Title: LACK OF MALIGNANT HYPERTHERMIA TRIGGER ACTIVITY WITH ATRACURIUM AND VECURONIUM IN MH POSITIVE MUSCLE BIOPSY SPECIMENS

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Introduction: The abrupt onset of the malignant hyperthermia (MH) syndrome is manifest by tachycardia, muscle rigidity and hyperthermia. The list of drugs known to trigger the malignant hyperthermia syndrome in susceptible individuals includes the muscle relaxant succinylcholine, but not tubocurarine or pancuronium. With the introduction of atracurium and vecuronium into anesthesia practice, the question of whether these newer muscle relaxants possess MH triggering potential has been raised. Vecuronium has been reported not to trigger MH susceptible pigs. The present study investigated the trigger potential of atracurium and vecuronium alone and in the presence of halothane on human muscle biopsy specimens from normal and MH susceptible individuals.

Methods: Ten consenting patients suspected of malignant hyperthermia presented for muscle biopsy and testing. Each patient had either a strong family history or a suspected reaction under general anesthesia. Ages of the patients ranged from 2 1/2 to 81. Three muscle biopsy specimens were taken from each patient's quadriceps muscle group and were tested for malignant hyperthermia susceptibility using the standard muscle contracture response to halothane alone, caffeine alone and the combination of halothane and caffeine. Following the malignant hyperthermia bioassay test which identified patient susceptibility to MH, the muscle specimens were then tested for a contracture response to increasing concentrations of atracurium and vecuronium alone and in the presence of 3% halothane vapor. For comparison purposes pancuronium and d-tubocurarine were also tested. Bioassay conditions included a 50 ml organ bath, Krebs bicarbonate buffer at pH 7.4, 37°C bath temperature and 95% 0_2/5% CO_2 gas addition to the bath. The muscle specimen was mounted to a holder and a Harvard #363 isometric force transducer with 2 grams of tension applied to the resting length. The muscle was directly stimulated to twitch at 0.2 Hz, 5.0 msec duration and supramaximal voltage (50+ volts). The calibrated gram tension displacement of the contracture and twitch responses were recorded on a pen writer. Each test relaxant was administered to the bath in sequential fashion such that the summated final bath concentration of each drug was 0.1, 0.6, 1.6, and 11.6 mcg/ml. This design allowed each drug to be tested within a concentration range that included the reported plasma mcg/ml concentration following an average intubating dose. At the conclusion of each experiment the muscle specimen was subjected to a caffeine dose response challenge identical to that used in the MH susceptibility test to confirm viability of the specimen.

Results: Muscle specimens from patients who tested negative for M.H. susceptibility responded to final bath concentrations of 0.1 and 0.6 mcg/ml vecuronium, atracurium, d-tubocurarine and pancuronium (below the estimated plasma intubating equivalent) with no change or a decrease in the resting gram tension. Even at the higher 1.6 and 11.6 mcg/ml final bath concentrations no contractures occurred. The addition of 3% halothane vapor to the bath with 11.6 mcg/ml vecuronium, atracurium, d-tubocurarine or pancuronium did not produce a contracture. response. Muscle specimens from patients who tested positive for MH susceptibility likewise did not exhibit contracture responses to vecuronium, atracurium, tubocurarine or pancuronium over the 0.1 to 11.6 mcg/ml final bath concentration range. The addition of 3% halothane vapor to the tissue bath containing 11.6 mcg/ml of each muscle relaxant produced a contracture response, but the response was not greater than the gram tension achieved when 3% halothane alone was added.

Discussion: The opportunity to test the MH trigger potential of atracurium and vecuronium utilizing this in vitro approach provides valuable information without subjecting suspect MH susceptible individuals to undue risk. The muscle bioassay results demonstrate a lack of MH trigger activity for atracurium and vecuronium over a wide range of concentrations including those of clinical importance and in the presence of halothane. While these in vitro findings cannot substitute for final testing in humans, they do offer convincing evidence for the safety of atracurium and vecuronium in MH susceptible individuals and should hasten the final testing of these drugs in vivo.