Pharmacokinetics and Pharmacodynamics of d-Tubocurarine during Hypothermia in the Cat

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To determine the effects of hypothermia on the pharmacokinetics and pharmacodynamics of d-tubocurarine (dTc), serum, biliary, and urinary concentrations were determined and twitch tension monitored following intravenous administration of dTc, 0.7 mg/kg, at 39 (n = 5), 34 (n = 5), and 28°C (n = 6) in cats anesthetized with chloralose and urethane. Time from injection of dTc to maximum neuromuscular blockade was prolonged by hypothermia (28°C). Similarly, moderate (28°C) but not mild (34°C) hypothermia delayed recovery from paralysis. The serum half-life was prolonged 76 per cent and the serum clearance rate decreased 60 per cent by hypothermia (28°C). The combined biliary and urinary elimination of dTc was decreased 47 per cent at 28°C compared with 34 and 39°C. The serum concentration of dTc necessary for neuromuscular blockade was less at 39°C (ED₅₀, 0.87 µg/ml) than at 34 or 28°C (ED₅₀, 1.15 µg/ml). It is concluded that, in vivo, hypothermia antagonizes a dTc-induced neuromuscular blockade but decreases the elimination of dTc. At 28°C the net effect is a prolongation of neuromuscular blockade. (Key words: Neuromuscular relaxants: d-tubocurarine, pharmacokinetics. Hypothermia.)

In 1951, Holmes et al.¹ found a 100 per cent increase in the d-tubocurarine (dTc) concentration necessary in the bath of rat phrenic nerve-diaphragm preparations to produce 50 per cent depression of twitch tension when temperature was lowered from 38 to 25°C. In 1958, Bigland et al.² found that hypothermia decreased the magnitude but not the duration of dTc-induced neuromuscular blockade in the cooled extremity of the cat or dog. In 1959, Cannard and Zaimis³ found similar results in the cooled extremity of man. In contrast, we found that less dTc or pancuronium was necessary by continuous infusion to maintain 90 per cent depression of twitch tension at 28°C compared with either 37 or 41°C in the cat in vivo.⁴ We suggested that decreased biliary and renal elimination may account for this finding. Therefore we examined simultaneously the effects of hypothermia on the pharmacodynamics and pharmacokinetics of dTc.

Methods

Sixteen cats weighing 2.2 to 4 kg were anesthetized with chloralose, 60 mg/kg, and urethane, 250 mg/kg, intraperitoneally. A tracheostomy was performed and ventilation controlled to maintain arterial carbon dioxide partial pressure (Paco₂) between 30 and 40 torr. A carotid artery was cannulated for blood pressure monitoring and sampling. An internal jugular vein was cannulated for fluid and drug administration. Bile was collected from a choledochojstomy after ligation of the common bile duct at the duodenum. Urine was collected from a bladder catheter. The tibialis anterior tendon was isolated, sectioned near its insertion, and secured to a Grass FT 03 force transducer. Supramaximal stimuli at 0.2 Hz were applied for 0.2 msec to the peroneal nerve through shielded platinum electrodes. Isometric twitch tension and arterial blood pressure were recorded on a polygraph.

The distal esophageal temperature was changed approximately 4 degrees C/hr by external warming or cooling and isometric twitch tension was monitored during this period. Temperature of the muscle monitored with Yellow Springs probes was kept within 0.5 degrees C of distal esophageal temperature throughout the study. Six cats were studied at 28°C, five at 34°C, three at 39°C, and two at 40°C. All the animals studied at 39 and 40°C were combined into one group called 39°C since there was no difference in the results. The study temperature was maintained for the duration of the experiment.

When the desired temperature had been constant for 15 to 30 min, dTc (Squibb), 0.7 mg/kg, was administered as a rapid intravenous bolus. Serum dTc concentrations were determined at 3, 15, 30, and 60 min and then every hour for eight hours by radioimmunoassay.⁵ Biliary and urinary dTc concentrations were determined every two hours for eight hours. Physiologic saline solution was administered at 4 ml/kg/hr. All blood withdrawn was replaced by three

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volumes of physiologic saline solution. Arterial blood pH was maintained between 7.32 to 7.45 units and base excess from -6 to +2 mEq/l by controlling ventilation or infusing sodium bicarbonate.

The twitch tension records were analyzed for the following variables: time from injection of $d$Tc to maximum neuromuscular blockade and times from injection of $d$Tc to the beginning of recovery and 25, 50, 75, and 100 per cent recovery of control twitch tension. The results were tested by analysis of variance and the Newman-Keuls multiple-range test.7

Serum $d$Tc measurements were analyzed using the pharmacokinetic model independent parameters of total body-clearance, steady-state volume of distribution, and terminal phase half-life.8 Clearance was calculated as dose divided by the area under the serum concentration time curve (AUC). The steady-state volume of distribution was calculated using the model independent method recently described by Benet and Galeazzi:*

\[ V_{d_{ss}} = \text{dose} \times (\text{AUMC})/(\text{AUC})^2 \]

where $V_{d_{ss}}$ is the steady-state volume of distribution, AUMC is the area under the curve of the first moment of the concentration time curve, i.e., $\int_{0}^{\infty} t \cdot Cdt$, and AUC. The terminal half-life ($t_{1/2n}$) of the serum concentration time curve was determined from the three-to-eight-hour serum measurements. In addition to these three model independent parameters, the data from each cat were fitted to a two-compartment body model so as to determine the fast disposition half-life ($t_{d_{ss}}$), which is generally considered to describe the distribution phase.8 The derived values


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** Fig. 1. Times (sec) from the intravenous injection of $d$Tc, 0.7 mg/kg, to peak neuromuscular blockade in cats at 28 ($n = 6$), 34 ($n = 5$), and 39 C ($n = 5$). Each symbol represents the mean ± SE. The * indicates statistical significance ($P < .05$) of the difference of the value at 28 C compared with either 34 or 39 C.

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** Fig. 2. Times (min) from the intravenous injection of $d$Tc, 0.7 mg/kg, to 25, 50, 75, and 100 per cent recovery of twitch tension in cats at 28 ($n = 6$), 34 ($n = 5$), and 39 C ($n = 5$). Each symbol represents the mean ± SE. The * indicates statistical significance ($P < .05$) of the difference of the value at 28 C compared with either 34 or 39 C.
Results

The time from injection of \( dTc \) to peak neuromuscular blockade was longer at 28°C than at 34 or 39°C (fig. 1). Similarly, the times from injection of \( dTc \) to 75 and 100 per cent recovery of twitch tension were longer at 28°C (fig. 2). The time value at 34°C was no different from that at 39°C.

Hypothermia retarded the serum elimination of \( dTc \) (fig. 3). Thus, serum \( dTc \) levels varied inversely with body temperature. During hypothermia, the elimination phase half-life \( (t_{1/2b}) \) increased and the serum clearance rate decreased (table 1). The distributive phase half-life \( (t_{1/2a}) \) was not significantly altered by changes in temperature. Hypothermia tended to decrease the steady-state volume of distribution, but the differences were not significant (table 1).

A lower serum concentration of \( dTc \) was necessary for blockade at 39°C than at 28 or 34°C (fig. 4). The regression at 28°C was not different from that at 34°C.

The serum concentrations at which 50 per cent depression of twitch tension from control occurred \( (ED_{50}) \) were 0.87 \( \mu \)g/ml at 39°C, 1.13 \( \mu \)g/ml at 34°C, and 1.12 \( \mu \)g/ml at 28°C.

The cumulative biliary excretion of \( dTc \) was less at 34°C and 28°C than at 39°C (table 2). The cumulative urinary excretion of \( dTc \) was no different at 34 and 39°C but was less at 28°C (table 3). The combined cumulative biliary and urinary \( dTc \) excretion was not different at 39 and 34°C but was less at 28°C (fig. 5).

Discussion

The results of this study suggest that hypothermia diminishes neuromuscular blockade. This is evidenced by the higher serum concentration of \( dTc \) necessary for neuromuscular blockade at 28 and 34°C compared with 39°C (fig. 4). Hypothermia simultaneously decreases the serum clearance and elimination of \( dTc \) (fig. 3). The net result of these opposing effects favors

Table 1. Pharmacokinetic Parameters (Mean ± SE)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>( t_{1/2a}^* ) (min)</th>
<th>( t_{1/2b}^* ) (hr)</th>
<th>Steady-state Volume of Distribution (ml/kg)</th>
<th>Serum Clearance Rate (ml/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>6.7 ± 0.5</td>
<td>3.28 ± 0.35‡</td>
<td>376.6 ± 29.5</td>
<td>95.6 ± 11.3‡</td>
</tr>
<tr>
<td>34</td>
<td>7.7 ± 1.2</td>
<td>2.44 ± 0.13‡</td>
<td>396.6 ± 17.6</td>
<td>137.5 ± 8.4‡</td>
</tr>
<tr>
<td>39</td>
<td>7.2 ± 1.4</td>
<td>1.86 ± 0.21‡</td>
<td>483.1 ± 68.8</td>
<td>243.6 ± 16.6‡</td>
</tr>
</tbody>
</table>

* Half-life distributive phase (alpha). ‡ Half-life elimination phase (beta). † \( P < .02 \), all groups.
prolongation of dTc-induced neuromuscular blockade at 28 °C (Fig. 2). At 34 °C the effects may balance, since the duration of neuromuscular blockade was not significantly longer than at 39 °C. Indeed, we found no significant difference in the rates of infusion required to maintain 90 per cent depression of twitch tension in cats at 37 and 41 °C suggesting a similar balancing of effects.4

Several mechanisms may explain the decreased sensitivity of the neuromuscular junction to dTc during hypothermia. These include decreased acetylcholinesterase activity,11,12 depolarization of the postjunctional membrane without a change in threshold voltage,13,14 an increase in readily releasable transmitter from the nerve terminal,15 increased sensitivity of the postjunctional membrane to transmitter,16,17 and changes in the mechanical contractile response.16,18 A recent clinical study has shown that neuromuscular function in patients with myasthenia gravis improves during cooling of involved muscles.20 Our finding of increased dTc concentrations necessary for neuromuscular blockade during hypothermia confirms the decreased potency of dTc during hypothermia but does not establish a mechanism.

The pharmacokinetics of dTc during hypothermia have not been described previously. We found a direct relationship between temperature and serum clearance of dTc. Conversely, after redistribution, the serum dTc levels are significantly higher at lower temperatures. The half-life of the elimination phase increased 76 per cent at 28 °C, compared with 39 °C. This may be related to the effects of temperature on hemodynamics, as well as renal and hepatic function. With cooling there is a decrease in cardiac output and a redistribution of blood away from the extremities, kidneys, liver, and intestinal tract to the cerebral and coronary circulations.21–23

Hypothermia (37 to 25 °C) decreases biliary excretion of several drugs, including atropine, procaine, and sulfanilamide, 50–70 per cent in the rat.24–27 This may be secondary to diminished hepatic blood flow, decreased bile formation, or depressed microsomal function. It was not surprising, then, to find that in this study hypothermia decreased biliary excretion of dTc by 79 per cent, on the average, in the range from 39 to 28 °C.

During hypothermia (37 to 25 °C), glomerular filtration rate (GFR) is decreased 65 per cent in the dog.28 In the normothermic dog 75 per cent of dTc is eliminated in the urine by glomerular filtration.29 We found a 39 per cent decrease in urinary dTc elimination from 34 to 28 °C; however, there was no difference between urinary excretion at 39 and 34 °C. Total combined biliary and urinary dTc elimination was decreased at 28 °C compared with 34 and 39 °C by 47 per cent two hours after dTc administration and 28 per cent eight hours after dTc. This does not account for the entire decrease in serum clearance of 60 per cent.

### Table 2. Cumulative Biliary Excretion of dTc

<table>
<thead>
<tr>
<th>Time after Injection (Hours)</th>
<th>Cumulative Percentage of dTc in Bile (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 °C</td>
</tr>
<tr>
<td>2</td>
<td>0.91 ± 0.63</td>
</tr>
<tr>
<td>4</td>
<td>1.51 ± 0.82</td>
</tr>
<tr>
<td>6</td>
<td>2.95 ± 1.02</td>
</tr>
<tr>
<td>8</td>
<td>4.81 ± 1.52</td>
</tr>
</tbody>
</table>

* P < .05, 34 < 39, 28 < 39 °C.

### Table 3. Cumulative Urinary Excretion of dTc

<table>
<thead>
<tr>
<th>Time after Injection (Hours)</th>
<th>Cumulative Percentage of dTc in Urine (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 °C</td>
</tr>
<tr>
<td>2</td>
<td>15.3 ± 3.1*</td>
</tr>
<tr>
<td>4</td>
<td>25.8 ± 4.8*</td>
</tr>
<tr>
<td>6</td>
<td>32.5 ± 5.3*</td>
</tr>
<tr>
<td>8</td>
<td>44.6 ± 7.7</td>
</tr>
</tbody>
</table>

* P < .05, 28 < 34, 28 < 39 °C.
cent by hypothermia. Although the difference may be due to tissue sequestration, we cannot explain it on the basis of the results of our study.

In addition, there is a trend for the urinary and total $d$Tc elimination to be greater at the two-hour sampling time at 39 C compared with 34 C (table 2 and fig. 5). Had samples been collected at earlier times, this difference might have been significant.

If our results can be extrapolated to man, then the extent of clinical hypothermia will determine the resultant effect on neuromuscular blockade. At mild levels of hypothermia (to 34 C), no prolongation of neuromuscular blockade is expected from standard doses of $d$Tc. At moderate levels of hypothermia (to 28 C), prolongation of $d$Tc-induced neuromuscular blockade may result and, when repeated doses are needed, the interval between subsequent doses should be increased.

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