CHLOROBUTANOL, A SEDATIVE HYPNOTIC, ANALGESIC AND PARENTERAL SOLUTION PRESERVATIVE, INHIBITS BRAIN TYPE VOLTAGE GATED SODIUM CHANNELS

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Introduction: Chlorobutanol is an analgesic and sedative hypnotic in man, and an experimental general anesthetic. It is also used chemical preservative for parenteral drugs such as methadone and local anesthetics, and in eye drops, mouth washes, and cosmetics. The mechanism of action of chlorobutanol is unclear. Our goal was to test whether chlorobutanol inhibits brain type, voltage gated sodium channels.

Methods: Mammalian Nav 1.2 voltage gated sodium channels were expressed in Xenopus oocytes by injecting the alpha subunit cRNA. Inward sodium currents were measured with two-electrode voltage clamp using standard depolarization protocols. One or two-tailed, paired, t tests were used to test for differences between control and drug treatment means. The study was approved by our institutional animal care and use committee.

Results: Chlorobutanol was tested at concentrations ranging from 0.03 to 10 mM. Chlorobutanol reversibly inhibited closed, resting channels and inactivated channels in a concentration dependent manner, IC50s=3.91±0.31 mM and 4.13±0.63 mM, respectively, n=5, $p>0.05$, N.S. The voltage dependence of activation was shifted 4.9±2.1 mV, n=9, $p<0.05$, in the depolarizing direction. Fast inactivation voltage dependence was not affected. There was little state dependent block and no apparent use dependence.

Discussion and Conclusions: Chlorobutanol inhibited Nav 1.2 channels at concentrations less than those used to preserve parenteral solutions. Its mechanism of inhibiting Na channels differs from that of local anesthetics in that it does not show use dependent or state dependent inhibition. Its use as a preservative in I.V. methadone and local anesthetic solutions, eye drops and analgesic gels likely adds an analgesic component to these solutions.