TITLE: INTERACTION OF NEUROMUSCULAR BLOCKING AGENTS WITH CALCIUM CHANNEL BLOCKERS

AUTHORS: G.B. BIKHAZI, M.D., I. LEUNG, B.S., F.F. FOLDES, M.D.

AFFILIATION: Department of Anesthesiology, University of Miami, School of Medicine

Introduction. Calcium-channel blockers (calcium antagonists; Ca)are being used with increasing frequency in the treatment of cardiovascular disorders. It is to be expected that surgical patients on Ca therapy will receive neuromuscular (NM) blocking agents (muscle relaxants; MR). Since Ca^{2+} is essential for NM transmission and muscular contraction, it is to be anticipated that Ca will inhibit NM function and will increase the NM effect of MR. The present study was undertaken to obtain quantitative information on the interaction of verapamil, which blocks both the "fast" Na- and the "slow" Ca-channels and nifedipine which blocks exclusively the slow Ca-channels[1], with two older (d-tubocurarine and pancuronium) and two newer [vecuronium (ORG NC45) and atracurium (BW33A)] nondepolarizing MR.

Methods. The experiments were carried out on the phrenic nerve-hemidiaphagm preparation of male Sprague-Dawley rats of 300 to 350 g body weight, suspended in modified Krebs' solution of 37°C and pH7.4, containing the same $[Ca^{++}]$ and $[Mg^{++}]$ as rat plasma, aerated with 95%O_2-5%CO_2.To simulate "physiologic" conditions the phrenic nerves were stimulated supramaximally with 0.1 sec trains of 50 Hz impulses of 0.2 msec duration every 20 sec. The indirectly elicited isotonic twitch tension (P) was continuously recorded with FT03 transducers on a polygraph. In 12 experiments, with each drug combination, when P became stable, cumulative dose response curves were determined for the 4 MR with or without the preliminary addition of 10 nmol/ml verapamil or 2 nmol/ml nifedipine. After greater than 90% steady state block had been established, 4 preparations were washed with drug-free Krebs' solution, to 4 neostigmine 0.75 nmol/ml and to 4 others 40 nmol/ml 4-aminopyridine (4-AP) was added.

Results. The concentrations of verapamil or nifedipine used in this study had no effect on P but significantly ($p<0.001$; Student's t test) decreased the ED50 of the 4 MR (see table). The effect of 2 nmol/ml nifedipine was about the same as that of 10 nmmol/ml verapamil. After washout,P recovered more in the absence, than in the presence of Ca ($p<0.001$ to 0.05). The partial antagonism of the NM block by neostigmine or 4-AP was about the same in the presence and absence of Ca.

Discussion. Both verapamil and nifedipine increased the NM effect of 4 MR studied. On a molar basis, nifedipine was about 4 times more potent than verapamil. In relation to their clinical dosage, however, the NM effect of the two compounds is about the same. The Ca concentrations for the in vitro potentiation of MR are not likely to be encountered at the NM junction after a single clinical dose of these compounds. In view of the incomplete reversal of the NM block in the presence of Ca by washout, it is conceivable that after prolonged use of clinical doses (verapamil 3x40 to 80, nifedipine 3x10 to 20 mg.p.o.) they may accumulate at the NM junction in concentrations, that will increase the effect of MR.

Reference.

1. Bayer R, Kalusche D, Kaufmann R and Mannhold R: Inotropic and electrophysiological actions of verapamil and D600 in mammalian myocardium. III. Effects of optical isomers on transmembrane action potential. Naunyn Schmiedebergs Arch Pharmacol 290:81-97, 1975

The Influence of Ca-channel Blockers on NM Blocking Agents

Compound(s)	ED50 (n mol/ml)	ED90	P (%) Wash.	of Control After Neost.	4-AP
d-Tubocur	0.47*	0.90	93†	68	57
d-Tc+Verap‡	0.25	0.58	74	65	57
d-Tc+Nifed	0.34	0.69	53	39	44
Pancuronium	2.19	3.73	98	42	64
Pancur+Verap	1.17	2.36	82	36	56
Pancur+Nifed	1.32	2.66	81	51	50
Vecuronium	3.77	7.23	101	42	59
Vecur+Verap	1.97	4.73	78	36	58
Vecur+Nifed	2.63	6.60	73	31	38
Atracurium	11.47	25.81	92	63	108
Atrac+verap	5.11	14.21	60	60	92
Atrac+Nifed	6.18	15.61	64	42	44

*The ED50 and ED90 values are mean±SEM of 12 experiments
†The recovery data are mean ±SEM of 4 experiments
‡The concentration of verapamil is 10 and that of nifedipine 2 nmol/ml