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

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The pharmacokinetics and pharmacodynamics of d-tubocurarine (dTc) 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, 0.38 MAC halothane anesthesia. dTc was administered by infusion, while blood for determination of plasma dTc concentrations was obtained, and the EMG of the adductor pollicis recorded. The plasma dTc concentration at which 50% depression of EMG twitch height occurs (Cp50(EMG)) 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 (Vdss) 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 (t1/2b) 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 D50, the product of Vdss and Cp50(EMG). D50, 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 dTc, as determined by Cp50(EMG). However, because of the larger Vdss in younger patients, dose size should not differ with age. In addition, because of the longer t1/2b 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 dTc remains unsettled. Several investigators have found neonates1-3 and children4 to be more sensitive to dTc compared to adults. However, Gould souxian et al.5 determined cumulative dose-response curves, and concluded that neonates and children are more resistant to dTc than adults. In contrast, several investigators6-8 have concluded that there is no difference in the sensitivity of infants, children, or adults to dTc.

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 dTc. As a result, these investigators have not separated pharmacokinetic from pharmacodynamic effects. Thus, to examine age-related changes in the dTc dose-response relationship, we studied neonates, infants, children, and adults, using simultaneous modeling of pharmacokinetics and pharmacodynamics of dTc during comparable nitrous oxide-halothane anesthesia.

Methods

Thirty-one patients, ASA I and II, who were scheduled for elective non-urolologic 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·kg⁻¹·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 age9 and 70% nitrous oxide. Ventilation was controlled to maintain end-tidal Pco₂ 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.

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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.


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0003-0322/82/0900/0203 $01.10 © The American Society of Anesthesiologists, Inc.

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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, 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. This assay is sensitive to 0.05 mg/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. A two-compartment, rather than three-compartment model was selected, since Stanski et al. have demonstrated that there is no statistical advantage to the addition of a third pharmacokinetic compartment to characterize the $d'Tc$ concentration-time curve for each patient.

![Graph showing 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.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931445/)

### Table 1. Pharmacokinetic and Pharmacodynamic Values (Mean ± SD)

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>N</th>
<th>$t_1/2$ (min)</th>
<th>$t_{90}/2$ (min)</th>
<th>$V_{1}$ (l/kg)</th>
<th>$V_{2}$ (l/kg)</th>
<th>$Cl$ (mg·kg⁻¹·min⁻¹)</th>
<th>$t_{1/2}$ (min)</th>
<th>$C_{P_{max}}$ (μg/ml)</th>
<th>$D_{90}$ (μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>7</td>
<td>4.1 ± 2.2</td>
<td>174 ± 60</td>
<td>0.19 ± 0.13</td>
<td>0.74 ± 0.33</td>
<td>3.7 ± 2.1</td>
<td>5.3 ± 3.5</td>
<td>0.18 ± 0.09</td>
<td>155 ± 126</td>
</tr>
<tr>
<td>Infants</td>
<td>7</td>
<td>7.0 ± 4.0</td>
<td>130 ± 54</td>
<td>0.16 ± 0.07</td>
<td>0.52 ± 0.22</td>
<td>3.3 ± 0.4</td>
<td>6.5 ± 3.5</td>
<td>0.27 ± 0.06</td>
<td>158 ± 82</td>
</tr>
<tr>
<td>Children</td>
<td>9</td>
<td>6.7 ± 2.4</td>
<td>90 ± 23</td>
<td>0.14 ± 0.05</td>
<td>0.41 ± 0.12</td>
<td>4.0 ± 1.1</td>
<td>7.9 ± 2.7</td>
<td>0.42 ± 0.14</td>
<td>163 ± 54</td>
</tr>
<tr>
<td>Adults</td>
<td>8</td>
<td>7.9 ± 4.1</td>
<td>89 ± 18</td>
<td>0.11 ± 0.02</td>
<td>0.30 ± 0.10</td>
<td>3.0 ± 0.8</td>
<td>6.8 ± 1.9</td>
<td>0.53 ± 0.14</td>
<td>152 ± 57</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tbody>
</table>

See text for explanation of symbols; NS = not significant.

* $t_{90}/2$: Neonates > children and adults.

† $V_{2}$: Neonates > infants, children, and adults.

‡ $C_{P_{max}}$: Neonates and infants < children and adults.
concentration–time relationship during a 4-h sampling period. Using standard formulas, we determined: \( t_{1/2 \text{a}} \), the apparent distribution half-life; \( t_{1/2 \text{c}} \), the apparent elimination half-life; \( V_1 \), the volume of the central compartment; \( V_{\text{ss}} \), 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. 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 \( C_{\text{p}50} \), the steady-state plasma concentration that results in 50% depression of neuromuscular function (a measure of neuromuscular junction sensitivity), and \( t_{1/2k_{\text{eo}}} \), the half-time for equilibration between neuromuscular junction and plasma (a reflection of neuromuscular junction perfusion). We also determined \( D_{50} \), the product of \( V_{\text{ss}} \) and \( C_{\text{p}50} \). \( D_{50} \) 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. 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. \( t_{1/2 \text{a}} \) did not differ between groups. \( t_{1/2 \text{c}} \) was greater in neonates than in children or adults. \( V_1 \) did not differ between groups. \( V_{\text{ss}} \) was greater in neonates than in the other groups. \( Cl \) did not differ between groups. \( t_{1/2 \text{c}} \), \( V_1 \), \( V_{\text{ss}} \), 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 \( d \text{Tc} \) concentration. \( C_{\text{p}50} \) was lower in neonates and infants compared to children and adults. \( C_{\text{p}50} \) did not differ between neonates and infants or between children and adults. \( t_{1/2k_{\text{eo}}} \) 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. \( d \text{Tc} \), because it is an ionized molecule, remains in the plasma and extracellular fluid (ECF). ECF varies with age, 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 \( d \text{Tc} \) \( V_{\text{ss}} \) 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. found
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 $C_{P_{50}}$ 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 $dTc$ dose requirements in children. The larger $V_{ds}$ 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 $V_{ds}$ and $C_{P_{50}}$. $D_{50}$ 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, $dTc$ 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 $dTc$ 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 This supports the belief that $dTc$ is eliminated by glomerular filtration.17

Recovery from neuromuscular blockade occurs as $dTc$ 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 $dTc$ clearance (ml·kg$^{-1}$·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 $dTc$ at the same intervals as adults, neuromuscular blockade may be prolonged. Second, and subsequent, $dTc$ 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 $dTc$ compared to adults but no objective measure of neuromuscular function was used. Waits et al.3 gave 4 mg/m$^2$ $dTc$ 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 $dTc$ compared to adults when doses are calculated by surface area. However, Waits et al. recalculated their dosage requirements by patient weight, and concluded that there was no difference in $dTc$ sensitivity between neonates and adults. This conclusion is consistent with our findings.

Churchill-Davidson et al.6 measured the EMG re-
response in children anesthetized with cyclopropane and found that the dose of 9Tc required to produce paralysis of the hypothenar muscles was similar for neonates and adults. Long et al. measured EMG following single doses of 0.22 mg/kg 9Tc 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 D50, 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. measured twitch height during nitrous oxide-halothane anesthesia. Incremental doses of 9Tc, 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. E50 was similar in four pediatric age groups, consistent with our finding of no difference in D50 between neonates, infants, and children. Goudsouzian et al. then concluded that children are resistant to 9Tc 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 as a valid technique to determine E50. 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. measured 9Tc 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 9Tc concentration that resulted in any degree of neuromuscular blockade. The remaining two neonates required 9Tc concentrations far in excess of the other patients to achieve comparable paralysis. These results are in marked contrast to our finding of Cp50 increasing with age. This may be explained by the effect of halothane in altering the intensity of neuromuscular blockade produced by any concentration of 9Tc. 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 9Tc at equal anesthetic depths of nitrous oxide and halothane. When sensitivity to 9Tc is determined by Cp50, neonates and infants display increased sensitivity to 9Tc 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

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