TITLE: DANTROLENE POTENTIATES THE TOXICITY OF BUPIVACAINE

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Introduction. Calcium plays an important role in nerve excitability and the action of local anesthetics. The toxicity of local anesthetics (LA) is potentiated when verapamil (V) is concurrently administered.[1] V acts by inhibiting the transmembrane conductance of calcium (Ca) and thus decreases its intracellular concentration. Whether other drugs that similarly alter the distribution of Ca will, in turn, modify the toxicity of LA is unknown. Dantrolene (D), a sodium hydantoin derivative, is structurally unrelated to the Ca-channel blockers, but inhibits the release of Ca from the sarcoplasmic reticulum. Based on prior research, we postulate that the combination of D and LA will result in a drug interaction evidenced by increased LA toxicity. The ability of Ca to alter the potential toxicity will also be evaluated.

Methods. The methodology used in the present study was described in detail by DeJong et al.[2] Briefly, adult outbred female Charles River mice (8-12 wks) were individually given intraperitoneal injections. Mice were housed in small groups away from males and injected between 9 a.m. - 11 a.m. to minimize the effects of estrus and circadian variations. Mice were randomly divided into three groups: Group I received bupivacaine (B) alone; Group II received B + pretreatment with D (10 mg/kg); Group III received B + pretreatment with D (10 mg/kg) and $CaCl_2$ (100 mg/kg). Various dosages of B were administered and from these data three linearized dose-response curves were derived using an iterative curve fitting technique.[3] The LD_{50}'s were then computed and the differences between groups analyzed for statistical significance using t-test for mean differences.

Results. Dose response curves are shown in fig 1. The toxicity of B was increased in both pretreatment groups. The respective LD_{50}'s with standard errors of the mean were: Group I, 71.2±3.3; Group II, 46.1 ± 1.8; Group III, 35.8±1.4. The rise in toxicity was statistically significant ($p < 0.05$).

Discussion. The intraperitoneal mouse model is a standard test used to assess the toxicity of LA.[2] These results confirm an interaction of B with D. The higher mortality and reduced LD_{50} with B + D is similar to that found for LA + V.[1] However, pretreatment with Ca reversed the latter drug interaction, while it further potentiated the toxicity of B + D. The physiologic alterations induced by D mimic in several aspects those produced by the Ca-channel blockers.[4] There are specific exceptions and the discrepancy in the pretreatment with Ca appears to confirm this finding. Further investigation in LA drug interactions is warranted and may prove to be clinically relevant.

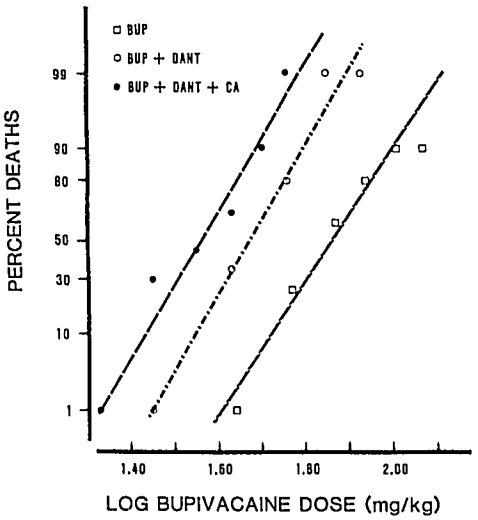

Figure 1.

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