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The Pharmacokinetics of d-Tubocurarine with Surgery Involving Salvaged Autologous Blood

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The disposition of *d*-tubocurarine (*d*Tc) was assessed when a bolus and infusion dosage regimen was used to obtain relaxation during major orthopedic surgery on the spine. Renal clearance of *d*Tc was 0.63 ± 0.23 ml·min^{-1}·kg^{-1} and was correlated with creatinine clearance. Total plasma clearance of 1.21 ± 0.40 ml·min·$^{-1}$·kg^{-1} was lower than that found in many previous studies, and the predetermined continuous *d*Tc infusion produced an apparent plateau in plasma concentrations of 1.8 ± 0.3 μg·ml^{-1}. Despite the operative blood loss, these concentrations were greater than anticipated and were associated with a more intense neuromuscular blockade than the infusion was designed to produce. Autologous blood transfusion was used to reduce the reliance on homologous donor blood, and the erythrocytes from the 2.2 ± 1.2 l of blood loss during the procedure were reinfused after intraoperative salvage, washing, and centrifugation. With 80 ± 23 mg *d*Tc administered, 1.4 ± 0.8% was recovered from the fluid discarded after centrifugation. These results indicate that even massive intraoperative blood loss will not entail a significant reduction in the amount of *d*Tc present in the body. (Key words: Neuromuscular relaxants: tubocurarine. Pharmacokinetics: tubocurarine. Transfusion: autologous.)

EACH BLOOD TRANSFUSION carries a certain risk, and reinfusion of the patient's own blood has advantages over the use of homologous donor blood. Although autologous blood transfusion is an old technique, recent technologic developments have suggested that it could be cost-effective for use in orthopedic surgery.[1] The Cell Saver® (Hemonetics, Braintree, Massachusetts) is a device that salvages blood removed by suction from the operative field, then filters, washes, and concentrates it to provide packed cells for return to the patient. When a drug does not enter erythrocytes, all the drug in the blood is carried in the plasma; plasma loss then would be equivalent to blood loss in decreasing the amount of drug in the patient, despite the reinfusion of washed red blood cells. As most of the plasma lost during surgery is included in the fluid discarded after centrifugation in the Cell Saver®, its use provides the opportunity to quantitate drug removal with intraoperative blood loss.

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This study was designed to examine the disposition of *d*-tubocurarine administered by a bolus and infusion technique[2] to a group of patients likely to lose blood during major orthopedic surgery.

Methods

SUBJECTS

The 10 adult patients studied were undergoing surgery for Luque subsegmental instrumentation of their scoliosis. Written informed consent was obtained according to the institutionally approved protocol. Demographics of the patient group are shown in table 1.

CONDUCT OF THE STUDY

Following premedication with morphine, 5–10 mg im, an intravenous infusion of 5% dextrose in lactated Ringer's solution was begun, to provide preoperative hemodilution. Fluids were administered at a rate of 15 ml·kg^{-1} in the first hour, and hemodilution was assessed by a reduction in hemoglobin concentration and colloid osmotic pressure (table 1). A radial artery catheter was placed before induction of anesthesia for later measurement of blood pressure, blood gases, and blood sampling. Anesthesia was induced with thiopental and maintained with enflurane in oxygen, supplemented with either nitrous oxide or fentanyl.

Sustained muscular relaxation was provided by a pharmacokinetically designed regimen for *d*-tubocurarine (*d*Tc), intended to produce 95% paralysis.[2] The "steady state" plasma concentration (C_{SS}) of *d*Tc associated with 95% paralysis can be calculated to average between 1.0 and 1.2 mg·l^{-1} by pharmacodynamic modeling.[3,4] A bolus of *d*Tc, 0.6 mg·kg^{-1}, administered simultaneously with commencement of an infusion at 0.18 mg·kg^{-1}·h^{-1} should be associated with a plateau of 1.1 mg·l^{-1} in the *d*Tc plasma concentrations.[2] Given the high therapeutic index of *d*Tc and its small volume of distribution, this regimen was able to be obtained from the apparent volume of distribution at steady state (V_{SS}) and the plasma elimination clearance (Cl_E), as described by Mitenko and Ogilvie[5]:

$$\text{Bolus dose} = V_{SS} \times C_{SS} \quad (1)$$

$$\text{Infusion rate} = Cl_E \times C_{SS} \quad (2)$$

TABLE 1. Clinical Details of the Patients (Mean ± SD)

Sex	2 M, 8 F
Age (yr)	37 ± 17
Wt (kg)	63 ± 15
Hemoglobin ($g \cdot dl^{-1}$)	12.8 ± 2.4
Colloid osmotic pressure ($mOsm \cdot l^{-1}$)	16.0 ± 3.2
Intraoperatively:	
Operation time (h)	4.4 ± 1.0
Minimum hemoglobin ($g \cdot dl^{-1}$)	10.0 ± 1.6
Minimum colloid osmotic pressure ($mOsm \cdot l^{-1}$)	11.6 ± 1.4
Intravenous crystalloid (l)	6.5 ± 2.6
Measured blood loss (l)	2.2 ± 1.2
Salvaged packed cells returned (l)	0.8 ± 0.3

Neuromuscular blockade was assessed at the hand by measuring the ratio of the fourth to the first twitch amplitudes resulting from four supramaximal stimuli delivered to the ulnar nerve at 2 Hz (train-of-four stimulation).

Plasma samples were obtained from the arterial blood taken at appropriate intervals until 12 h after the infusion was discontinued. Urine samples were collected, volumes were recorded, and aliquots were saved at half hourly intervals during the infusion, with further collections in the remainder of the intraoperative period, and for 24 h postoperatively. Following the final centrifugation of blood in the Cell Saver,® the volume of extracted fluid was measured and an aliquot was taken.

Assay Procedures

The Cell Saver® fluid, the urine, and blood samples were stored at −30° C for later *d*Tc analysis. Total concentrations of *d*Tc were determined in duplicate by a specific high-performance liquid chromatographic technique sensitive to 25 $ng \cdot ml^{-1}$ (coefficient of variation: less than 5% above 50 $ng \cdot ml^{-1}$).[6] Plasma and urine creatinine concentrations were assayed by using a modified Jaffé reaction.[7]

Data Analysis

Pharmacokinetic analyses were made with the SAAM 23 computer program¶ implemented on a Control Data Corporation Cyber 170/730® computer. Tubocurarine distribution and elimination kinetics were modeled with a three-compartment open mammillary system with elimination from the central compartment. The three-compartment structure of this model reflects the heterogeneity of interstitial fluid space.[8] The nonlinear least-squares regression program was used to characterize the disposition of *d*Tc, simultaneously modeling data from plasma, urine, and Cell Saver® fluid, to derive estimates of the apparent volume of distribution of the central compartment (V_C), the intercompartmental rate constants, and the elimination rate constant. These were used to calculate[9] the volumes of the fast and slow compartments (V_F and V_S in fig. 1), their intercompartmental clearances (Cl_F and Cl_S), and the elimination clearance (Cl_E), using the general equation for clearance (Cl), volume (V), and its associated rate constant (k):

$$Cl = k_{ij}V_i = k_{ji}V_j \quad (3)$$

The volume of distribution at steady state (V_{SS}) is the sum of V_C, V_F and V_S.

Renal clearance (Cl_R) of *d*Tc was determined from the ratio of the urinary excretion rate of unchanged drug to the simultaneous plasma concentration at the midpoint of the collection period:

$$Cl_R = \frac{\text{urine flow} \times \text{urine concentration}}{\text{plasma concentration}} \quad (4)$$

The three-compartment model was modified as shown in figure 1 by using the time-interrupt feature of the SAAM program to include the Cell Saver® clearance (Cl_{CS}), derived from plasma *d*Tc concentration and *d*Tc recovered from the centrifuged fluid, as previously described for calculating dialytic clearance.[10]

Postoperative creatinine clearances were calculated from the 24-h urine collections. Estimates of the 24-h renal clearances of creatinine were correlated by linear least-squares regression analysis with estimates of the renal clearance of *d*Tc obtained from the model.

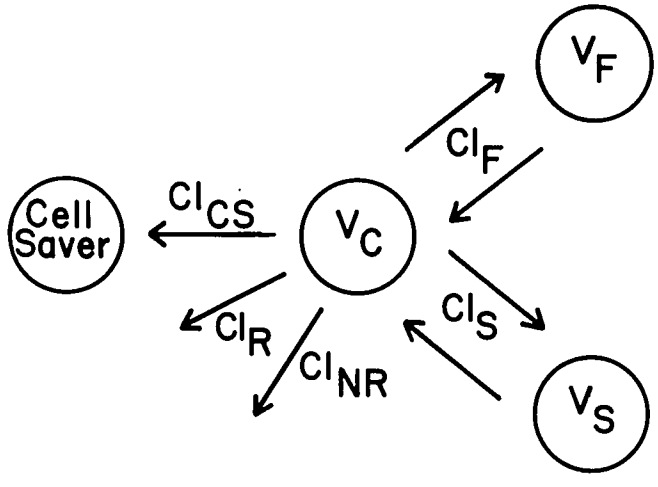

FIG. 1. The multicompartmental model used to characterize the disposition of *d*Tc. Drug in the central compartment (V_C) redistributes into the fast volume (V_F) and slow volume (V_S) peripheral compartments at rates dictated by the intercompartmental clearances (Cl_F and Cl_S). Plasma elimination clearance comprised renal clearance (Cl_R) and nonrenal clearance (Cl_{NR}). Clearance via the Cell Saver® (Cl_{CS}) was not included in nonrenal clearance.

¶ Berman M, Weiss MF: SAAM Manual (Public Health Service Publication No. 1703). Washington, D. C., U. S. Government Printing Office, 1967.

Results

Intravenous infusion of crystalloids prior to major blood loss produced hemodilution in the patients with the hemoglobin concentration decreasing to as low as 8 $g \cdot dl^{-1}$ and colloid osmotic pressures to 10 $mOsm \cdot l^{-1}$ (table 1). Measured blood loss ranged from 1.0 to 4.8 l, with most lost in the latter part of the procedure, following extensive dissection of the thoracolumbar vertebrae and the iliac donor site. Almost all of this was collected by suction, washed, and returned to the patient as packed cells as it accumulated: previous studies suggest a red blood cell harvest of 52–54%.[1] Homologous donor blood was not used in the intraoperative care of four patients, of the remainder, only one then received more than one unit of donor blood.

A typical *d*Tc plasma concentration–time curve is shown in figure 2. The initial dose of *d*Tc, 0.6 $mg \cdot kg^{-1}$, provided conditions suitable for tracheal intubation in all but one subject. The *d*Tc infusion maintained good relaxation throughout its 2.8 to 6.0 h of infusion. The *d*Tc plasma concentrations at the end of its infusion was 1.8 ± 0.3 $mg \cdot l^{-1}$, a level in excess of the expected 1.1 $mg \cdot l^{-1}$, the plasma concentration associated with 95% paralysis.[2–4] During *d*Tc infusion, the twitch response was absent in all but one of the patients. The decision to discontinue *d*Tc administration during the concluding

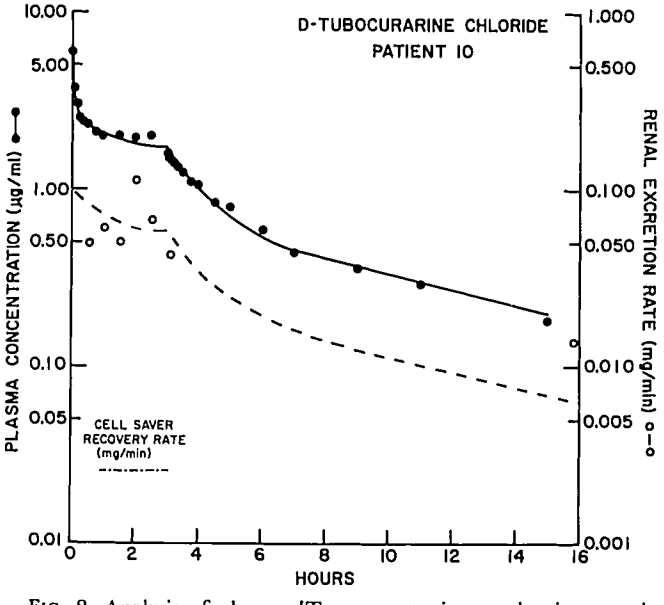

FIG. 2. Analysis of plasma *d*Tc concentrations and urinary and Cell Saver® elimination in patient 10, whose *d*Tc infusion was continued for 3 h. The curves represent two computer-generated least-squares fits of the experimental data and the Cell Saver,® elimination rate during its operation. All the plasma, Cell Saver®, and urinary data were modeled simultaneously. The urine datum point at 16 h represents the midpoint of the postoperative 24 h urine collection begun at the fourth hour, the end of surgery. The lowermost line (Cell Saver® recovery rate) indicates the duration of blood salvage, and its single value is referenced to the right-hand ordinate scale.

TABLE 2. Tubocurarine Dosages and Recovery

Total dose (mg)	80 ± 23
Infusion time (h)	3.8 ± 1.0
Amount discarded from Cell Saver®	
mg	1.2 ± 0.8
% dose	1.4 ± 0.8
Amount recovered intraoperatively from urine	
mg	13.6 ± 7.9
% dose	15.3 ± 5.9
Total amount recovered from urine intraoperatively and 24 h postoperatively	
mg	44.7 ± 16.8
% dose	54.0 ± 17.0

stages of surgery was timed by the intensity of paralysis. Neuromuscular blockade therefore could be reversed easily in all patients to permit early postoperative assessment of cord function. The *d*Tc infusion and the use of the Cell Saver® were completed at approximately the same time. The average amount of *d*Tc recovered from the discarded cell-washing fluid represents 1.4 ± 0.8% of the dose administered (table 2), an order of magnitude less than that recovered intraoperatively from the urine. The amount of *d*Tc recovered in the urine intraoperatively and for the subsequent 24 h averaged 15% and 37% of the dose, respectively, to total 54 ± 17% recovery.

The pharmacokinetic parameters shown in table 3 were derived when plasma, Cell Saver,® and urinary data were fitted simultaneously. The apparent volume of distribution at steady state (V_{SS}) was 587 ± 114 $ml \cdot kg^{-1}$, of which 9% was the central volume. When the mean V_{SS} is substituted in equation (1), the calculated bolus dose of *d*Tc increases from 0.6 $mg \cdot kg^{-1}$ to 0.65 $mg \cdot kg^{-1}$. The plasma clearance (Cl_E) of 75 ± 26 $ml \cdot min^{-1}$ was the summation of renal and nonrenal clearances in approximately equal proportions. On a weight basis, Cl_E is 1.22 ± 0.40 $ml \cdot kg^{-1} \cdot min^{-1}$; substituted in equation (2) for a C_{SS} of 1.1 $mg \cdot l^{-1}$, the calculated infusion rate decreases from 0.18 $mg \cdot kg^{-1} \cdot h^{-1}$ to 0.08 $mg \cdot kg^{-1} \cdot h^{-1}$. Were the actual infusion to have continued, this clearance would have been associated with a C_{SS} of 2.5 $mg \cdot l^{-1}$, confirming that the plateau value of 1.8 ± 0.3 $mg \cdot l^{-1}$ was not a true steady state.

With the plasma concentration–time data fitted to the model in figure 1, the time-averaged plasma renal clearance for the study period was 0.63 ± 0.23 $ml \cdot min^{-1} \cdot kg^{-1}$. The regression line relating the (24 h) creatinine clearances with the plasma renal clearances shown in table 3 is $Cl_{R(dTc)} = 0.32\ Cl_{Cr} + 0.08$, with r = 0.90 (fig. 3).

When red blood cell partitioning was measured for five subjects, in the range 50–5000 $ng \cdot ml^{-1}$, 14 ± 7% of the *d*Tc was in erythrocytes.

TABLE 3. The Disposition of Tubocurarine* in 10 Patients

Pt. no.	Wt. (kg)	Distribution Volumes (ml·kg^{-1})				Clearances (ml·min^{-1})						Elimination Half-life, (h)
		V_C	V_F	V_S	V_{SS}	Cl_F	Cl_S	Cl_R	Cl_{NR}	Cl_E	Cl_{CS}	
1	95	38	120	508	666	812	98	62	49	111	6.3	7.90
2	55	38	140	300	478	465	92	44	37	81	5.7	5.25
3	60	89	130	268	487	594	128	64	48	112	8.5	3.99
4	47	43	188	220	451	437	23	14	35	49	1.7	5.81
5	51	33	191	598	822	386	62	37	20	57	5.0	11.00
6	65	28	93	396	517	412	88	29	25	54	6.3	9.97
7	69	43	116	474	633	548	139	23	15	38	2.8	15.40
8	57	88	188	392	668	507	46	41	56	97	1.5	6.56
9	80	40	105	460	605	715	90	49	33	82	13.9	10.74
10	55	71	127	345	543	729	59	34	39	73	1.3	7.47
Mean ± SD	63 ± 15	51 ± 23	140 ± 36	396 ± 117	587 ± 114	560 ± 148	83 ± 36	40 ± 16	36 ± 13	75 ± 26	5.3 ± 3.9	8.41 ± 3.40

* Shown schematically in figure 1, the volumes of the central, fast, and slow compartments (V_C, V_F, and V_S) summate to give the apparent volume of distribution at steady state (V_{SS}). Multiplication with the appropriate rate constant gives the clearance to the fast and slow compartments (Cl_F and Cl_S) and the elimination rate constant (Cl_E). Renal clearance (Cl_R) and Cell Saver® clearance (Cl_{CS}) were derived by urine and discarded fluid collection, respectively. Cl_E is the sum of Cl_R and nonrenal clearance (Cl_{NR}).

Discussion

This study reports the pharmacokinetics of *d*Tc in a group of adult patients undergoing extensive surgery to the thoracolumbar spine. Measures taken to combat operative blood loss included the prior intravenous administration of 2–3 l of crystalloid solution and the reinfusion of washed red blood cells harvested by surgical suction from the prone patient. It would seem likely that organ functions were affected by hemodynamics because of the intraoperative posture and the administration of enflurane; there is no reason to assume the restoration of normal hepatic or renal function with resumption of supine posture and return of consciousness. Continuing depression of organ function after a potent inhalation agent has been demonstrated in sheep.** These factors may account for the difference found in these patients and the pharmacokinetics parameters reported elsewhere.

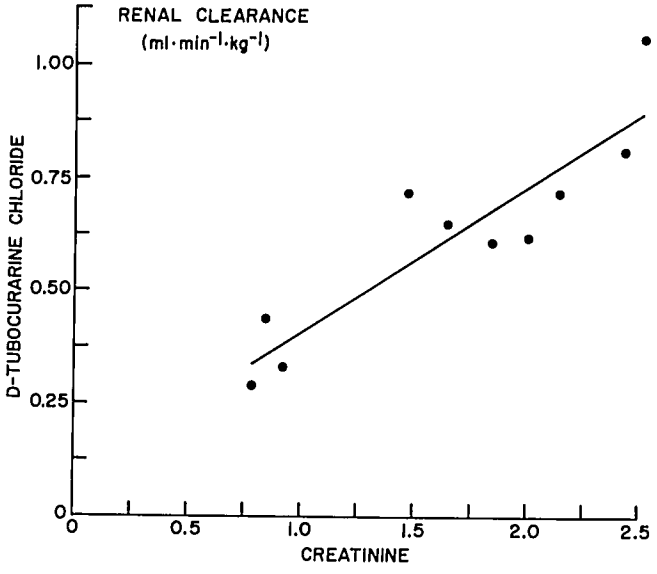

FIG. 3. The renal clearances of creatinine and *d*Tc: $Cl_{R(dTc)} = 0.32\ Cl_{Cr} + 0.08$, r = 0.90.

The mean elimination half-life exceeded 8 h, longer than the 1.3–5.7 h reported by most investigators,[11–18] and was associated with a low mean plasma clearance of 1.2 ml·min^{-1}·kg^{-1}. The low total plasma clearance of *d*Tc in our patients was reflected in the apparent plateau of *d*Tc concentrations at 1.8 mg·l^{-1}, rather than the desired 1.1 mg·l^{-1}, with abolition of the twitch response. This resulted in an early termination of the *d*Tc infusion, recognizing that spontaneous recovery from paralysis would be slower than usual when the twitch response returned. Although these data imply considerable differences in the disposition of *d*Tc in our patients, this was not reflected in its total renal excretion in 24 h (table 2).

Three groups recently have reported urinary recovery of *d*Tc in humans of 65, 38, and 44% of the dose.[12,16,18] We have found that renal mechanisms account for approximately 52% of *d*Tc elimination (table 3), and our results suggest that renal *d*Tc clearance is a function of glomerular filtration rate (fig. 3). This is consistent with the results of previous investigators who have shown that administration of mannitol markedly increases urinary volume without increasing *d*Tc excretion.[16] Binding of *d*Tc to plasma proteins[19] appears to restrict its renal elimination and to account for the fact that renal *d*Tc clearance is less than glomerular filtration rate.

** Mather LE, personal communication.

In the present study we found that nonrenal mechanisms account for approximately 48% of *d*Tc elimination (table 3). Meijer *et al.*, using tritiated *d*Tc, reported that in 48 h nearly 63% of the dose was excreted in the urine, and, of the 37% estimated to be cleared by nonrenal mechanisms, only 12% could be accounted for by biliary excretion of unmetabolized drug.[12] Their failure to account for the total dose may be due in part to difficulties with total bile collection and to exchange of tritium with the body water during the study period.

In rat studies, these workers reported that 51% of the administered *d*Tc was excreted in the bile during 2 h of perfusion.[20] This compared with only 16% for metocurine; neither substance showed biotransformation. The octanol/water partitioning for *d*Tc was 15, while that for metocurine was 1. This greater lipophilicity is in agreement with the entry of *d*Tc into the erythrocytes.

Early studies suggested that *d*Tc initially is distributed in plasma water and that its total apparent volume of distribution is slightly less than extracellular space.[21] The present study also found a central volume of distribution, 51 $ml \cdot kg^{-1}$, that is similar to the expected volume of plasma water. The total apparent volume of distribution in our study, 587 $ml \cdot kg^{-1}$, is greater than that expected for extracellular fluid, in part due to deliberate fluid loading (table 1). Our average result is larger than the 248 to 523 $ml \cdot kg^{-1}$ reported elsewhere.[11-18]

Blood loss, salvaged by the Cell Saver®, augmented total *d*Tc clearance by 7.2% (table 3). A total of 1.4% of the *d*Tc dose was recovered from the fluid after the erythrocytes were salvaged (table 2), drug that had been distributed in the central compartment. Most of the *d*Tc in blood is in the plasma. If the plasma concentration of 1.8 $mg \cdot l^{-1}$ was a true steady state, then this would have been the concentration throughout the distribution volume. By multiplication with the mean V_{SS}, the average amount of *d*Tc in the body would be estimated conservatively to be 68 mg. Loss of the complete central volume then would result in a loss of 9% of this, less than 6 mg of *d*Tc. These results indicate that even massive blood loss will not entail a significant reduction in total body *d*Tc content.

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