Title: PHARMACODYNAMICS OF VECURONIUM AND ATRACURIUM IN THE OBESE

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Introduction. Prolonged action and elimination of the muscle relaxant metocurine has been documented in obese patients.[1] Decreased urinary excretion of metocurine in the obese was the suggested etiology of this difference. The purpose of this study was to see if the intermediate duration muscle relaxants, which are eliminated by other routes, also had prolonged action in the obese. Vecuronium, eliminated primarily by the liver, and atracurium,[2] eliminated by Hofmann elimination and ester hydrolysis, were studied in obese patients and controls.

Methods. Following institutional review board approval, informed consent was obtained from all patients. Twelve obese patients and 12 controls undergoing elective neurosurgery were studied. Obese patients were at least 130% of ideal body weight (IBW) based on the formula of the Metropolitan Life Insurance Co. The obese patients averaged 143% IBW with a range of 130-168% IBW. Control patients averaged 102% IBW with a range of 91-113% IBW. The percent of the patient's body weight consisting of fat (% fat) was calculated by the method of Weisberg.[3] Patients were excluded from the study if they had cardiac, hepatic, renal, or neuromuscular disease; or if they were taking medications known to affect neuromuscular blockade. Six obese patients and 6 controls received atracurium. Vecuronium was given to the other 6 obese and 6 control patients. The sex distribution was the same in the obese and control groups. In the vecuronium study, there was no difference in the age of the obese and control patients. Age does not affect atracurium dynamics in adults[4] and was therefore not controlled for that portion of the study.

Anesthesia was induced with thiopental, N_2O, O_2 and halothane 1%. The ulnar nerve was stimulated at the wrist with a supramaximal square wave of 0.2 msec duration at 0.1 Hz from a Grass Model S-44. The response was measured with a force-displacement transducer, Grass Model FT-10, applied to the thumb. After a control twitch height was established, the patients received either 0.1 mg/kg of vecuronium or 0.5 mg/kg atracurium iv bolus. Maintenance anesthesia was 60% N_2O, 40% O_2, and 1% halothane. End-tidal CO_2 was kept between 25-35 mmHg. There was no significant difference in Et CO_2 between groups. Esophageal temperature was maintained between 34.3 - 36.6°C with warming blankets. There was no significant difference in temperature between the groups. The times for 5-25% recovery and for 25-75% recovery were compared between the obese and control groups using two-tailed Student's t-test. The groups' characteristics and intraoperative conditions were similarly compared. The male:female breakdown was compared using Chi-Square. The threshold for statistical significance was $P < 0.05$. Percent fat and % IBW were compared with recovery times using linear regression analysis.

Results. The obese patients receiving vecuronium had significantly prolonged 5-25% and 25-75% recovery indexes (Table 1). The regression of % IBW to 25-75% recovery index ($r = .81$, $P < 0.005$) was significant for vecuronium. The regression of % fat to 25-75% recovery ($r = .91$, $P < 0.005$) was more closely correlated. The regression of % IBW to 5-25% recovery was weakly correlated ($r = .61$, $P < 0.05$). Multiple regression on age and % IBW compared to 25-75% recovery showed that age was not significantly related to recovery in this study. Atracurium, in contrast to vecuronium, demonstrated no change in its recovery index in relation to % IBW or % fat.

Discussion. Obese patients had prolonged recovery of neuromuscular blockade from vecuronium but not from atracurium. Based on the regression of 25-75% recovery index to % IBW for each 1% IBW, recovery index is 0.6 min longer. As % fat increases 1%, the 25-75% recovery is prolonged by 1.1 min. Similarly, the regression of 5-25% recovery and obesity indicates that 0.18 min is added for each 1% increase in IBW. Possible explanations for the difference between atracurium and vecuronium in the obese could be: 1) increased sensitivity of the neuromuscular junction in the obese to vecuronium, and 2) delayed excretion of vecuronium in the obese. A previous study of metocurine in the obese showed no difference in the plasma concentration response relationship.[1] Therefore, delayed excretion seems to be a more likely explanation. Recovery from atracurium in the obese was unchanged apparently because atracurium is eliminated from all body compartments and does not depend on regional blood flow or organ function. Vecuronium, on the other hand, must be cleared by the liver. Abnormal liver histopathology is often present in the obese despite normal liver function tests.[5] In addition, liver blood flow as a percentage of total body weight is reduced in the obese.[6] Therefore the mechanism for the delayed recovery from vecuronium in the obese demonstrated by this study is likely to be impaired hepatic clearance. The pharmacokinetics of vecuronium in the obese need to be studied to clarify this issue.

References.

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Table 1. Recovery Indexes and Obesity (Mean ± SD)

Vecuronium	Obese	Control	P
5-25% (min)	14.6±6.7	6.9±1.9	0.05
25-75% (min)	33.0±15.0	13.2±1.9	0.01
Atracurium			
5-25% (min)	10.9±3.9	10.6±2.7	0.91
25-75% (min)	9.7±4.1	9.3±2.6	0.87