Anesthesiology
57:203–208, 1982

Pharmacokinetics and Pharmacodynamics of d*-Tubocurarine in Infants, Children, and Adults*

Dennis M. Fisher, M.D., Colette O'Keeffe, M.D.,* Donald R. Stanski, M.D.,† Roy Cronnelly, M.D., Ph.D.,‡ Ronald D. Miller, M.D.,§ George A. Gregory, M.D.¶*

The pharmacokinetics and pharmacodynamics of *d*-tubocurarine (*d*Tc) were determined in neonates (0–2 months, n = 7), infants (2–12 months, n = 7), children (1–12 years, n = 9), and adults (12–30 years, n = 8) during 70% nitrous oxide, 0.58 MAC halothane anesthesia. *d*Tc was administered by infusion, while blood for determination of plasma *d*Tc concentrations was obtained, and the EMG of the adductor pollicis recorded. The plasma *d*Tc concentration at which 50% depression of EMG twitch height occurs ($Cp_{ss(50)}$) was 0.18 ± 0.09 μg/ml in neonates, and 0.27 ± 0.06 μg/ml in infants, both significantly lower than the values of 0.42 ± 0.14 and 0.53 ± 0.14 μg/ml for children and adults, respectively. The steady-state distribution volume (Vd_{ss}) was 0.74 ± 0.33 l/kg in neonates, significantly greater than the values of 0.52 ± 0.22, 0.41 ± 0.12, and 0.30 ± 0.10 l/kg in infants, children, and adults, respectively. The elimination half-life ($t_{\beta 1/2}$) was 174 ± 60 min in neonates, significantly longer than the values of 90 ± 23 and 89 ± 18 min in children and adults, respectively. Plasma clearance did not differ with age. We also determined D_{50}, the product of Vd_{ss} and $Cp_{ss(50)}$. D_{50}, the quantity of drug present at steady-state to produce 50% paralysis, did not differ between groups. The authors conclude that during comparable nitrous oxide–halothane anesthesia, neonates and infants have an increased sensitivity to *d*Tc, as determined by $Cp_{ss(50)}$. However, because of the larger Vd_{ss} in younger patients, dose size should not differ with age. In addition, because of the longer $t_{\beta 1/2}$ in neonates, second and subsequent doses should be required at less frequent intervals. (Key words: Anesthesia: pediatric. Neuromuscular relaxants: *d*-tubocurarine. Pharmacokinetics. Potency, anesthetic: age factors.)

DESPITE MANY STUDIES, the response of infants and children to *d* Tc remains unsettled. Several investigators have found neonates[1–3] and children[4] to be more sensitive to *d* Tc compared to adults. However, Goudsouzian *et al.*[5] determined cumulative dose-response curves, and concluded that neonates and children are more resistant to *d* Tc than adults. In contrast, several investigators[6–8] have concluded that there is no difference in the sensitivity of infants, children, or adults to *d* Tc.

Many of these conflicting results can be explained by methodologic differences between studies, including anesthetic depth and measurement techniques. In addition, all but one of these studies have used the dose-response relationship to estimate neuromuscular junction sensitivity to *d* Tc. As a result, these investigators have not separated pharmacokinetic from pharmacodynamic effects. Thus, to examine age-related changes in the *d* Tc dose-response relationship, we studied neonates, infants, children, and adults, using simultaneous modeling of pharmacokinetics and pharmacodynamics of *d* Tc during comparable nitrous oxide–halothane anesthesia.

Methods

Thirty-one patients, ASA I and II, who were scheduled for elective non-urologic surgery, were studied after obtaining approval from our Committee on Human Research and informed consent. The patients were divided into four groups by age: neonates, one day through two months; infants, two months through one year; children, one through 12 years; adults, 12–30 years. No patient had any disease or was receiving any drugs known to alter neuromuscular function. During surgery patients received 5% dextrose in lactated Ringer's solution at 5–15 $ml \cdot kg^{-1} \cdot h^{-1}$ and no blood products. Intraoperative blood loss was less than 10 ml/kg.

Anesthesia was induced with nitrous oxide and halothane, and the trachea was intubated without the aid of muscle relaxants. Anesthesia was maintained with an end-tidal halothane concentration equivalent to 0.58 MAC (0.45–0.63%), adjusted for age[9] and 70% nitrous oxide. Ventilation was controlled to maintain end-tidal P_{CO_2} at 30 to 44 mmHg. Nasopharyngeal temperature was monitored and maintained at 35.3°C to 37.5°C.

After induction of anesthesia, the ulnar nerve was stimulated with a Grass S-44® stimulator through 27-gauge needle electrodes inserted at the wrist. Single supramaximal square wave stimuli of 0.15-ms duration were administered at 0.15 Hz. The electromyographic (EMG) response was monitored through an active electrode over the adductor pollicis muscle, with reference and ground electrodes placed elsewhere on the hand. This device records a compound muscle action potential

* Research Fellow in Anesthesia.

† Assistant Professor of Anesthesia and Medicine (Clinical Pharmacology).

‡ Assistant Professor of Anesthesia.

§ Professor, Anesthesia and Pharmacology.

¶ Professor, Anesthesia and Pediatrics.

Received from The Department of Anesthesia, University of California, San Francisco Medical Center, San Francisco, California, and the Department of Anesthesia, Stanford University Medical Center, Palo Alto, California. Received for publication February 12, 1982. Supported in part by NIH Grant GM 24603, and the Anesthesia Pharmacology Research Foundation. Dr. Fisher is the recipient of a National Research Service Award. Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, October 1981. Awarded third prize in the 1981 American Society of Anesthesiologists Resident Research Contest.

Address reprint requests to Dr. Fisher: Department of Anesthesia, C-225, University of California, San Francisco Medical Center, San Francisco, California 94143.

0003-3022/82/0900/0203 $01.10

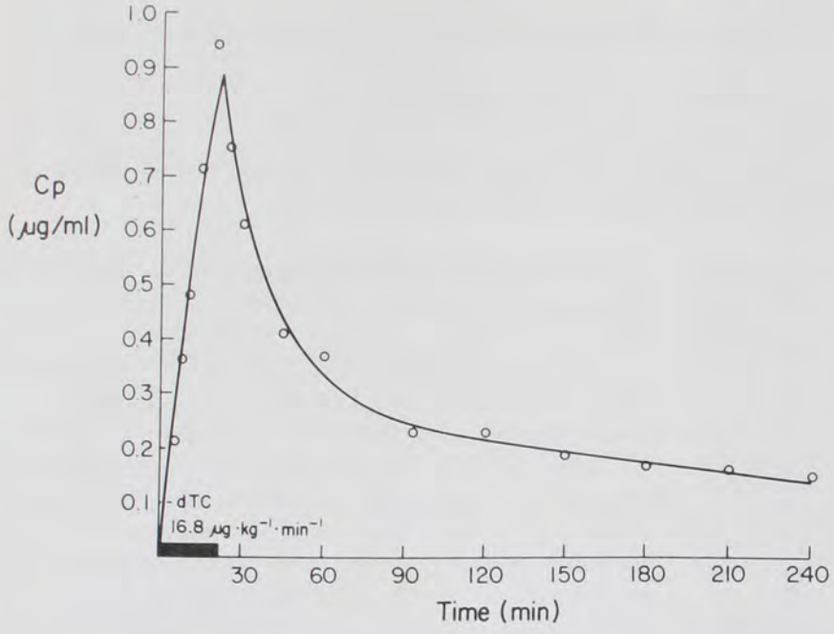

FIG. 1. Pharmacokinetic data from a 12-week-old patient. *d*Tc was administered by infusion during the first 22 min. Circles represent measured *d*Tc concentrations; the solid line represents the fitted function as determined by nonlinear regression.

during a 16-ms interval, beginning 2.5 ms after the stimulus is applied. This time interval eliminates stimulus artifact. Through an analog-to-digital conversion and digital memory storage techniques,[10] the EMG is slowed by a factor of 80, enabling transcription on a recorder at a paper speed of 5 mm/min.

*d*Tc was then administered by continuous infusion at approximately 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$. When 70–90% depression of the EMG twitch height was achieved, the infusion was terminated and no further *d*Tc was administered. Blood samples, 0.5 ml each, were obtained from a separate venous catheter at 2- to 3-min intervals during the infusion, 5- to 10-min intervals for 30 min after the infusion, and at 30-min intervals for the remainder of a 4-h sampling period. At the termination of the procedure, nitrous oxide and halothane were discontinued and the appropriate antagonist drugs administered.

*d*Tc concentrations were determined by radioimmunoassay.[11] This assay is sensitive to 0.05 μg/ml, and has a coefficient of variation of 8%. The plasma *d*Tc concentration-time curve for each patient was then fitted to a two-compartment, first-order pharmacokinetic model using a nonlinear, least-squares regression.[12] A two-compartment, rather than three-compartment model was selected, since Stanski *et al.*[13] have demonstrated that there is no statistical advantage to the addition of a third pharmacokinetic compartment to characterize the *d*Tc con-

TABLE 1. Pharmacokinetic and Pharmacodynamic Values (Mean ± SD)

	Pharmacokinetic Values						Pharmacodynamic Values			
Patient Group	N	$t_{\alpha 1/2}$ (min)	$t_{\beta 1/2}$ (min)	V_1 (l/kg)	Vd_{ss} (l/kg)	Cl ($mg \cdot kg^{-1} \cdot min^{-1}$)	N	$t_{1/2k_{eo}}$ (min)	$Cp_{ss(50)}$ (μg/ml)	D_{50} (μg/kg)
Neonates	7	4.1 ± 2.2	174 ± 60	0.19 ± .13	0.74 ± .33	3.7 ± 2.1	5	6.3 ± 3.5	0.18 ± .09	155 ± 126
Infants	7	7.0 ± 4.0	130 ± 54	0.16 ± .07	0.52 ± .22	3.3 ± 0.4	6	7.5 ± 3.5	0.27 ± .06	158 ± 82
Children	9	6.7 ± 2.4	90 ± 23	0.14 ± .05	0.41 ± .12	4.0 ± 1.1	9	7.9 ± 2.7	0.42 ± .14	163 ± 54
Adults	8	7.9 ± 4.1	89 ± 18	0.11 ± .02	0.30 ± .10	3.0 ± 0.8	7	6.8 ± 1.9	0.53 ± .14	152 ± 57
Significance ($P < 0.05$)		NS	*	NS	†	NS		NS	‡	NS

See text for explanation of symbols; NS = not significant.
* $t_{\beta 1/2}$: Neonates > children and adults.
† Vd_{ss}: Neonates > infants, children, and adults.
‡ $Cp_{ss(50)}$: Neonates and infants < children and adults.

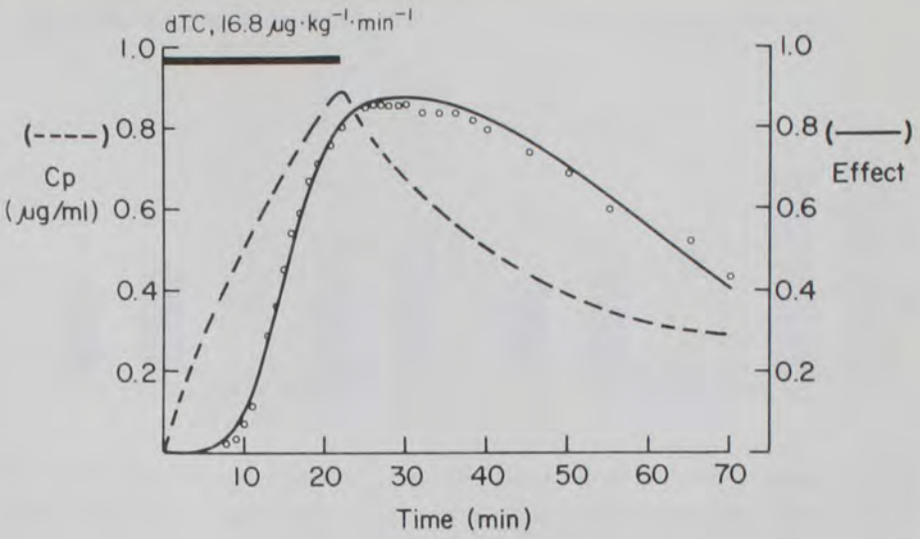

FIG. 2. Pharmacodynamic data from the same 12-week-old patient as in figure 1. *d*Tc was administered by infusion during the first 22 min. Circles represent measured EMG depression; the solid line represents the fitted pharmacodynamic function as determined by nonlinear regression. The dashed line represents the kinetic function displayed in figure 1.

centration-time relationship during a 4-h sampling period. Using standard formulas,[14] we determined: $t_{\alpha 1/2}$, the apparent distribution half-life; $t_{\beta 1/2}$, the apparent elimination half-life; V_1, the volume of the central compartment; Vd_{ss}, the volume of distribution at steady state; and Cl, the total plasma clearance.

The paralysis data were then fitted to the estimates of the kinetic parameters using a pharmacodynamic model developed by Sheiner *et al.*[15] A third, "effect" compartment was added to the kinetic model. Through selection of a small first-order input rate constant, this compartment receives a negligible mass of drug and does not alter the overall kinetics. Plasma drug concentration was related to effect through the Hill equation, which characterizes the sigmoidal relationship between concentration and paralysis. This allows estimation of $Cp_{ss(50)}$, the steady-state plasma concentration that results in 50% depression of neuromuscular function (a measure of neuromuscular junction sensitivity), and $t_{1/2}k_{eo}$, the half-time for equilibration between neuromuscular junction and plasma (a reflection of neuromuscular junction perfusion). We also determined D_{50}, the product of Vd_{ss} and $Cp_{ss(50)}$. D_{50} is the total drug present at steady-state at 50% paralysis.

Mean values of pharmacokinetic and pharmacodynamic data for the four age groups were compared by analysis of variance and Student-Neuman-Keuls test.[16] A $P < 0.05$ was considered to be statistically significant.

Results

There was excellent agreement between the measured plasma concentrations and those predicted with the two-compartment model. This is demonstrated by the plasma concentration-time curve displayed in figure 1. Pharmacokinetic and pharmacodynamic data for the four age groups are displayed in table 1. $t_{\alpha 1/2}$ did not differ between groups. $t_{\beta 1/2}$ was greater in neonates than in children or adults. V_1 did not differ between groups. Vd_{ss} was greater in neonates than in the other groups. Cl did not differ between groups. $t_{\beta 1/2}$, V_1, Vd_{ss}, and Cl were more variable in younger patients than in adults.

Pharmacodynamic data were available for 27 of 31 patients; for the remaining four patients, the EMG recording device failed. The pharmacodynamic model was able to characterize the plasma concentration-paralysis relationship for these 27 patients. Data from a representative patient are shown in figure 2; changes in effect lagged several minutes behind the increase and decrease of *d*Tc concentration. $Cp_{ss(50)}$ was lower in neonates and infants compared to children and adults. $Cp_{ss(50)}$ did not differ between neonates and infants or between children and adults. $t_{1/2}k_{eo}$ did not differ between groups. D_{50} did not differ between groups, but was more variable in younger patients.

Discussion

Changes in body composition and organ function occur with maturation and produce variations in pharmacokinetic and pharmacodynamic responses to drug administration. *d*Tc, because it is an ionized molecule, remains in the plasma and extracellular fluid (ECF).[17] ECF varies with age,[18] decreasing from 44% of body weight in the newborn to 23% of body weight of the adult. Although apparent volumes of distribution do not correspond to true body compartments, these marked changes in ECF would be expected to be reflected in distribution volumes. Thus, our finding of *d*Tc Vd_{ss} differing between neonates and older patients is expected: changes in ECF are mirrored by differences in distribution volume (fig. 3).

Sensitivity at the neuromuscular junction may also differ with age. By measuring muscle action potentials of unanesthetized infants, Koenigsberger *et al.*[19] found

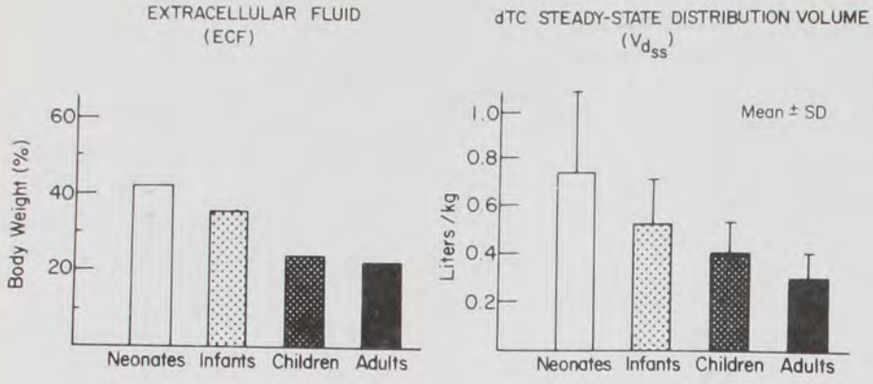

FIG. 3. Known values for extracellular fluid (ECF)[18] are compared to values for *d*Tc Vd_{ss} (steady-state distribution volume) obtained in this study. Changes in ECF are mirrored by differences in distribution volume.

that premature infants showed posttetanic exhaustion at 20 Hz, and term infants at 50 Hz. Adults, in contrast, do not demonstrate exhaustion at either stimulation rate. Crumrine *et al.*[20] found with frequency sweep EMGs, that high frequency exhaustion of neuromuscular transmission occurs in infants in the presence of nitrous oxide and methohexital. Based on these studies, we expected increased sensitivity to nondepolarizing relaxants in neonates. This is consistent with our finding of a lower $Cp_{ss(50)}$ in neonates compared to children and adults. Age-related changes in protein binding or other factors independent of receptor sensitivity may further contribute to differences in the plasma concentration required to produce neuromuscular blockade.

Although these age-related changes in distribution volume and neuromuscular junction sensitivity are important, they do not answer the clinical question of *d*Tc dose requirements in children. The larger Vd_{ss} in neonates results in increased dose requirements to achieve comparable plasma concentrations. However, in neonates and infants, neuromuscular blockade is achieved at a lower plasma concentration. To determine the combined effects of these differences, we have calculated D_{50}, the product of Vd_{ss} and $Cp_{ss(50)}$. D_{50} is the total drug present in the body at steady-state at 50% paralysis.

In this study, we have not determined traditional dose-response curves. Instead, using D_{50}, we are able to compare dose requirements of patients of different ages. D_{50} was similar in the four age groups indicating that dose requirements of neonates, infants, children, and adults should not differ. However, D_{50} was highly variable in neonates, ranging from 70 to 350 μg/kg. This variability suggests that, in neonates, *d*Tc should be given in small incremental doses until the desired effect is achieved. A large predetermined dose may result in excessive and prolonged neuromuscular blockade.

For many drugs, elimination kinetics and clearance differ between children and adults.[21] The magnitude of this difference will depend upon the route of elimination, the maturity of the specific elimination pathway, and the distribution volume. We found a prolonged elimination half-life for *d*Tc in neonates compared to older children. Clearance, however, did not change with age. Therefore, the prolonged half-life resulted from the larger distribution volume because less drug is available for excretion. When clearance is recalculated by surface area, the difference between age-groups can be seen to resemble known age-related changes in glomerular filtration[22] (fig. 4). This supports the belief that *d*Tc is eliminated by glomerular filtration.[17]

Recovery from neuromuscular blockade occurs as *d*Tc is eliminated from the neuromuscular junction and the plasma.[13] Shanks *et al.*[23] have demonstrated an inverse relationship between half-life and the rate of neuromuscular recovery. Our results demonstrate that *d*Tc clearance ($ml \cdot kg^{-1} \cdot min^{-1}$) is similar in all age groups. However, because of the neonate's larger distribution volume, a smaller percentage of total drug is eliminated during each minute; this is expressed through the longer elimination half-life. This longer elimination half-life results in a slower rate of recovery from neuromuscular blockade in newborns. Therefore, if neonates are given repeated doses of *d*Tc at the same intervals as adults, neuromuscular blockade may be prolonged. Second, and subsequent, *d*Tc doses should be given only when indicated by recovery of neuromuscular function.

Several investigators have compared the effects of relaxants in infants, children, and adults. Three early studies, Stead,[1] Bush *et al.*,[2] and Lim *et al.*,[4] suggested that newborns and children are more sensitive to *d*Tc compared to adults but no objective measure of neuromuscular function was used. Walts *et al.*[3] gave 4 mg/m^2 *d*Tc to neonates and adults anesthetized with nitrous oxide and halothane, 0.5–1.5%. Twitch depression was greater in newborns than adults; therefore, they concluded that neonates are more sensitive to *d*Tc compared to adults when doses are calculated by surface area. However, Walts *et al.* recalculated their dosage requirements by patient weight, and concluded that there was no difference in *d*Tc sensitivity between neonates and adults. This conclusion is consistent with our findings.

Churchill-Davidson *et al.*[6] measured the EMG re-

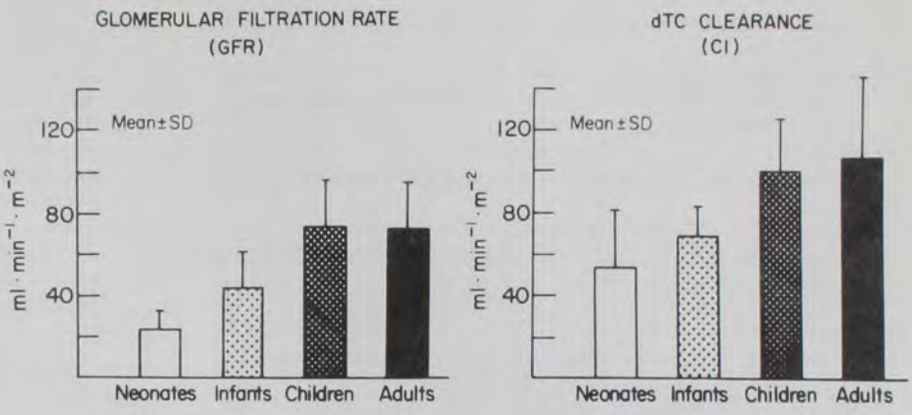

FIG. 4. Known values for glomerular filtration (adapted from reference 20) are compared to values for *d*Tc Cl (total plasma clearance) obtained in this study. Cl values in this figure are expressed in $ml \cdot min^{-1} \cdot m^{-2}$. *d*Tc Cl values in table 1 are expressed in $ml \cdot kg^{-1} \cdot min^{-1}$.

sponse in children anesthetized with cyclopropane and found that the dose of *d*Tc required to produce paralysis of the hypothenar muscles was similar for neonates and adults. Long *et al.*[7] measured EMG following single doses of 0.22 mg/kg *d*Tc in patients anesthetized with nitrous oxide and halothane. Maximal depression of EMG did not differ between age groups, and recovery proceeded more slowly in younger patients. These conclusions are similar to our findings of no age-related difference in D_{50}, and a prolonged elimination half-life in neonates. We have supplemented the findings of Long *et al.* by examining the contribution of pharmacokinetics and pharmacodynamics to these age-related changes.

Goudsouzian *et al.*[5] measured twitch height during nitrous oxide–halothane anesthesia. Incremental doses of *d*Tc, 0.025 to 0.1 mg/kg, were given until 95 to 99% depression of twitch height occurred, and dose requirements and recovery times were calculated. ED_{50} was similar in four pediatric age groups, consistent with our finding of no difference in D_{50} between neonates, infants, and children. Goudsouzian *et al.* then concluded that children are resistant to *d*Tc compared to adults. They based their conclusion on adult values obtained in other institutions under noncomparable anesthetic conditions. In addition, no statistical analysis was applied to this conclusion.

Goudsouzian *et al.* found that the rate of twitch recovery was more rapid in children than adults. However, recovery times in children were calculated following cumulative doses (CDR) and compared to recovery following single doses in adults. CDR has been demonstrated[24] as a valid technique to determine ED_{50}. However, recovery times may differ after single versus cumulative doses. In addition, recovery times in children were compared to recovery times in adults under different anesthetic conditions.

Matteo *et al.*[8] measured *d*Tc levels during recovery from neuromuscular blockade during nitrous oxide and halothane anesthesia. They found no difference between adults, children, infants, and three of five neonates in the plasma *d*Tc concentration that resulted in any degree of neuromuscular blockade. The remaining two neonates required *d*Tc concentrations far in excess of the other patients to achieve comparable paralysis. These results are in marked contrast to our finding of $Cp_{ss(50)}$ increasing with age. This may be explained by the effect of halothane in altering the intensity of neuromuscular blockade produced by any concentration of *d*Tc.[13] Matteo *et al.* did not report the halothane concentrations used intraoperatively. We maintained anesthesia in all our subjects with comparable concentrations of halothane (0.58 MAC, adjusted for age), in addition to 70% nitrous oxide.

In summary, we found age-related differences in the response to *d*Tc at equal anesthetic depths of nitrous oxide and halothane. When sensitivity to *d*Tc is determined by $Cp_{ss(50)}$, neonates and infants display increased sensitivity to *d*Tc as compared to adults. However, in younger patients, the drug is distributed to a larger volume resulting in lower plasma concentrations with equivalent doses. As a result, dose requirements do not differ with age. In neonates, the elimination half-life is longer than in older patients; therefore, second and subsequent doses will be required at less frequent intervals.

References

1. Stead AL: The response of the newborn infant to muscle relaxants. Br J Anaesth 27:124–130, 1955
2. Bush GH, Stead AL: The use of *d*-tubocurarine in neonatal anaesthesia. Br J Anaesth 34:721–728, 1962
3. Walts LF, Dillon JB: The response of newborns to succinylcholine and *d*-tubocurarine. ANESTHESIOLOGY 31:35–38, 1969
4. Lim HS, Davenport HT, Robson JG: The response of infants and children to muscle relaxants. ANESTHESIOLOGY 25:161–168, 1964
5. Goudsouzian N, Donlon JV, Savarese JJ, Ryan JF: Reevaluation of dosage and duration of *d*-tubocurarine in the pediatric age group. ANESTHESIOLOGY 43:416–425, 1975
6. Churchill-Davidson HC, Wise RP: The response of the newborn infant to muscle relaxants. Can Anaesth Soc J 11:1–5, 1964
7. Long G, Bachman L: Neuromuscular blockade by *d*-tubocurarine in children. ANESTHESIOLOGY 28:723–729, 1967
8. Matteo RS, Lieberman IG, Salanitre E, Diaz J: *d*-Tubocurarine concentration and neuromuscular blockade in the neonate. ANESTHESIOLOGY 53:S281, 1980
9. Gregory GA, Eger EI, Munson ES: The relationship between age

and halothane requirement in man. ANESTHESIOLOGY 30:488–491, 1969
10. Lee C, Katz RL, Lee ASJ, Glaser B: A new instrument for continuous recording of the evoked compound electromyogram in the clinical setting. Anesth Analg (Cleve) 56:260–270, 1977
11. Horowitz PE, Spector S: Determination of serum *d*-tubocurarine concentration by radioimmunoassay. J Pharmacol Exp Ther 185:94–100, 1973
12. Metzler CM: NONLIN. Kalamazoo, The Upjohn Co., 1969
13. Stanski DR, Ham J, Miller RD, Sheiner LB: Pharmacokinetics and pharmacodynamics of *d*Tc during nitrous oxide–narcotic and halothane anesthesia in man. ANESTHESIOLOGY 51:235–241, 1979
14. Gibaldi M, Perrier D: Pharmacokinetics. New York, Dekker, 1975, pp 48–55, 66–69, 72–74, 175–180
15. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to *d*-tubocurarine. Clin Pharmacol Ther 25:358–371, 1979
16. Zar J: Biostatistical Analysis. Englewood Cliffs, Prentice-Hall, 1974, pp 130–137, 151–155
17. Crankshaw DP, Cohen EN: Uptake, distribution and elimination of skeletal muscle relaxants, Muscle Relaxants. Edited by Katz RL. New York, American Elsevier, 1975, pp 125–141
18. Friis-Hansen B: Body composition during growth. Pediatrics 47:264–274, 1971
19. Koenigsberger MR, Patten B, Lovelace RE: Studies of neuromuscular function in the newborn. 1. A comparison of myoneural function in the full term and the premature infant. Neuropaediatrie 4:350–361, 1973
20. Crumrine RS, Yodlowski EH: Assessment of neuromuscular function in infants. ANESTHESIOLOGY 54:29–32, 1981
21. Morselli P, Franco-Morselli R, Bossi L: Clinical pharmacokinetics in newborns and infants. Clin Pharmacokinet 5:485–527, 1980
22. Chantler C: Evaluation of laboratory and other methods of measuring renal function, Clinical Pediatric Nephrology. Edited by Lieberman E. Philadelphia, JB Lippincott, 1976, p 515
23. Shanks CA, Somogyi AA, Triggs EJ: Dose-response and plasma concentration response relationships of pancuronium in man. ANESTHESIOLOGY 51:111–118, 1979
24. Donlon JV, Savarese JJ, Ali HH, Teplik RS: Human dose-response curves for neuromuscular blocking drugs: a comparison of two methods of construction and analysis. ANESTHESIOLOGY 53:161–166, 1980