TITLE: VASOCONSTRICTION AND VECURONIUM NEUROMUSCULAR BLOCKADE IN HUMANS

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The evoked response of the adductor pollicis (AP) muscle is used frequently to monitor neuromuscular function. We have previously shown that both central[1] and local AP[2] hypothermia decreases AP twitch tension in humans and have demonstrated that thermoregulatory vasoconstriction during general anesthesia decreases skin temperature ~ 10 °C.[3] Therefore, we tested the hypothesis that thermoregulatory vasoconstriction (and consequent AP hypothermia) decreases AP twitch tension during vecuronium-induced neuromuscular blockade.

With informed consent, and the approval of our Committee for Human Research, we studied four healthy volunteers. Anesthesia was induced with 70% N_2O and isoflurane 4-5%, and maintained with isoflurane, 0.8-1.2%, in O_2 . Following train-of-four stimulation of the ulnar nerve, the AP twitch tension of the first response in each train (T1), and the ratio of the fourth to the first twitch (TOF ratio) were recorded. A stable plama concentration of vecuronium was produced by administering, 20 ug/kg iv bolus, plus infusion at 25 ug/kg/h for at least 60 min before the onset of vasoconstriction. Deep esophageal temperature, AP muscle temperature, and skin temperatures from the thenar emminence, index finger tip, and forearm were recorded. The volunteers cooled spontaneously by exposure to room air and the onset of significant vasoconstriction was defined as a lower arm-finger tip gradient of > 4 °C. Following vasoconstriction, AP twitch tensions were recorded for an additional 90 min.

Vasoconstriction occurred at esophageal temperatures of 34.4-35.1 °C; over the next 90 min, central temperature changed < 0.2 °C, the AP temperature decreased in all subjects by 1.9-3.4 °C and T1 and TOF ratio decreased (see figure). We conclude that, following peripheral vasoconstriction, there are temperature-related decreases in AP evoked responses. However, the magnitude of these changes is small and unlikely to be significant in terms of clinical neuromuscular function monitoring.

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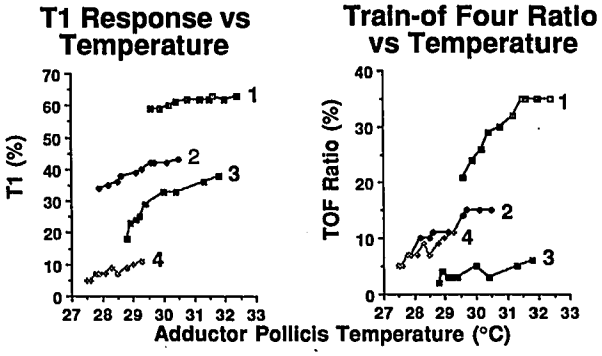

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TITLE: G1-64, A NEW, RAPIDLY ACTING NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENT

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Inspite of considerable efforts aiming at the development of surgical muscle relaxants with rapid onset time and short lasting nondepolarizing neuromuscular blocking (NMB) action, no such agent of clinical usefulness has been produced. The design of G1-64, a tropanyl ester derivative, was based on our early (1) and recent, extensive structure-activity studies.

G1-64 was evaluated for NMB and side effects (with approval of the Animal Research Committee) on anesthetized rats, rabbits, cats, ferrets, pigs and cynamolgus monkeys. NMB effects were determined on the anterior tibial muscle using supramaximal train-of-four (TOF), and periodically, tetanic nerve stimulation of the sciatic nerve. Blood pressure was transduced from a cannulated carotid artery. Cardiac vagal block (CVB) was assessed by inhibition of the bradycardic response to stimulation of the vagus nerve. IV ED values of onset, recovery index, duration of NMB (to 90% recovery of the twitch response), fade of TOF and tetanic responses and reversibility by edrophonium (E) or neostigmine (N) were determined.

Results are summarized in the TABLE

G1-64 shows short onset and relatively short duration of action. Onset of NMB, dependent on the species, was 1.2-3 times shorter than with atracurium or vecuronium. Duration of action was generally comparible with these two agents. The type of NMB is nondepolarizing, characterized by TOF fade, tetanic fade, posttetanic potentiation and reversibility by E and N. CVB was present to a varying degree at doses above the ED_{80-90} of NMB. Heart rate changes in the absence of vagal stimulation were slight on the monkey and the pig. The cardiac vagal safety margin of G1-64 was 1.3-3.0 (rat, ferret, cat) which is 1.5-10 times better than that of gallamine or fazadinium. Only on the cat was it slightly more vagolytic than pancuronium. Sympathetic ganglion blocking effect was absent and, at the NMB dose range, G1-64 showed no hyper- or hypotensive effects.

G1-64 is a member of a class of tropanyl esters characterized by bulky quaternary ammonium groups, o acid ester moiety and interonium distances of 16-34 A (extended form). Because of its rapid onset and short duration of action, G1-64 deserves further evaluation.

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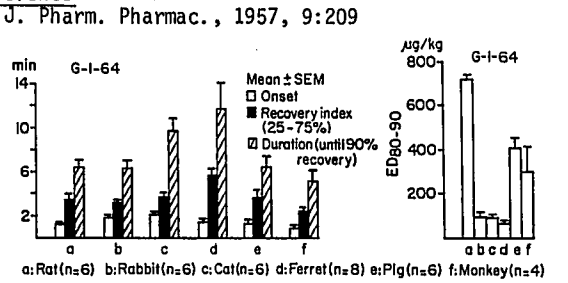

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