Pharmacokinetics and Dynamics of d-Tubocurarine during Hypothermia in Humans

Jay Ham, M.D.,* Donald R. Stanski, M.D.,† Philippa Newfield, M.D.,‡ Ronald D. Miller, M.D.§

To determine the influence of hypothermia on the pharmacokinetics and dynamics of d-tubocurarine (dTc), 17 patients were studied during halothane 0.5–0.7 per cent end-tidal and 60 per cent nitrous oxide anesthesia with controlled hyperventilation (Paco2 ~ 25 torr) during craniotomy. Ten patients were deliberately cooled to an esophageal temperature of 31.9 ± 0.3°C (mean ± SE) and a hypothalamic muscle temperature of 31.8 ± 0.3°C while seven patients had an esophageal temperature maintained at 35.8 ± 0.1°C and a hypothalamic muscle temperature of 36.7 ± 0.2°C. Hypothermia did not affect the pharmacokinetics of dTc. Using 75 per cent to 25 per cent recovery times, dTc neuromuscular blockade was prolonged in the hypothermic patients by 82 per cent, compared with the normothermic patients, as measured by twitch tension of the thumb adductors, but was unchanged as measured by the compound electromyogram (EMG). The steady state serum concentration necessary to produce 50 per cent paralysis (IC50(50)), was not significantly different during hypothermia (0.46 ± 0.07 μg/ml) relative to normothermia (0.57 ± 0.07 μg/ml). The half-life for equilibrium between serum dTc concentration and paralysis (t1/2 K(tw)) was 0.06× (P = 0.06) but was not significantly different during hypothermia (9.2 ± 1.2 min) versus normothermia (5.4 ± 0.7 min). However, four of the nine patients in the hypothermic group had a marked prolongation (>10 min) of this value. This suggests that hypothermia reduces blood flow to the neuromuscular junction, delaying onset of paralysis after administration of dTc. Other than a delayed half-time for equilibrium and differential effect on EMG vs. twitch tension, we conclude that a decrease in body temperature to 31.9°C does not significantly alter the pharmacokinetics and pharmacodynamics of d-tubocurarine. (Key words: Hypothermia. Neuromuscular relaxants: d-tubocurarine. Pharmacokinetics: kinetics. Pharmacology: pharmacodynamics.)

TOTAL BODY HYPOTHERMIA prolongs neuromuscular blockade induced by d-tubocurarine (dTc) and pancuronium in the cat, apparently because of decreased renal and biliary clearance. These findings have not been confirmed in humans. Yet during clinical anesthesia, hypothermia is deliberately employed for cardiac and neurosurgical procedures and frequently occurs inadvertently from body exposure to the cold operating room environment. The authors, therefore, determined the effect of hypothermia on the pharmacokinetics (distribution and elimination) and pharmacodynamics (neuromuscular junction sensitivity and rate of serum concentration-paralysis equilibration) of dTc in patients undergoing neurosurgical procedures.

Methods

Seventeen patients were studied after obtaining informed consent for protocols approved by our Committee on Human Research. The hypothermic group consisted of ten patients undergoing craniotomy for aneurysm, arteriovenous malformation, or tumor. For surgical indications, hypothermia was induced by reduction of the environmental temperature and using cooling blankets. The normothermic group consisted of seven patients also undergoing craniotomy for tumor whose body temperatures were maintained close to normal. All patients were ambulatory and did not possess chronic sequella of central nervous system pathology. Three patients in each group were administered phenytoin on a continuous basis prior to surgery, while two patients in the hypothermic group received epsilon aminocaproic acid.

Both groups received either no premedication or 5–10 mg diazepam, per os. Anesthesia was induced with iv thiopental, diazepam, and fentanyl during controlled hyperventilation with oxygen. Table 1 details patient characteristics and drug doses used to induce anesthesia. The trachea was intubated following intravenous administration of 1–1.5 mg/kg succinylcholine. Subsequently, anesthesia was maintained with halothane 0.5–0.7 per cent end-tidal (on-line mass spectrophotometer) and 60 per cent nitrous oxide during hypocapnic controlled ventilation (Paco2 ~ 25 torr). All patients received 20 mg decadron and 100 g mannitol intravenously after induction of anesthesia.

A Grass® S-44 nerve stimulator was used to administer supramaximal square-wave bipolar pulses of 0.1 ms duration at 0.15 Hz to the ulnar nerve at the wrist through thin wall needle electrodes. The resultant force of thumb adduction was quantitated with a Grass FT 10 force transducer and recorded on a polygraph. In addition, by means of two surface electrodes on the thenar muscles and an indifferent electrode on a finger, the compound electromyogram (EMG) was recorded on a polygraph using instrumentation described by Lee et al.

Neuromuscular blockade was monitored during the

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Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (Years)</th>
<th>Weight (Kg)</th>
<th>Diazepam (Mg)</th>
<th>Thiopental (Mg)</th>
<th>Fentanyl (Mg)</th>
<th>PaCO₂ (torr)</th>
<th>pH</th>
<th>Distal Esophagus (°C)</th>
<th>Thernar Muscle (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermic</td>
<td>45 ± 5</td>
<td>62 ± 5</td>
<td>14 ± 2</td>
<td>598 ± 64</td>
<td>275 ± 40</td>
<td>23 ± 1*</td>
<td>7.54 ± 0.02</td>
<td>31.9 ± 0.3*</td>
<td>31.8 ± 0.3*</td>
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<td>(N = 10)</td>
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<tr>
<td>Normothermic</td>
<td>44 ± 6</td>
<td>67 ± 8</td>
<td>14 ± 3</td>
<td>621 ± 82</td>
<td>195 ± 30</td>
<td>28 ± 1</td>
<td>7.49 ± 0.02</td>
<td>35.8 ± 0.1</td>
<td>36.9 ± 0.2</td>
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<td>(N = 7)</td>
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</table>

Values are means ± SE.

* P < 0.05, hypothermic vs normothermic.

cooling phase of the hypothermic patients. Any changes in response were noticed and the baseline was readjusted at the hypothermic temperature just prior to beginning the dTc infusion. The temperature was monitored with a YSI 401 esophageal temperature probe in the distal esophagus and a YSI 514-22 gauge needle temperature probe inserted into the hypotheran muscles of the hand being monitored for neuromuscular blockade.

In both groups, after the desired temperature had been obtained, an intravenous infusion of dTc was administered at a rate of 16.8 μg·kg⁻¹·min⁻¹ by a Harvard® pump until 80–90 per cent mechanical (twitch) neuromuscular blockade was established. The infusion was then terminated and spontaneous recovery of neuromuscular function observed. Arterial blood samples were obtained every minute during the dTc infusion, and at the following times after termination of the infusion: 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 80, 120, 150, 180, and 240 min. Serum samples were analyzed for dTc concentrations using a radioimmunoassay. Sensitivity of the assay was 0.05 μg/ml and the coefficient of variation was 8 per cent at three different concentrations.

The serum concentration curves obtained for individual patients were fit to a biexponential equation, interpreted as a two-compartment mammillary model, using nonlinear least-squares regression analysis. The following pharmacokinetic parameters were derived for each patient: distribution half-life (t₁/₂a); elimination half-life (t₁/₂b); volume of the central compartment (V₁); volume of distribution at steady state (Vdss); and total serum clearance (Cl).

The estimates of pharmacokinetic parameters were used to fit their individual effect (paralysis) data to a pharmacodynamic model. This model characterizes the sensitivity and temporal components of the serum concentration–paralysis relationship. The sensitivity component measures the steady-state serum concentration that would result in 50 per cent paralysis (Cps(50)). If the plasma concentration and paralysis data are gathered when a steady state is not present, there occurs a dysequilibrium between the concentration of drug in serum and the site of action, resulting in a concentration–paralysis dysequilibrium. The pharmacodynamic model that has been developed models and adjusts for the temporal concentration–paralysis dysequilibrium and allows one to calculate what would occur if a steady state were present. In addition, the model allows estimation of the half time for equilibration between the serum concentration and paralysis (t₁/₂ Keo) which is determined mainly by muscle perfusion. It was possible to obtain pharmacodynamic estimates on only nine of the ten hypothermic patients. In one patient, complete paralysis from the dTc infusion persisted for a prolonged period of time, preventing pharmacodynamic analysis. Spontaneous recovery of neuromuscular function was measured by mechanical (twitch) and electrical (EMG) activity. The rate of spontaneous recovery was defined by recovery time from 75 to 25 per cent of neuromuscular blockade.

The nonparametric two-tailed Mann-Whitney U test was used to compare the normothermic and hypothermic

Table 2. Pharmacokinetic and Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>t₁/₂a (min)</th>
<th>t₁/₂b (min)</th>
<th>V₁ (ml/kg)</th>
<th>Vdss (ml/kg)</th>
<th>Cl (ml·kg⁻¹·min⁻¹)</th>
<th>Cps(50)* (μg/ml)</th>
<th>t₁/₂ Keo* (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermic</td>
<td>4.3 ± 0.4</td>
<td>85 ± 8</td>
<td>61 ± 5</td>
<td>236 ± 13</td>
<td>2.5 ± 0.3</td>
<td>0.46 ± 0.07</td>
<td>9.2 ± 1.2</td>
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<td>(N = 10)</td>
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<tr>
<td>Normothermic</td>
<td>4.4 ± 0.2</td>
<td>76 ± 6</td>
<td>79 ± 9</td>
<td>292 ± 36</td>
<td>3.8 ± 0.8</td>
<td>0.57 ± 0.07</td>
<td>5.4 ± 0.7</td>
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<td>(N = 7)</td>
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Values are means ± SE.

* N = 9.
groups. A value of $P < 0.05$ was considered statistically significant.

**Results**

The two groups of patients were similar in age, weight, and induction drug dosage (table 1). The hypothermic group had a significantly lower $P_{aCO_2}$ and higher $pH$. The hypothermic group had a significantly lower esophageal and hand muscle temperature relative to the normothermic group. The muscle temperature in the hypothermic group was $0.1 \pm 0.1^\circ C$ (mean $\pm$ SEM) less than the esophageal value, whereas it was $0.9 \pm 0.2^\circ C$ more than the esophageal value in the normothermic group.

During the initial cooling phase in the hypothermic group, the changes in twitch or EMG were relatively unpredictable. Two patients had no changes in twitch or EMG response. Three patients had changes in the EMG between $35^\circ - 32^\circ C$, decreasing 34 per cent in one and increasing 22–36 per cent in the other two. Seven patients had changes in the twitch response: three showed decreases of 6–36 per cent, two showed increases of 12–20 per cent, and two had a biphasic response in opposite directions at approximately $32^\circ - 33^\circ C$.

Hypothermia did not affect the pharmacokinetics of $dTc$ (table 2). Sensitivity of the neuromuscular junction, as measured by the $Cpss(50)$ of our pharmacodynamic model, was not affected by hypothermia (fig. 1). The $Cpss(50)$ of the hypothermic group was $0.46 \pm 0.07 \, \mu g/ml$ and $0.57 \pm 0.07 \, \mu g/ml$ for the normothermic group. The mean value for $t_{1/2} \, Keo$, the measure of the half-time for equilibration between the serum concentration and paralysis, was greater ($9.2 \pm 1.2$ min) in the hypothermic group than in the normothermic group ($5.4 \pm 0.7$ min). This difference approached ($P = 0.06$) but was not statistically significant, due mainly to the greater variability in the hypothermic group (range = 3.1 to 15.1 min) relative to the normothermic group (range = 3.5 to 7.7 min) (fig. 2). Four of the nine hypothermic patients had long half-times of serum concentration-paralysis equilibration (10.5, 11.9, 12.7, and 15.1 min).

**Fig. 1.** The $Cpss(50)$ (\mu g/ml) or sensitivity of the neuromuscular junction as determined by the pharmacodynamic model. The solid line represents the mean and the dashed line the standard error.

**Fig. 2.** The $t_{1/2} \, Keo$ (min) or half-time for equilibration of the serum concentration and paralysis as determined by the pharmacodynamic model. The solid line represents the mean and the dashed line the standard error.
Spontaneous recovery of neuromuscular function was similar for electrical activity (EMG) in the normothermic and hypothermic groups, but prolonged in the hypothermic group for mechanical activity (twitch) (fig. 3). The spontaneous recovery of twitch tension from 75 to 25 per cent neuromuscular blockade increased from 23.2 ± 5.4 min at 35.8 °C to 42.1 ± 5.2 min at 31.9 °C.

One patient in the hypothermic group (who could not be characterized pharmacodynamically) had a very slow spontaneous rate of recovery of neuromuscular function at 32 °C. Attempts to antagonize neuromuscular blockade with neostigmine totaling 5 mg were unsuccessful. Train-of-four stimulus revealed a ratio of 41 per cent and there was immediate, profound fade to 100 Hz tetanic stimulation. After operation, the patient required controlled ventilation for over an hour until the body temperature had increased to 34 °C and train-of-four and tetanic stimuli produced normal responses.

Discussion

In both humans and cats,2 hypothermia prolongs the neuromuscular blockade of dTc. However, the pharmacokinetic and pharmacodynamic mechanisms differ. In the human, hypothermia did not affect the pharmacokinetic variables. In the cat, however, hypothermia markedly changed drug clearance; thus, for a given dose of dTc, the rate of decline of the serum concentration was slower throughout the terminal elimination phase and caused a slower rate of recovery of paralysis. This mechanistic difference might be explained by a smaller temperature difference in this study (i.e., 35.8 °C versus 31.9 °C, Δ = 3.9 °C), compared with the cat study (39 °C versus 28 °C, Δ = 11 °C). This represents a difference in temperature extremes of 2.8-fold between the cat and human studies. In cats, the serum dTc clearance decreased from 4.1 ml·kg⁻¹·min⁻¹ at 39 °C to 1.6 ml·kg⁻¹·min⁻¹ at 28 °C, a 61 per cent decrease.2 Had the temperature values been more extreme in this study, the differences in clearance values might have been statistically significant.

The prolonged t½ Keo in the hypothermic group approached, but did not reach statistical significance due to a larger variability relative to the normothermic group (fig. 2). More importantly, four of nine patients had a marked prolongation of this value, up to 112 per cent greater than the mean time in the normothermic group. Since the onset of paralysis is governed by muscle perfusion, the markedly prolonged t½ Keo suggests a decrease of muscle blood flow. A similar phenomenon was seen when the pharmacodynamics of dTc during nitrous oxide-narcotic versus halothane anesthesia were compared.6 Clinically, a prolonged t½ Keo will be manifested by a delayed onset of paralysis. An anesthesiologist administering dTc to hypothermic patients may erroneously interpret delayed onset as relative insensitivity to dTc and administer additional doses. This may result in overdosage.

In contrast to the previous cat study, no change was found in the neuromuscular junction sensitivity to dTc during hypothermia, as measured by the Cooper(50) of the pharmacodynamic model. This, again, may be due to the more extreme change in temperature in the cat study. The mean ± SE Coop(50) of the normothermic group (0.57 ± 0.07 μg/ml) was larger and more variable than that obtained in a previous study7 at a similar temperature (0.36 ± 0.02 μg/ml) undergoing ENT or GU surgical procedures and normocapnia. This may be due to a difference in patient population, the presence of hyperventilation and the concurrent drug therapy (anti-convulsants, steroids, mannitol) present in this study.

In previous studies of dTc and panceuronium during hypothermia, neuromuscular blockade has been monitored using the mechanical twitch response alone. The monitoring of both the mechanical twitch response and electrical (EMG) response simultaneously in this study revealed a possible new factor in understanding the effect of hypothermia on the neuromuscular unit (fig. 3). That mechanical recovery of neuromuscular blockade is prolonged by hypothermia and electrical recovery is not, suggests that neuromuscular transmission per se is not significantly affected by hypothermia, at least within the design of this study. That hypothermia may affect the mechanical properties of muscle itself has been demonstrated previously.10,11 This point is emphasized by the
one patient in the hypothermic group who had marked prolongation of $dTc$ neuromuscular block which could not be fully antagonized by neostigmine and necessitated mechanical ventilation after operation until body temperature returned toward normal.

In conclusion, hypothermia in man does not affect $dTc$ pharmacokinetics or the sensitivity of the neuromuscular junction of $dTc$. It did, however, markedly prolong, in some hypothermic patients, the rate at which the serum concentration and paralysis equilibrated. Clinically, this will manifest by a marked delay in the onset of paralysis which could be misinterpreted as a decreased sensitivity to $dTc$. We recommend that under conditions of hypothermia, neuromuscular blockade be monitored with a peripheral nerve stimulator and that a longer time interval than usual be utilized between the initial administration and subsequent $dTc$ dose to avoid overdosage.

References


