Title: PHARMACOKINETICS OF d-TUBOCURARINE IN THE AGED

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Introduction. It has been well established that the pharmacokinetics of numerous drugs in the elderly differ from young patients.[1,2,3] There is also considerable evidence that these differences in the distribution and elimination of drugs may account in large part for the increase in adverse drug reactions in aged patients. This study was undertaken to determine the distribution and elimination of d-tubocurarine (dTc) in elderly patients (age greater than 70 yrs).

Methods. Six elderly neurosurgical patients (70-87 yrs) and six younger adults (30-54 yrs) undergoing craniotomy or urological procedures were studied after obtaining institutional approval and informed consent. All patients had serum creatinine and BUN values within normal limits. Patients were given an iv infusion of 500 to 800 ml of Ringer's lactate solution prior to induction of anesthesia. During anesthesia and in the immediate postoperative period, Normosol-R and 5% dextrose in water were infused at the rate of 3-4 ml/kg/hr. Anesthesia was induced with thiopental, the trachea intubated with the aid of succinylcholine and anesthesia maintained with nitrous oxide-oxygen (60-40%) and halothane (0.5-1.0%). At this point a single intravenous dose of dTc (0.3 mg/kg) was given. Blood samples were obtained from an arterial catheter at 1, 3, 5, 10, 15, 25, 35, 45 min; and also at 1, 2, 3, 4, 5, 6, and 9 hrs; between 12 and 24 hrs either 4 or 5 samples were drawn with at least 3 hrs between each sample. The plasma was separated and frozen until analyzed. dTc concentration in the plasma was determined by radioimmunoassay. Time-concentration curves of plasma concentrations of dTc were analyzed statistically by the method of Wagner for bolus iv injection of a drug.[4]

Results. Plasma decrement curves of dTc for both groups are best described by a three-compartment model. The relationship between plasma concentration and time for the elderly group is described by the equation $C = 8.65e^{-.34t} + 2.21e^{-.042t} + .849e^{-.0028t}$; for the younger group, $C = 5.94e^{-.48t} + 1.42e^{-.04t} + .517e^{-.0041t}$, where C = concentration in µg/ml and t = time in minutes. The pharmacokinetic parameters are presented in Table 1.

Discussion. The difference noted in the elimination half-lives ($t_{½}$ elim) between the elderly and younger patients was not unexpected since the most common finding in the literature on pharmacokinetics in the aged is a prolonged elimination half-life.[3] The decreased volume of distribution (Vd_{area}) may represent tissue loss seen with increasing age and a concurrent decrease in total body and intracellular fluid.[2] The decreased plasma clearance (Clp) observed in this study is in agreement with McLeod, who, in studying the effects of aging on the pharmacokinetics of pancuronium, found that the Clp was the only kinetic parameter that correlated with increasing age.[5] In contrast to McLeod, who studied pancuronium, we have found many differences in the pharmacokinetic parameters of the elderly receiving dTc when compared with younger patients (Table 1). A recent preliminary study of the pharmacokinetics of metocurine in elderly patients also suggests many of their pharmacokinetic parameters are significantly different from younger controls.[6] The mean plasma concentrations of dTc of the elderly throughout the entire 24 hrs of this study are higher than that of the younger controls. This is reflected in the decreased plasma clearance and elimination rate constant seen in the elderly patients. In addition, the reduced volumes of distribution (V_i and Vd_{area}) in the elderly would decrease the volume available for distribution of the drug and contribute to an increase in the plasma concentration.

This study has shown that the pharmacokinetics of dTc in the elderly differ significantly from younger patients; it does not tell us if these changes cause measurable alterations in the action of dTc at the myoneural junction.

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Table 1. Pharmacokinetic Parameters (Mean ± SE)

	Aged, n=6 (70-87 yrs)	Controls, n=6 (30-54 yrs)	P
$t_{½}$ elim (min)	268 ± 33	185 ± 63	<.02
Clp ($ml \cdot kg^{-1} \cdot min^{-1}$)	0.77 ± .09	1.7 ± .18	<.00
V_i (l/kg)	.027 ± .03	.039 ± .03	<.02
Vd_{area} (l/kg)	.280 ± .02	.426 ± .04	<.01
k_{12} (min^{-1})	.169 ± .03	.261 ± .03	<.05
k_{21} (min^{-1})	.109 ± .02	.143 ± .01	<.05
k_{13} (min^{-1})	.069 ± .01	.071 ± .02	NS
k_{31} (min^{-1})	.012 ± .002	.013 ± .002	NS
k_{10} (min^{-1})	.03 ± .005	.044 ± .005	<.01

k_{12}, k_{21}, k_{13}, k_{31} = rate constants for bidirectional transport of drug between compartments (1 and 2, and 1 and 3, indicating fraction of drug transferred between compartments) in one min. k_{10} = rate constant for elimination from central compartment.