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Pharmacodynamics and Pharmacokinetics of Metocurine in Humans: Comparison to d-*Tubocurarine*

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The relation of serum concentrations of metocurine and *d*-tubocurarine to neuromuscular blockade, and the distribution and urinary excretion of metocurine were determined in humans, using radioimmunoassay for measurement of drug concentrations. Metocurine was administered at two dose levels (0.15 or 0.3 mg/kg) to a total of 14 neurosurgical patients. Serum concentrations of metocurine were correlated with the response of the adductor muscle of the thumb to supramaximal stimulation of the ulnar nerve as measured simultaneously by twitch tension and evoked compound electromyelography (ECEMG). A similar study was performed in another eight neurosurgical patients, using 0.3 mg/kg *d*-tubocurarine (*d*Tc), and using only the ECEMG to monitor neuromuscular transmission. The log plasma concentration-response relationship for all groups produced a sigmoid curve that was linear in the range of 20–80% paralysis. When the metocurine serum concentrations were compared at any one response level, there were no significant differences between the two dosage groups or the two methods employed to measure neuromuscular transmission. The mean serum metocurine concentrations (mean ± SE) for the pooled data from all four groups at 5, 25, 50, 75, and 95% of paralysis were 0.15 ± 0.03, 0.23 ± 0.04, 0.30 ± 0.05, 0.39 ± 0.06, and 0.63 ± 0.09 μg/ml. The serum *d*Tc concentrations (mean ± SE) at similar per cent of paralysis were 0.34 ± 0.05, 0.50 ± 0.06, 0.62 ± 0.07, 0.78 ± 0.08, and 1.15 ± 0.1 μg/ml. Thus, the potency ratio of metocurine to *d*Tc based on serum concentration was approximately 1:2. If equipotent doses of metocurine (0.15 mg/kg) and *d*Tc (0.3 mg/kg) were given, there was no significant difference in the time required for 50% recovery of ECEMG (53 *vs.* 57 min). Mean cumulative urinary excretion of metocurine at 24 h was 42 ± 5%. Small quantities of metocurine (5% total dose) could be detected in the urine of all patients from 24 to 96 h after injection of the drug. This suggests that metocurine is stored in body tissues and is released slowly over a period of days. Analysis of the average serum concentration-time course for metocurine and *d*Tc, using data from a previous study for *d*Tc, gave a triexponential equation for each drug. Significant differences between the pharmacokinetic parameters for the two drugs were $t_{1/2}$ terminal phase (metocurine, 345 *vs. d*Tc 190 min), plasma clearance (metocurine, 1.07 *vs. d*Tc, 1.86 $ml \cdot kg^{-1} \cdot min^{-1}$), volume of distribution, area (metocurine, 0.513 *vs. d*Tc, 0.470 l/kg), elimination rate constant (metocurine, 0.025 *vs. d*Tc, 0.046 min^{-1}), and the entrance and exit rate constants to the "shallow" peripheral compartment were larger for *d*Tc. These differences may reflect the decreased free tissue fraction of metocurine and a greater fraction of the drug bound to body tissues when in comparison to *d*Tc. (Key words: Measurement techniques: radioimmunoassay; metocurine, *d*-tubocurarine; evoked compound electromyelography; twitch tension. Neuromuscular relaxants: metocurine; *d*-tubocurarine. Pharmacodynamics: metocurine; *d*-tubocurarine. Pharmacokinetics: metocurine; *d*-tubocurarine.)

RECENTLY, there has been renewed interest in the long-acting, nondepolarizing neuromuscular-blocking drug, metocurine (dimethyl-*d*-tubocurarine). Savarese *et al.* reported that metocurine exhibits appreciably less autonomic-blocking and histamine-releasing actions than *d*-tubocurarine, and may be indicated whenever hypotension and tachycardia might be deleterious.[1]

In this study, we documented the distribution and urinary excretion of metocurine in humans. The pharmacokinetic parameters of metocurine are compared with *d*-tubocurarine. In addition, the serum concentrations of metocurine are correlated with neuromuscular transmission, as measured by both the twitch tension and evoked compound electromyelograph (ECEMG) of the adductor muscle of the thumb. A comparison is also made between the serum concentrations of metocurine and *d*-tubocurarine required to depress neuromuscular transmission measured by the ECEMG.

Methods

Fourteen neurosurgical patients undergoing craniotomy were studied to determine the relation of serum metocurine concentrations to neuromuscular blockade. Informed consent was obtained from all patients studied. This work was approved by the Institutional Review Board of Columbia University. Their mean age was 49 ± 3 yr (mean ± SE) and their mean weight, 69 ± 4 kg (mean ± SE). In these and other patients studied, serum electrolytes and hemoglobin values were within normal limits. All patients studied were classified ASA 2 on the basis of their disease, usually brain tumor.

Preanesthetic medication consisted of intramuscular injection of 50–100 mg secobarbital, and 0.4–0.6 mg atropine. Every patient was given an intravenous infusion of lactated Ringer's solution, 500–800 ml, prior to the induction of anesthesia. Anesthesia was induced with thiopental (200–300 mg). Nitrous oxide 50% and halo-

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thane, 1.0–1.5%, inspired, was used for tracheal intubation. Anesthesia was maintained with 60% nitrous oxide and 0.5–1.0% halothane, inspired. In each individual patient the anesthetic concentration was not altered during the study. Mechanical ventilation maintained moderate hyperventilation (Pa_{CO_2}, 25–35 mmHg) and the esophageal temperature varied between 35.6 and 37.0° C in all patients. Throughout the anesthesia and surgical procedures, all patients received intravenous fluids, which consisted of Ringer's solution or Normosol-R (Abbott) and 5% dextrose in water at a rate of 3–4 $ml \cdot kg^{-1} \cdot h^{-1}$. They also received oxacillin and dexamethasone intravenously during surgery. Seven patients received a single iv dose of 0.15 mg/kg metocurine; the other seven received a dose of 0.3 mg/kg.

Prior to the administration of metocurine, the patient's forearm and hand were firmly fixed to a metal armboard, and the thumb was abducted in a yoke connected to a Grass® force-displacement transducer (FT-10) to measure twitch tension. A needle also was placed overlying the adductor muscle of the thumb to detect the ECEMG. The ulnar nerve was stimulated at the wrist with subcutaneous needle electrodes with supramaximal stimuli from a Grass® stimulator (Model S8) in conjunction with a Grass® stimulus isolation unit. The responses to single stimuli of 0.2-ms duration delivered at a frequency of 0.1 Hz (6/min) were observed.

A stable baseline of twitch tension and ECEMG was recorded for 10 min, then the selected intravenous dose of metocurine was given. As the ECEMG and twitch tension began to recover, blood samples were withdrawn to be analyzed for metocurine.

The twitch tension and ECEMG at the moment the blood sample was taken were compared with the control values. The times elapsed from injection of metocurine until the twitch and ECEMG returned to 50% of control were recorded. Two patients whose twitch response had not returned to 80% of control at the termination of the procedure were excluded from the study.

To be sure that there had been no shift in the baseline in those patients whose twitch responses or ECEMG had not returned to control on completion of the study, atropine sulfate (1.0 mg) and then neostigmine methylsulfate (2.5–5.0 mg) were given intravenously. One patient, whose twitch responses exceeded the control value, was not included in the analysis.

Another group of eight neurosurgical patients, age 46 ± 4 yr (mean ± SE), weight 64 ± 4 kg, undergoing craniotomy was studied. Their premedication, induction, maintenance of anesthesia, and intravenous fluid and drug therapy were the same as those for patients given metocurine. The differences from the first group were that instead of receiving 0.15–0.3 mg/kg metocurine, they were given an intravenous dose of 0.3 mg/kg *d*-tubocurarine (*d*Tc), and only the ECEMG was used to monitor neuromuscular transmission.

The distribution and excretion of metocurine was studied in a total of eight neurosurgical patients undergoing craniotomy, three of whom were also included in the study of metocurine concentration and neuromuscular blockade. The mean age of this group was 47 ± 3 yr (mean ± SE), mean weight was 72 ± 2 kg (mean ± SE). Anesthetic management of these patients was the same as for the other groups, described above. The patient's bladder was catheterized with an indwelling Foley catheter and emptied. At this point a single intravenous dose of metocurine (0.3 mg/kg) was given. Blood samples were obtained from either an arterial or central venous catheter at 1, 3, 5, 10, 15, 25, 35, and 45 min; and 1, 2, 3, 4, 5, 6, 24, 48, 72, and 96 h. Serum was separated 1–2 h after the sample was obtained, and frozen until analyzed.

Urines were collected at 1, 2, 3, 4, 5, 6, 12, 24, 48, 72, and 96 h. The urine volume was measured, and an aliquot was taken to be analyzed for metocurine. Serum *d*Tc was analyzed employing the radioimmunoassay of Horowitz and Spector.[2] Metocurine concentrations in the serum and urine were determined by a modification of this radioimmunoassay. The modification consisted of using metocurine as standards at 10 times the concentration used for *d*Tc and increasing the incubation time to 48 h. The lower limit of sensitivity was 1 ng/ml. The concentration of metocurine which inhibits antigen-antibody binding by 50% is 2.5 ng/ml. The maximum variation of the assay is ±5% at all concentrations.

To make comparisons between the pharmacokinetics of metocurine and *d*Tc, previously obtained data on the pharmacokinetics of *d*Tc were reanalyzed.[3] The new analysis consisted of deriving the pharmacokinetic parameters of *d*Tc from plasma sampling to 48 h, and in addition, determining the intercompartmental transfer rate constants.

In the study of the pharmacodynamics of metocurine and *d*Tc, the Hill equation was employed to relate pharmacologic response (per cent paralysis) to log of the serum concentration of the two drugs. The form of the Hill equation used was:

$$E = \frac{E_M \cdot V^s}{EV_{50}s + V^s}$$

In this equation, E is the response (per cent paralysis), whose maximum is E_M (100% paralysis). V is the variable to be examined (serum concentration). EV_{50} is the value of the variable at 50% paralysis, while s is the slope factor. The use of this equation was first suggested by Wagner,[4] and has been recently discussed by Sheiner *et al.*[5] The log serum concentration-response curve pro-

duced by the Hill equation is sigmoid in form, although it is linear between 20 and 80% of paralysis.

In handling the data, a logit transformation was performed on the observed response (% paralysis). The relationship between serum concentration and response is then

$$y = \log \frac{(\%\ \text{paralysis})}{(100 - \%\ \text{paralysis})}$$

while x = log serum concentration. This transformation converts a sigmoid curve of the Hill equation to a straight line and permits statistical analysis by linear regression. In each patient studied, the appropriate equation for the concentration of metocurine was plotted against the two methods of measuring response (twitch tension and ECEMG). This was also done for *d*Tc (0.3 mg/kg) with the response measured by ECEMG. No measurements from the distribution phase of the study (α phase) were included in the data since there may be a disequilibrium between serum concentration and concentration of the drug at the neuromuscular junction during this time. The concentration of metocurine and *d*Tc at 95, 75, 50, 25, and 5% paralysis, together with the correlation coefficient, was determined for each patient. Comparison between the serum concentrations obtained for the various groups of patients at the above per cent paralysis was made by applying Student's *t* test (two-tailed) for unpaired data.

Further log serum concentration-response curves for metocurine were constructed for the linear portion of the serum concentration-response curve between 20 and 80% paralysis.[6] In constructing these regression lines, y = % paralysis measured by the twitch response of ECEMG, while x = log serum concentration of metocurine. Significance between these was measured by analysis of variance. F was calculated for each group.

In analyzing the pharmacokinetic data, the serum metocurine or *d*Tc concentrations for the individual patient were fitted to both two and three exponential terms using log-linear regression analysis.[7] The multiple terms of the equation were determined by the peeling (or stripping) method, each term having three or more points. Statistical methods described by Boxenbaum, Riegelman, and Elashoff[8] were employed to determine whether the two or three exponential term best-described the experimental data. The plasma clearance (Cl_p), half-life of elimination ($t_{1/2}$), initial volume of distribution (V_1), and volume of distribution (Vd_{area}), were calculated from the coefficients and exponents of the derived polyexponential equation by the method described by Wagner.[9] The apparent first-order rate constant from the central compartment and the apparent first-order intercompartmental transfer rate constants were calculated employing equations described by Gibaldi and Perrier.[10] Comparison between the pharmacokinetic parameters of metocurine and *d*Tc were made by applying Student's *t* test for unpaired data.

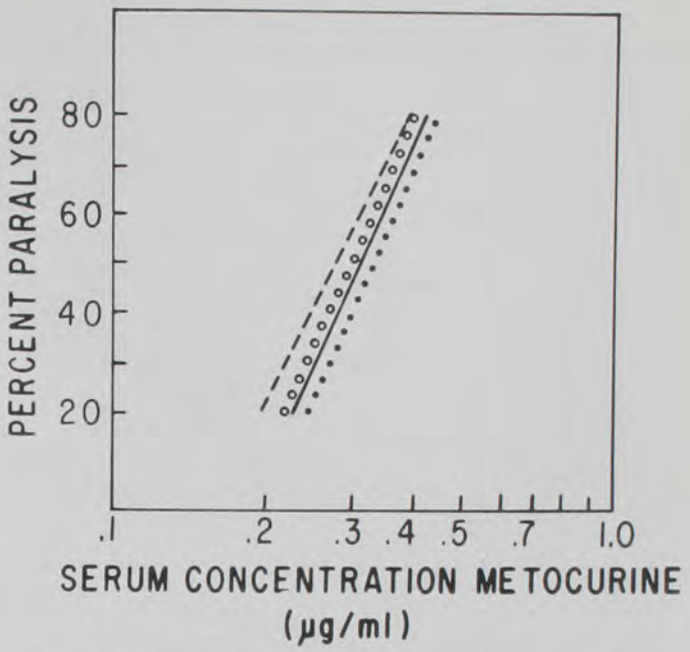

FIG. 1. Regression lines for the four groups of patients, log serum concentration-response between 20 and 80% paralysis. Group 1: twitch tension with 0.15 mg/kg metocurine (——), n = 7. Group 2: twitch tension with 0.3 mg/kg metocurine (-----), n = 7. Group 3: ECEMG with 0.15 mg/kg metocurine (●●●●), n = 7. Group 4: ECEMG with 0.3 mg/kg metocurine (○○○○), n = 7.

Results

There was a significant linear correlation between the log serum concentration of metocurine for both twitch and ECEMG responses between 20–80% paralysis (fig. 1). The formulae for the regression lines, based on the mean values derived from the individual patients were Group 1 (0.15 mg/kg), twitch tension, y = −48 + 311x, r = 0.9521; ECEMG, y = −48 + 310x, r = 0.9605; Group 2 (0.3 mg/kg), twitch tension, y = −39 + 311x, r = 0.9413; ECEMG, y = −45 + 321x, r = 0.9427. The correlation coefficients in the individual patients in all the groups ranged from r = 0.8987 to r = 0.9970. There were no significant differences between the two dosage groups or the two methods employed to measure neuromuscular blockade.

When the entire range of per cent paralysis (E) was related to the log serum concentration of metocurine in μg/ml (C) sigmoid curves were produced. The equations describing the responses based on the mean values from the individual patients were Group 1 (0.15 mg/kg),

$$\text{twitch, } E = \frac{100\ C^{0.252}}{0.31^{0.252} + C^{0.252}};$$

$$\text{ECEMG, } E = \frac{100\ C^{0.274}}{0.31^{0.274} + C^{0.274}};$$

TABLE 1. Serum Concentrations of Metocurine (Mean ± SE, μg/ml) Correlated with Neuromuscular Blockade

Groups of Patients	% Paralysis				
	95	75	50	25	5
Group 1 Twitch tension, metocurine, 0.15 mg/kg	0.64 ± 0.05	0.40 ± 0.04	0.31 ± 0.03	0.24 ± 0.03	0.16 ± 0.03
Group 2 Twitch tension, metocurine, 0.3 mg/kg	0.63 ± 0.1	0.37 ± 0.05	0.28 ± 0.04	0.21 ± 0.03	0.14 ± 0.03
Group 3 ECEMG, metocurine, 0.15 mg/kg	0.65 ± 0.05	0.40 ± 0.04	0.31 ± 0.03	0.24 ± 0.03	0.15 ± 0.02
Group 4 ECEMG, metocurine, 0.3 mg/kg	0.61 ± 0.09	0.38 ± 0.07	0.29 ± 0.05	0.23 ± 0.04	0.16 ± 0.04

n = 7 for each group.

Group 2 (0.3 mg/kg),

$$\text{twitch, } E = \frac{100\ C^{0.296}}{0.28^{0.296} + C^{0.296}};$$

$$\text{ECEMG, } E = \frac{100\ C^{0.242}}{0.29^{0.242} + C^{0.242}}.$$

The serum concentrations of metocurine at 95, 75, 50, 25, 5% paralysis are listed in table 1. There was no significant difference between serum metocurine concentrations at any one degree of paralysis for either dose level or method of measuring neuromuscular blockade.

After 0.15 mg/kg metocurine, the mean time of 50% recovery of twitch tension was 56 ± 5 min (mean ± SE) and for ECEMG, 53 ± 6 min. Following 0.3 mg/kg metocurine, the time for 50% recovery of twitch tension was 229 ± 31 min, and for ECEMG, 219 ± 30 min. Within each dosage group, the time for 50% recovery was not significantly different between the twitch tension and ECEMG.

The group of nine neurosurgical patients who were given 0.3 mg/kg *d*Tc also exhibited significant linear correlation between log serum concentration of *d*Tc (x) and per cent paralysis as measured by ECEMG (y) in the range between 20 and 80% paralysis. The formula for the regression line for *d*Tc, based on the mean values derived from individual patients was $y = -62 + 177x$, $r = 0.9607$, ranging from $r = 0.9045$ to $r = 0.9987$. Again when the entire log serum concentration-per cent paralysis data were plotted, a sigmoid curve resulted. The relation between the serum *d*Tc concentration in μg/ml (C) and per cent paralysis (E) is

$$E = \frac{100\ C^{0.216}}{0.62^{0.216} - C^{0.216}}.$$

In analyzing the data, a logit transformation was performed on the observed response (per cent paralysis). This converts the sigmoid curve of the Hill equation to a straight line, and permits statistical analysis by linear regression. The serum *d*Tc concentrations at 95, 75, 50, 25, 5% paralysis were derived and compared with those of metocurine (table 2). The potency ratio of metocurine to *d*Tc is approximately 1:2. After 0.3 mg/kg *d*Tc, the time for 50% recovery of the ECEMG response was 57 ± 7 (mean ± SE) min. After an equipotent dose of metocurine (0.15 mg/kg) the time required for 50% recovery of ECEMG was 53 ± 6 min. The difference was not significant.

The serum concentration-time course curve following intravenous injection of 0.3 mg/kg metocurine to 6 h from eight patients is displayed in figure 2. The serum concentration-time course curve to 48 h is shown in figure 3. These figures also show concentration-time course curves for *d*Tc derived from a previous study.[3] Small quantities of metocurine could be detected in the serum of seven of the eight patients 48 h after injection of the drug (2 ± 0.8 ng/ml). In only one patient could it be detected 72 h after injection. When the metocurine serum decay curve was compared to that of *d*Tc, the serum concentration of *d*Tc was significantly lower than that of metocurine ($P < 0.05$) at 6 h. There was a small but not significant difference at 24 h, while by 48 h, the metocurine concentration was now significantly lower than that of *d*Tc ($P < 0.001$).

TABLE 2. Ratio of Serum Concentrations of Metocurine and *d*-Tubocurarine to Degree of Paralysis (ECEMG)

% Paralysis	Metocurine μg/ml (7)	*d*Tc μg/ml (8)	Metocurine:*d*Tc
95	0.61 ± 0.09	1.15 ± 0.1	1:1.9
75	0.38 ± 0.07	0.78 ± 0.08	1:2.1
50	0.29 ± 0.05	0.62 ± 0.07	1:2.1
25	0.23 ± 0.04	0.50 ± 0.06	1:2.2
5	0.16 ± 0.04	0.34 ± 0.05	1:2.1

Values are means ± SE.
Number of patients is in parentheses.

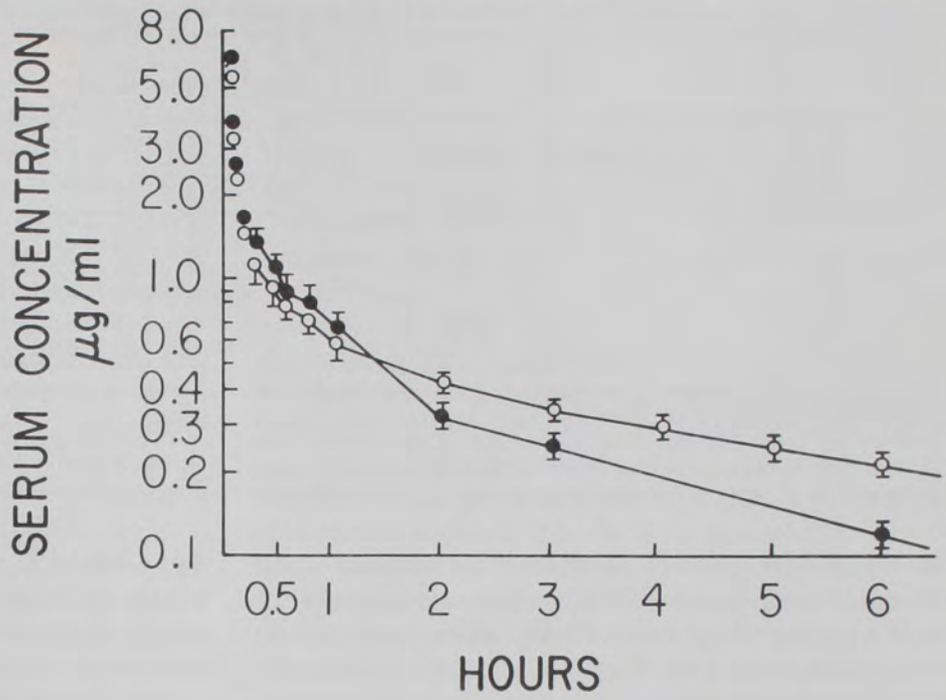

FIG. 2. Serum decay curves for metocurine (○——○) and *d*Tc (●——●) following a single intravenous injection (0.3 mg/kg) of each drug. Time is from 0 to 6 h. Values are means ± SE, n = 8 for each drug.

Analysis of the average serum concentration-time course for metocurine gave a triexponential equation: $C = 5.98e^{-.413t} + 1.14e^{-.073t} + 0.31e^{-.0016t}$, where C = concentration in μg/ml, and t = time in min. Similar analysis of the serum concentration-time course data for *d*Tc gave the equation: $C = 6.29e^{-.48t} + 1.26e^{-.032t} + 0.44e^{-.004t}$. Pharmacokinetic parameters were then derived from these equations. A summary of these data is presented in table 3.

The mean cumulative urinary excretion of metocurine in 24 h was 42 ± 5%, ranging from 30–75%. Small quantities of metocurine could be detected in the urine of all patients 96 h after injection of the drug (table 4).

Discussion

There is a significant linear correlation in the 20–80% response range between the log serum concentrations of

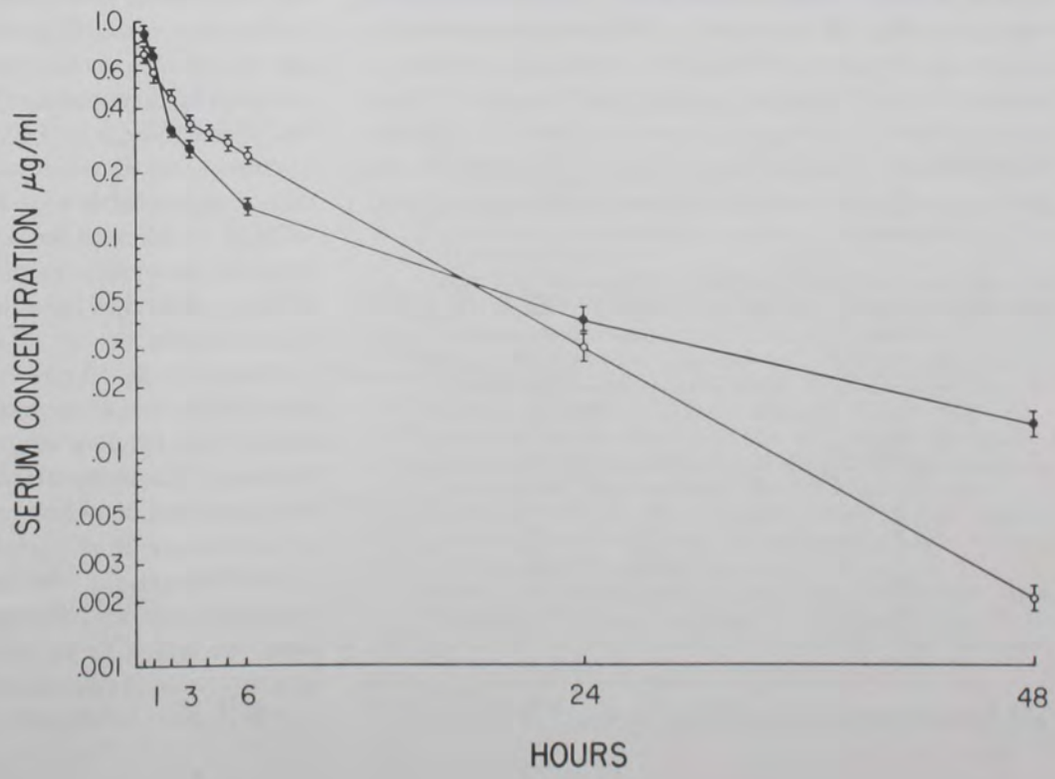

FIG. 3. Serum decay curves for metocurine (○——○) and *d*Tc (●——●) following a single intravenous injection (0.3 mg/kg) of each drug. Time is from 0.5 to 48 h. Values are means ± SE, n = 8 for each drug.

TABLE 3. Pharmacokinetic Data of Metocurine and *d*-Tubocurarine in Human (Mean ± SE)

	Metocurine	*d*-Tubocurarine
$t_{1/2}$ terminal phase (min)	345 ± 30	190 ± 19†
Plasma clearance (Cl_p) ($ml \cdot kg^{-1} \cdot min^{-1}$)	1.07 ± 0.1	1.86 ± 0.2†
Initial volume of distribution (V_1) (ml/kg)	46 ± 5	41 ± 4
Volume of distribution (Vd_{area}) (1/kg)	0.513 ± 0.05	0.470 ± 0.03*
k_{12}	0.202 ± 0.026 min^{-1}	0.27 ± 0.03 min^{-1}*
k_{13}	0.074 ± 0.011 min^{-1}	0.052 ± 0.007 min^{-1}
k_{21}	0.107 ± 0.01 min^{-1}	0.118 ± 0.01 min^{-1}*
k_{31}	0.011 ± 0.001 min^{-1}	0.011 ± 0.001 min^{-1}
k_{10}	0.025 ± 0.005 min^{-1}	0.046 ± 0.005 min^{-1}*

k_{12} = apparent rate constant between the central compartment and the "shallow" peripheral compartment; k_{13} = apparent rate constant between the central compartment and the "deep" peripheral compartment; k_{21} = exit rate constant from the "shallow" peripheral compartment; k_{31} = exit rate constant from the "deep" peripheral compartment; k_{10} = elimination rate constant from the central compartment.

Values are means ± SE; n = 8.

* Significantly different, $P < 0.05$.

† Significantly different, $P < 0.01$.

metocurine and per cent paralysis of the adductor of the thumb as measured by either evoked twitch tension or ECEMG (fig. 1). This correlation appears independent of the initial dose of the drug. The correlation of response to serum concentration of the drug was not surprising, as the other nondepolarizing muscle relaxants behave in a similar manner. Matteo *et al.*[11] have found a direct correlation between serum *d*Tc concentration and neuromuscular blockade during recovery from paralysis. Agoston *et al.*[12] found a similar relationship for pancuronium. Somogyi, Shanks, and Triggs[13] also determined that the plasma concentration of pancuronium is related to magnitude of neuromuscular blockade during the offset of paralysis. The same group further demonstrated that although the log plasma concentration-response curve for pancuronium was linear in the 20–80% response range of paralysis in relation to plasma concentration of pancuronium, it was best-described by a sigmoid curve.[14] Ramzan, Triggs, and Shanks[15,16] have demonstrated a similar relationship between the plasma concentration of gallamine and degree of paralysis, employing single and multiple doses of gallamine (2 mg/kg), and also higher single intravenous dose levels (4 and 6 mg/kg). Also, in the present study, there is no statistically significant difference between the regression lines using either the twitch tension or the ECEMG.

TABLE 4. Urinary Excretion of Metocurine in Humans

Time (h)	Metocurine Excreted (Cumulative %)
1	14 ± 2
2	21 ± 3
3	26 ± 4
4	29 ± 4
5	31 ± 4
6	33 ± 4
12	38 ± 5
24	42 ± 5
48	45 ± 6
72	46 ± 6
96	47 ± 6

Values are means ± SE; n = 8.

When the complete log serum concentration-response curve for metocurine was plotted, a sigmoid curve was produced. This sigmoid relation was predicted by Wagner,[4] and has in fact been determined for a number of nondepolarizing muscle relaxants by Shanks and coworkers.[13–16] When the serum concentrations of metocurine for the two dosage groups and the two methods of analysis were compared at 95, 75, 50, 25, and 5% paralysis (table 1), there was no significant difference between the serum metocurine concentrations at any one particular per cent of paralysis. This study again confirms the close relationship between serum concentration of metocurine and degree of paralysis, and the fact that the relationship is not altered by the dose of metocurine. It further demonstrates that twitch tension and the ECEMG appear to be equally sensitive in measuring the degree of neuromuscular blockade following a dose of nondepolarizing muscle relaxant. The ECEMG does offer a number of advantages over the evoked twitch tension, however, particularly in pediatric patients. These advantages have been described fully by Lee and his associates.[17]

The ratio of *d*Tc to metocurine required to produce similar degrees of neuromuscular blockade is approximately 1:2. This is slightly greater than the results of Savarese, Ali, and Antonio,[1] who, relating dose of drugs to depression of twitch tension, found the potency ratio of metocurine to *d*Tc to be 1:1.8.

In this study, it was determined that a triexponential equation best described the serum decay curves for metocurine and *d*Tc to 48 h. This is in accord with the previous work reported by Gibaldi *et al.*,[18] Wingard and Cook,[19] and Miller *et al.*[20] for *d*Tc, Brotherton and

Matteo[21] for metocurine, and Meijer *et al.*[22] for both drugs.

When the pharmacokinetic data for metocurine is compared with that of *d*-tubocurarine (table 3), a number of differences appear. Compared to metocurine, *d* Tc has a significantly greater plasma clearance, a smaller volume of distribution, and a shorter $t_{1/2}$ terminal phase. In addition, the elimination rate constant (k_{10}) and the entrance (k_{12}) and exit (k_{21}) rate constants are greater for *d* Tc than for metocurine. The significantly lower *d* Tc serum concentration seen at 6 h compared to metocurine ($P < 0.05$) is undoubtedly a reflection of the greater plasma clearance and elimination constant of *d* Tc. Urinary excretion of the two drugs is almost identical at 24 h, 42% for metocurine, and 45% for *d* Tc.

Meijer *et al.*[22] have demonstrated that biliary excretion is a less important route of elimination for metocurine than for *d* Tc (metocurine, 2% *vs.* *d* Tc, 12%). Biliary excretion may in part account for the greater plasma clearance and shorter $t_{1/2}$ seen with *d* Tc. In all but one patient, metocurine could not be detected in the plasma beyond 48 h. This is different from measurements made in patients receiving *d* Tc, where small quantities of *d* Tc could be measured up to 96 h after the injection.[3] The lower limits of sensitivity for the radioimmunoassay for both metocurine and *d* Tc is 1 ng/ml. Thus, the inability to detect metocurine beyond 48 h is not due to differences in sensitivity between the two assays.

Metocurine is a bisquaternary nitrogen compound, while *d*-tubocurarine has a quarternary ammonium and a tertiary ammonium group. It has yet to be demonstrated if this modest difference in molecular structure could alter the binding of the two drugs in body tissues, and thus influence their plasma decay curves. Tissue binding of metocurine must be invoked to account for elimination of the drug from plasma. At 24 h, only 42% of a dose of metocurine is excreted in the urine. No metabolite of the drug has been demonstrated, and biliary excretion accounts for only 2% of an injected dose.[22]

These facts, plus the prolonged urinary excretion of metocurine, detectable for at least 96 h, suggest that metocurine is attached to sites in the body from which it is released very slowly. In support of this concept, Chagas found that acidic mucopolysaccharides bind large quantities of metocurine, and these may act as the principal storage sites for the drug.[23] Olsen *et al.*[24] have also demonstrated that metocurine binds to cartilage chondroitin sulfate, a mucopolysaccharide. Olsen suggested that it may be an important storage site for the drug.

Gibaldi *et al.*[18] suggest the term "nonrecoverable" elimination for that quantity of *d* Tc which could not be accounted for by urinary or biliary elimination. This is equivalent to the tissue depot of the drug. Brotherton[21] calculated the per cent of "nonrecoverable" elimination of metocurine in patients with normal renal function and those with renal failure. He found in patients with renal failure, after a single iv dose of metocurine (0.3 mg/kg), the "nonrecoverable" elimination of the drug increased by over one third (normal, 53% *vs.* renal failure, 73%). This suggests that the body has the capacity to store large quantities of metocurine. All these facts strongly support the concept that metocurine and *d* Tc are stored in certain tissues in the body, most likely in the connective tissue, cartilage, or ground substance.

There are some differences between the pharmacokinetic data in this study and that of Meijer *et al.*[22] Our $t_{1/2}$ terminal phase is longer, and the volume of distribution (Vd_{area}) larger for both drugs. We also found the elimination constant (k_{10}) for *d* Tc significantly greater for *d* Tc than for metocurine. Meijer *et al.* found the reverse to be true. These differences may be due to the design of the studies. In our study, serum samples were taken up to 48 h, while Meijer's last plasma sample was obtained at 12 h. The initial volume of distribution (V_1) is a parameter that would not be affected by the length of the study. Meijer found V_1 was significantly larger for metocurine than for *d* Tc. He attributed this difference to the fact that only 35% of metocurine in plasma is bound to protein versus 50% for *d* Tc, so more free metocurine is available for initial distribution. Although we did not find a significant difference between the V_1 for metocurine and *d* Tc, the mean value for metocurine was greater than that for *d* Tc.

Pharmacodynamically, we found no significant difference in the duration of action of single equipotent doses of metocurine and *d* Tc.

References

1. Savarese JJ, Ali HH, Antonio RP: The clinical pharmacology of metocurine. ANESTHESIOLOGY 47:277–284, 1977
2. Horowitz PE, Spector S: Determination of serum *d*-tubocurarine concentration by radioimmunoassay. J Pharmacol Exp Ther 185:94–100, 1973
3. Matteo RS, Nishitateno K, Pua EK, et al: Pharmacokinetics of *d*-tubocurarine in man—Effect of osmotic diuretic on urinary excretion. ANESTHESIOLOGY 52:335–338, 1980
4. Wagner JG: Kinetics of pharmacologic response. 1. Proposed relationships between response and drug concentration in the intact animal and man. J Theor Biol 20:173–201, 1968
5. Sheiner LB, Stanski DR, Vozeh S, et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to *d*-tubocurarine. Clin Pharmacol Ther 25:358–371, 1979
6. Gibaldi M, Levy G: Dose-dependent decline of pharmacologic effects of drugs with linear pharmacokinetic characteristics. J Pharm Sci 61:567–569, 1972
7. Wagner JG: Fundamentals of Clinical Pharmacokinetics. Hamilton, Illinois, Drug Intelligence Publications, 1975, pp 57–128
8. Boxenbaum HG, Riegelman S, Elashoff RM: Statistical estimation of pharmacokinetics. J Pharmacokinet Biopharm 2:123–148, 1974
9. Wagner JG: Linear pharmacokinetic equations allowing direct

calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J Pharmacokinet Biopharm 4:443–467, 1976

10. Gibaldi M, Perrier D: Pharmacokinetics. New York, Marcel Dekker, Inc, 1975, pp 89–96
11. Matteo RS, Spector S, Horowitz PE: Relation of serum *d*-tubocurarine concentration to neuromuscular blockade in man. ANESTHESIOLOGY 41:440–443, 1974
12. Agoston S, Crul JF, Kersten AHJ, et al: Relationship of serum concentration of pancuronium to its neuromuscular activity in man. ANESTHESIOLOGY 47:509–512, 1977
13. Somogyi AA, Shanks CA, Triggs EJ: Plasma concentrations of pancuronium at predetermined intensities of neuromuscular blockade. Br J Anaesth 50:235–239, 1978
14. Shanks CA, Somogyi AA, Triggs EJ: Dose-response and plasma concentration—Response relationships of pancuronium in man. ANESTHESIOLOGY 51:111–118, 1979
15. Ramzan MI, Triggs EJ, Shanks CA: Pharmacokinetic studies in man with gallamine triethiodide. I. Single and multiple clinical doses. Eur J Clin Pharmacol 17:135–143, 1980
16. Ramzan, MI, Triggs EJ, Shanks CA: Pharmacokinetic studies in man with gallamine triethiodide. II. Single 4 and 6 mg/kg iv doses. Eur J Clin Pharmacol 17:145–152, 1980
17. Lee C, Katz RL, Lee ASJ, et al: New instrument for continuous recording of the evoked compound electromyogram in the clinical setting. Anesth Analg (Cleve) 56:260–270, 1977
18. Gibaldi M, Levy G, Hayton WL: Kinetics of the elimination and neuromuscular blocking effect of *d*-tubocurarine in man. ANESTHESIOLOGY 36:213–218, 1972
19. Wingard IB, Cook DR: Pharmacodynamics of *d*-tubocurarine in humans. Br J Anaesth 48:839–844, 1976
20. Miller RD, Matteo RS, Benet ZL, et al: The pharmacokinetics of *d*-tubocurarine in man with and without renal failure. J Pharmacol Exp Ther 202:1–7, 1977
21. Brotherton WP, Matteo RS: Pharmacokinetics and pharmacodynamics of metocurine in man with and without renal failure. ANESTHESIOLOGY 55:273–276, 1981
22. Meijer DKF, Weitering JG, Vermeer GA, et al: Comparative pharmacokinetics of *d*-tubocurarine and metocurine in man. ANESTHESIOLOGY 51:402–407, 1979
23. Chagas C: Fate of curare during curarization, Curare and Curare-like Agents. Ciba Foundation Study Group, no. 12. Edited by De Reuck AVS. Boston, Little, Brown and Co, 1962, pp 2–10
24. Olsen GD, Chan EM, Riker WK: Binding of *d*-tubocurarine di(methyl-^{14}C) ether iodide and other amines to cartilage, chondroitin sulfate and human plasma proteins. J Pharmacol Exp Ther 195:242–250, 1975