antagonized and lido. meth. increased the n.m. effect of SCh. The data summarized in table 2 indicate that the continuous infusion of subeffective doses of d-Tc and SCh increased the n.m. effects of all local anesthetics. d-Tc and SCh alone had no significant effect on i.a. B.P. and H.R. Local anesthetics, especially the tertiary compounds in n.m. blocking doses significantly decreased H.R. and i.a. B.P.

Discussion. The findings of this study indicate that the n.m. potency of the quaternary local anesthetics is greater and their negative chronotropic and hypotensive effect is smaller than those of the corresponding tertiary analogs. While continuous infusion of all local anesthetics increase n.m. potency of d-Tc their effect on the ED50 of SCh is variable (table 1). In contrast the continuous infusion of d-Tc or SCh invariably decreased the ED50 of local anesthetics. The variation in the interactions of different n.m. blocking agents and local anesthetics may be explained by differences in the mechanism of the n.m. effects of depolarizing and nondepolarizing relaxants[2] and different local anesthetics.[3]

References.
1. Matsuo S, Rao DBS, Chaudry I, et al: Interaction of muscle relaxants and local anesthetics at the neuromuscular junction. Anesth Analg 57:580-587, 1978.
2. Foldes FF, Wnuck BS, Hodges RJH, et al: The mode of action of depolarizing relaxants. Anesth Analg 36:23-37, 1957.
3. Maeno T, Edwards C, Hashimura S: Difference in effects and endplate potentials between procaine and lidocaine as revealed by voltage-clamp experiments. J Neurophysiol 34:32-46, 1971.

Table 1. Influence of Continuous Infusion of Local Anesthetics on the ED50 of d-Tc and SCh

	ED50[1] (µg/kg)				
		During Continuous i.v. Infusion of Subeffective Doses of			
Muscle Relax.	Alone	Proc.	Proc. Meth.	Lido.	Lido. Meth.
d-Tc	57.0	24.2**	31.2**	28.2**	27.6*
SCh	229.4	200.8	253.9	327.7	168.9

Explanation of symbols under table 2.

Table 2. Influence of Continuous Infusion of Neuromuscular Blocking Agents on the ED50 of Local Anesthetics.

	ED50 (mg/kg)		
		During Continuous i.v. Infusion of Subeffective Doses of	
Local Anesthetic	Alone	d-Tc	SCh
Proc.	129.1	23.8**	59.5***
Proc. Meth.	12.7	7.6	8.9
Lido.	>160.0[3]	31.2[s]	102.1[s]
Lido. Meth.	25.3	6.6***	7.0***

[1]Mean of 4 to 6 experiments; SEM not given to conserve space.
[2]During the first 5 min the infusion rates of proc. and proc. meth. were 3.32, that of lido. 1.66 and that of lido. meth. 1 mg/kg/min; d-Tc and SCh were infused at the rates of 11.6 and 3.32 µg/kg/min. After 5 min all infusion rates were halved.
[3]A mean dose of 160 mg lido. caused about 30% n.m. block, but the animals succumbed to profound hypotension.
*,**, *** Indicate significance from "alone" values at the $p<0.02$, 0.01 and 0.001 levels.
[s]Lack of control values prevents calculation of significance.