Title: VERAPAMIL REDUCES INDIRECT MUSCLE TWITCH AMPLITUDE AND POTENTIATES PANCURONIUM IN VITRO

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Introduction. The slow channel inhibitor, verapamil, possesses local anesthetic activity in vitro equivalent to procaine on an equimolar basis.[1] We further reported our qualitative findings that intra-arterially injected verapamil in anesthetized cats significantly reduced muscle twitch amplitude to indirect and direct electrical stimulation. We postulated that the in vivo effect is likely due to a dual action on slow and fast channel inhibition, as well as interference with neuromuscular transmission.[2] A study was designed to investigate the effect of verapamil on neuromuscular transmission in vitro and compare it to the action of pancuronium.

Methods. Isolated bullfrog (Rana catesebeiana) sciatic nerve-sartorius muscle preparations were used in Genell's Ringer buffer (pH 7.4) at room temperature in a double-chambered organ bath. The nerve was mounted on platinum wire electrodes and pulled through a hole separating the nerve and muscle chambers. The hole was sealed and the other end of the muscle was attached by nylon suture to a force-displacement transducer. Muscle twitch amplitude was recorded on a physiograph. The muscle was indirectly stimulated with a supramaximal stimulus at a rate of 12 per minute. In another study, we established effective concentration ranges for verapamil and pancuronium. In this study, we examined the effects of 5 mM of verapamil and 0.07 mM of pancuronium. Control amplitudes were obtained. The drugs were then added to the bath surrounding the muscle either singly or in combination. Fifteen minutes later, indirect muscle twitch amplitude was recorded.

Results. The results are shown in Table 1. Verapamil at the single dose tested, reduced indirect muscle twitch amplitude 44%; whereas pancuronium reduced amplitude by 35% (no significant difference at the 0.05 level from each other by paired t-test analysis but significantly different from control.) The two drugs in combination, after 15 minutes incubation, reduced indirect muscle twitch amplitude by 88% (significant difference from other two groups and control $p < 0.05$).

Discussion. This study confirms and extends our previous in vivo findings in cats that verapamil reduces indirect and direct twitch amplitude. Pancuronium significantly potentiated verapamil's depressant action. Verapamil may act by reducing the conductance of the presynaptic membrane to calcium. Pancuronium possesses both prejunctional and post-junctional activity. Prejunctional and post-junctional effects by verapamil and pancuronium may account for the observed potentiation. In as much as calcium regulates a wide variety of biologic functions, our findings are not unexpected. As yet, the pharmacologic effects of slow channel inhibitors seems to be almost solely confined to the cardiovascular system. Verapamil, through interaction with other anesthetic agents and adjuncts, may present an unrecognized source of respiratory embarrassment and muscular weakness in surgical patients. A phenomenon similar to mycin antibiotics. Although such consequences have not yet been clinically reported, we feel that as the use of verapamil increases, such experiences may be anticipated. Further studies are needed to completely evaluate our observation and to fully define possible clinical significance.

Table 1

Drug	Twitch Amplitude (% of Control; Mean + SEM)
Verapamil (N=5)	56 ± 6
Pancuronium (N=6)	65 ± 3
Verapamil + Pancuronium (N=3)	12 ± 7

References.

1. Kraynack BJ, Lawson N, Gintautas J: Local anesthetic effect of verapamil in vitro. (abstract) Annual Meeting, American Society Regional Anesthesia, March, 1982

2. Kraynack BJ, Gintautas J, Lawson NW: Effects of verapamil on excitable membranes. Proc West Pharmacol Soc 25 (in press), 1982