Title: PHARMACOKINETICS OF ATRACURIUM IN ELDERLY AND YOUNG ADULTS

Authors: JB Kitts M.D., DM Fisher M.D., PC Canfell M.S., M J Spellman, JE Caldwell FFARCS, T Heier M.D., MR Fahey M.D., RD Miller M.D.

Affiliation: Department of Anesthesia, University of California, San Francisco, CA. 94143-0648

Introduction. Elimination of most nondepolarizing muscle relaxants is prolonged in elderly patients due to decreases in metabolic function of the liver and kidney.[1] Because atracurium is eliminated through several pathways, some independent of organ metabolism or excretion,[2] elimination of atracurium might be less affected by age. Therefore, we determined the pharmacokinetics of atracurium in elderly patients and compared them to young adults.

Methods. With informed consent and approval from the Committee on Human Research, five patients (74-76 yr of age, ASA physical class I or II) undergoing elective surgery were studied. Anesthesia was induced with thiopental (1-2 mg/kg) and halothane. Endotracheal intubation was accomplished without the use of muscle relaxants. Anesthesia was maintained with nitrous oxide, 60% and halothane, 0.5% (end-tidal concentrations). Esophageal temperature was maintained at 35-37°C and end-tidal PCO_2 at 30-40 mmHg. Neuromuscular blockade was assessed by measuring the evoked twitch response of the adductor pollicis muscle to supramaximal stimulation (0.1 Hz) of the ulnar nerve at the wrist. After stabilization of anesthesia and twitch response, atracurium was infused iv at a constant rate in each patient, (16.3 ± 2.8 μg/kg/min, mean ± SD), until the twitch was depressed approximately 70%. The duration of infusion was 10.2 ± 2.2 min. Heparinized venous blood samples were drawn from the contralateral arm prior to and 2, 4, 6, 8, 10, 15, 20, 25, 30, 37.5, 45, 52.5, 60, 70, 80, 90, 100, 110, and 120 min after the start of the infusion. Samples were immediately acidified, centrifuged and frozen at -20°C until assayed by liquid chromatography. This assay is sensitive to 10 ng/ml and has a coefficient of variation of 7% at a concentration of 50 ng/ml. Plasma concentrations of atracurium were plotted against time and fitted to a two-compartment pharmacokinetic model, modified to account for different elimination rate constants from the central ($k_{organ}+k_{nonorgan}$) and peripheral ($k_{nonorgan}$) compartments[2], using nonlinear least-squares regression analysis. We estimated the elimination of atracurium *in vitro* (sum of rate constants for Hofmann elimination and ester hydrolysis) for each patient, by obtaining 25 ml of blood prior to the administration of atracurium. After equilibration of this blood with 5% CO_2 and 95% O_2 at body temperature and *p*H, atracurium 100 μg was added and plasma samples obtained to determine atracurium concentration at 30, 60, 90, and 120 min. The log plasma concentration was plotted against time and least squares linear regression was used to determine the slope ($-k_{nonorgan}$). These values were then used to determine the volume of distribution at steady state (V_{ss}), elimination half-life, drug clearance by pathways other than Hofmann elimination and ester hydrolysis (Cl_{organ}), drug clearance by Hofmann elimination and ester hydrolysis ($Cl_{nonorgan}$), and total drug clearance (Cl_{total}). Mean values were compared to those obtained previously in healthy young adults[2] using the Mann-Whitney *U* test. Statistical differences were considered significant at $P < 0.05$.

Results. All pharmacokinetic parameters except Cl_{organ} changed with age (table 1).

Discussion. We found that the pharmacokinetics of atracurium differ between young and elderly adults. We do not know whether this more rapid elimination *in vitro* results from age-related changes in Hofmann elimination or ester hydrolysis. V_{ss} was larger in elderly subjects. Because atracurium probably distributes into the extracellular fluid (ECF) space, we might expect maturational decreases in ECF volume to decrease V_{ss}. In contrast, the larger V_{ss} in the elderly may result from age-related changes in atracurium's protein binding. These age-related changes resulted in $Cl_{nonorgan}$ being greater in elderly subjects. We expected and found, that Cl_{organ} decreased with age; however, differences did not achieve statistical significance ($p=0.06$), probably a result of the small sample size. The finding that the increase in V_{ss} with age was greater than the age-related increase in Cl_{total} results in elimination half-life being longer in the elderly. These results suggest that recovery from comparable degrees of neuromuscular blockade will be slightly longer in the elderly compared to young adults.

TABLE. Values (mean ± SD) for pharmacokinetic parameters for atracurium in elderly and young adults.

	Elderly adults (n = 5)	Young adults (n = 5)
Age (yrs)	75 ± 1*	32 ± 10
$k_{nonorgan}$	0.025 ± 0.001*	0.021 ± 0.002
$t_{1/2}\beta$ (min)	21.8 ± 3.3*	15.5 ± 2.6
V_{ss} (ml/kg)	188 ± 61*	87 ± 31
Cl_{total} (ml/kg/min)	6.5 ± 1.1*	4.8 ± 1.1
$Cl_{nonorgan}$ (ml/kg/min)	4.7 ± 1.6*	1.9 ± 0.6
Cl_{organ} (ml/kg/min)	1.7 ± 0.9	3.0 ± 0.9

* Different ($P<0.05$) from young adults by Mann-Whitney *U* test.

References.

1. Miller RD, Savarese JJ: Pharmacology of Muscle Relaxants and Their Antagonists. Miller RD (ed): Anesthesia (second edition) Churchill Livingstone, New York, 1986, pp 904-905
2. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD: Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. ANESTHESIOLOGY 65:6-12, 1986