

Title: PHARMACOKINETICS OF d-TUBOCURARINE IN NEONATES, INFANTS AND CHILDREN
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Introduction. It has been reported that neonates are (1) unusually sensitive to the effects of d-tubocurarine (dTc),¹ (2) that they react as adults provided they are not overdosed,² or (3) they appear resistant to dTc.³ A study of the pharmacokinetics of dTc may be of value in resolving conflicting reports of the potency of dTc in neonates.

Methods. Four groups of neurosurgical and general surgical patients have been studied after obtaining informed consent with institutional review board approval. The groups were neonates, 0-1 mo (n=4); infants, 1-12 mos (n=5); children, 1-4 yrs (n=5) and adults (n=6). Premedication consisted of secobarbital (20-100 mg) and atropine (0.1-0.5 mg) in the infants, children and adults. Neonates received either no premedication or atropine 0.1 mg. Anesthesia was induced with either thiopental or halothane. A nitrous oxide-(60-40%)halothane (inspired concentration 1.0-2.0%) mixture was used for tracheal intubation. Following induction, halothane concentration was maintained between 0.5-1.0%, inspired concentration. Either central venous or arterial catheters were placed, and the patient's bladder was catheterized with an indwelling catheter and emptied. At this point a single intravenous dose of dTc (0.3 mg/kg) was given. Blood samples were obtained from the venous or arterial catheters in heparinized tubes at 1, 3, 5, 10, 15, 25, 35, 45 min; and at 1, 2, 3, 4, 5, 6, 9 hrs; between 12 and 24 hrs either 3 or 4 samples were drawn with at least 3 hrs between each sample. The plasma was separated and frozen until analyzed. The total urine excreted for 24 hrs was collected, measured and an aliquot taken to be analyzed for dTc. dTc concentrations in the plasma and urine were determined by radioimmunoassay. Time-concentration curves of plasma concentration of dTc were analyzed by the method of Wagner for bolus iv injection of a drug.⁴

Results. Plasma decrement curves of dTc for all four groups are best described by three-compartment models. The relationship between plasma concentration and time for the neonates is described by the equation $C = 6.66e^{-.65t} + .79e^{-.045t} + .53e^{-.0022t}$; for infants, $C = 6.11e^{-.35t} + 1.56e^{-.030t} + .48e^{-.0023t}$; for children, $C = 5.7e^{-.45t} + 2.33e^{-.035t} + .56e^{-.0043t}$; and adults, $C = 6.82e^{-.56t} + 1.04e^{-.035t} + .62e^{-.0043t}$, where C = concentration in $\mu\text{g/ml}$ and t = time in minutes. The pharmacokinetic parameters are presented in Table 1. The 24-hr urinary excretions were: neonates, $27 \pm 3\%$ (mean \pm SE); infants, $48 \pm 4\%$; children, $45 \pm 3\%$; and adults, $47 \pm 6\%$. There was no significant difference in the 24-hr urinary excretion of dTc between adults, children and infants. The neonates' 24-hr urinary excretion was significantly lower than the adult values, $P < 0.05$.

Discussion. In this study, elimination half-life ($t_{1/2}$ elim) was significantly prolonged in both infants and children, which was also accompanied by a decrease in the Clp. In addition, the $V_{d\text{area}}$ in neonates was

significantly greater than in adults, while in infants, although the mean value for the $V_{d\text{area}}$ was greater than in adults, it was not significantly so. The pharmacokinetic parameters in children more closely resemble adult values. The larger volumes of distribution in neonates and infants may be a reflection of their larger extracellular volumes compared to the adult. The increased $t_{1/2}$ elim and decreased Clp in the neonates are most likely related to the fact that the newborns glomerular filtration rate and renal plasma flow is 30-40% of the adult value.^{5,6} As further proof, the neonates' ability to excrete dTc in our study is significantly decreased. The reason for the infants' increased $t_{1/2}$ elim and decreased Clp of dTc is not clear. It is not related to a decrease in the ability to excrete dTc by the kidney. The pharmacodynamic results in this study are opposite to those of O'Keeffe⁷ who found that the $t_{1/2}$ elim of dTc was shorter in infants and children than in adults, the Clp was greater and there was no difference in the volumes of distribution. The fact that O'Keeffe et al infused dTc over a period of minutes in their study and found that a two-compartment model best fitted their data cannot fully explain these differences. Neonates exhibit a prolonged $t_{1/2}$ elim, decreased Clp and decreased urinary excretion of dTc, suggesting that the action of the drug might be prolonged in them. Goudsouzian et al³ studying the time of return of twitch or stimulus height after a dose of dTc have not found significantly different return times for neonates, infants or children.

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Table 1. Pharmacokinetic Parameters (Mean \pm SE)

	Neonates (n=4)	Infants (n=5)	Children (n=5)	Adults (n=6)
$t_{1/2}$ elim (min)	336 \pm 40*	321 \pm 44*	172 \pm 12	164 \pm 9
Clp (ml \cdot kg $^{-1}$ \cdot min $^{-1}$)	1.1 \pm .1†	1.1 \pm .1†	1.3 \pm .1	1.7 \pm .1
V_j (l/kg)	.039 \pm .04	.042 \pm .09	.040 \pm .06	.039 \pm .06
$V_{d\text{area}}$ (l/kg)	.523 \pm .03†	.473 \pm .02	.333 \pm .06‡	.399 \pm .05

$t_{1/2}$ elim = elimination half-life; Clp = plasma clearance; V_j = initial volume of distribution; $V_{d\text{area}}$ = volume of distribution. * $P < .001$, † $P < .01$, ‡ $P < .05$, significantly different when value is compared to that of adult.