Respiratory, neuromuscular, and cardiovascular effects of neosaxitoxin in isoflurane-anesthetized sheep

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Background: Neosaxitoxin (NeoSTX) is a potent site-1 sodium-channel blocker being developed as a local anesthetic. Doses of 100 ?g have been used by local infiltration in anesthetized adult humans without adverse effect. We hypothesized that similar doses could cause significant respiratory, neuromuscular, and cardiovascular impairment and sought to test this hypothesis in sheep. Methods: Procedures were approved by the Institutional Animal Care and Use Committee. In neuromuscular/respiratory experiments, 33 intubated, isoflurane-anesthetized sheep were randomized to 6 NeoSTX treatment groups: saline control, 1 ?g/kg subcutaneous (SC), 1 ?g/kg intravenous (IV), 2 ?g/kg SC, 2 ?g/kg SC with bupivacaine 0.25%, and 3 ?g/kg SC. Primary outcome measures were doxapram-stimulated inspired volume (DSIV) and quantitative limb acceleration. In cardiovascular experiments, 8 sheep received escalating IV doses of NeoSTX (1, 2, and 3 ?g), with hemodynamic and electrocardiographic measurements. Data w