

Title : INTERACTIONS OF PANCURONIUM, GALLAMINE, TUBOCURARINE, METOCURINE
IN THE RAT PHRENIC NERVE-HEMIDIAPHRAGM PREPARATION

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Introduction: The neuromuscular blocking effect of pancuronium (P), gallamine (G), tubocurarine (D), metocurine (M) and a mixture of each pair of these drugs were studied in the rat phrenic nerve-hemidiaphragm preparation in order to investigate the phenomenon of non-depolarizing relaxant synergy and to further elucidate the possible mechanisms of this effect.

Methods and Materials: Sprague Dawley rats weighing between 200 and 275g were decapitated and both hemidiaphragms were dissected out with the accompanying phrenic nerves. The preparations were attached to carrier assemblies and placed in identical organ baths of 50 ml capacity containing oxygenated Krebs solution maintained at 36.5 C. The hemidiaphragms were stimulated indirectly and directly, using supramaximal square wave stimuli of .2msec duration at .15Hz with a Grass S88 stimulator. Muscle force (twitch) was isometrically transduced through a capacitance semiconductor transducer and recorded on a Gould Brush 2400 recorder. Basal muscle tension was maintained at 2g. Only one drug pair and their mixture were randomly assessed per diaphragm. Preliminary dose response curves (DRCs) were constructed for P, G, D and M (N ≥6). The concentration required to depress twitch height by 50% was defined as a dose equivalent unit (DU). The maximum depression of twitch height after each dose was measured and expressed as a percentage reduction of the twitch height immediately preceding the DRC of that drug. Cumulative doses in the range of .4 to 1.6 DU of each relaxant of a pair or its mixture were added to the bath in a volume of 0.2-0.8 mls to obtain the final correct concentration. Equal proportions (in DU) of the relaxants were administered simultaneously to arrive at the appropriate dose range of the mixtures. The ED-50's (in DU) for the relaxants and their mixtures were calculated from the linear regression lines constructed on the basis of at least 3 points between 20-80% response. A wash period of 6 x 5 min followed each DRC. This was repeated on at least 8 separate phrenic-nerve hemidiaphragm preparations for each muscle relaxant of a pair and their mixture. The results were compared for significance using the Paired t-test.

Results: One DU of pancuronium was 3.13×10^{-6} M. One DU of gallamine was 1.25×10^{-4} M. One DU of tubocurarine

was 9.15×10^{-7} M. One DU of metocurine was 2.88×10^{-7} M. The ED-50's of the D+P, M+P and M+G mixtures were significantly lower than the ED-50's of either D or P individually ($p < 0.0005$), the ED-50's of either M or P individually ($p < 0.0005$) and the ED-50's of either M or G individually ($p < 0.05$), respectively. The ED-50's of the M+D and G+D mixtures were not significantly different from either relaxant individually. The ED-50 of the P+G mixture was significantly higher ($p > 0.005$) than the ED-50 of P but not significantly different from the ED-50 of G.

Discussion: This data demonstrates nondepolarizing relaxant synergy for the mixtures M+P, D+P, and M+G in-vitro. This is in agreement with previous findings of synergy of D+P in-vitro.¹ This model excludes the possibility of differences on account of altered pharmacokinetics or protein binding as is present in the in-vivo model. This data is consistent with hypotheses of different modes and/or multiple sites of action of nondepolarizing relaxants such as the pre and post-junctional acetylcholine receptors and their corresponding ion channels.² Results of previous work on nondepolarizing relaxant interactions of gallamine (in-vivo: man, cat) have varied.³ The possibility of different binding sites and modification of binding properties of muscarinic receptors by gallamine has been demonstrated.⁴ This study reveals a disparity in the effects of different nondepolarizing relaxants when combined with gallamine. The results indicating synergy (M+G), additivity (D+G) and suggesting antagonism (P+G) underscores the variety of effects and possibly the multiple binding sites involved.

References:

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