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Pharmacokinetics and Pharmacodynamics of d-*Tubocurarine during Nitrous Oxide–Narcotic and Halothane Anesthesia in Man*

Donald R. Stanski, M.D., Jay Ham, M.D.,† Ronald D. Miller, M.D.,‡ Lewis B. Sheiner, M.D.§*

The relative contributions of changes in pharmacokinetics and pharmacodynamics to the potentiation of *d*-tubocurarine (*d*Tc)-induced paralysis by halothane in comparison with nitrous oxide (N_2O)–narcotic anesthesia were studied in three groups of patients. Fourteen patients received N_2O–narcotic maintenance anesthesia, while seven patients received halothane, 0.5–0.7 per cent, end-tidal, with N_2O, 70 per cent, and seven patients received halothane, 1.0–1.2 per cent, end-tidal, with N_2O, 70 per cent. The steady-state plasma concentration necessary to cause 50 per cent paralysis ($C_{pss(50)}$) was highest in the N_2O–narcotic group at 0.6 μg/ml; it was 0.36 μg/ml with halothane, 0.5–0.7 per cent, and 0.22 μg/ml with halothane, 1.0–1.2 per cent. Greater absolute and relative variability of the $C_{pss(50)}$ was present in the N_2O–narcotic group when compared with halothane, 0.5–0.7 per cent. The equilibration half-times $t_{1/2}K_{e0}$ between plasma concentration and pharmacologic effect (paralysis) were 4.7 min for the N_2O–narcotic group, 6.9 min for the halothane, 0.5–0.7 per cent, group and 7.9 min for the halothane, 1.0–1.2 per cent, group. The greater $t_{1/2}K_{e0}$ with halothane anesthesia is interpreted as decreased muscle perfusion. Halothane did not alter the pharmacokinetics of *d*Tc in comparison with N_2O–narcotic anesthesia. It affected the pharmacodynamics by prolonging the equilibration between plasma concentration and pharmacologic effect and increasing the sensitivity of the neuromuscular junction to *d*Tc. (Key words: Anesthetics, volatile: halothane. Neuromuscular relaxants: *d*-tubocurarine. Pharmacokinetics: kinetics. Pharmacology: pharmacodynamics.)

General anesthetics alter the pharmacologic responses to nondepolarizing neuromuscular blocking agents. Larger doses of muscle relaxants are needed when nitrous oxide (N_2O)–narcotic anesthesia is used, relative to inhalational anesthetics,[1] and as the end-tidal concentration of inhalational anesthetic is increased, relaxant requirement decreases.[2] The exact magnitude of the difference in neuromuscular blocking agent requirements with N_2O–narcotic and inhalational anesthesia has not been quantified. Also, investigation of the mechanism of potentiation of neuromuscular blockade by inhalational anesthetics has been limited to examining sensitivity at the neuromuscular junction (pharmacodynamics).[3] The effects of changes in regional blood flow produced by the inhalational anesthetics on the distribution and elimination (pharmacokinetics) of neuromuscular blocking agents have not been examined.

This study evaluates the relative contributions of alterations in the pharmacokinetics and pharmacodynamics of *d*-tubocurarine (*d*Tc) to the potentiation of response seen with halothane anesthesia compared with N_2O–narcotic anesthesia, and quantifies the magnitude of the difference in drug requirements with these two anesthetic techniques. To achieve this, a pharmacodynamic model that characterizes the plasma concentration–pharmacologic effect relationship was developed.[4] This model allows estimation of the steady-state sensitivity of the neuromuscular junction to *d*Tc by characterizing the temporal dysequilibrium between plasma concentration and pharmacologic effect when steady-state conditions are not achieved.

Materials and Methods

Twenty-eight healthy (ASA I) patients undergoing elective surgical procedures were studied after obtaining informed consent from the patients and the local committee on human experimentation. All patients received diazepam, 0.15 mg/kg, orally, and morphine sulfate, 0.15 mg/kg, intramuscularly, an hour prior to operation. Anesthesia was induced

Abbreviations

$C_{pss(50)}$	= steady-state plasma concentration that results in 50 per cent paralysis
$t_{1/2}K_{e0}$	= half time for equilibration between plasma concentration and paralysis
$t\alpha_{1/2}$	= apparent distribution half-life
$t\beta_{1/2}$	= apparent elimination half-life
V_1	= volume of the central compartment
$V_{D_{ss}}$	= volume of distribution at steady state
Cl	= total plasma clearance

* Clinical Pharmacology Fellow, Department of Medicine and Anesthesia.

† Assistant Professor, Department of Anesthesia.

‡ Professor, Department of Anesthesia and Pharmacology.

§ Associate Professor, Laboratory Medicine and Medicine.

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Address reprints requests to Dr. Stanski: Department of Anesthesia, Stanford University Medical Center, Stanford, California 94305.

with thiopental, 3–4 mg/kg, and the trachea intubated with the aid of succinylcholine, 1 mg/kg. Patients were divided into three groups relative to the subsequent maintenance anesthesia (table 1). Group I consisted of 14 patients receiving N_2O–narcotic anesthesia, diazepam, 0.3 mg/kg, and morphine sulfate, 0.3 mg/kg, intravenously, prior to and during induction. Anesthesia was maintained with N_2O, 70 per cent, and supplemental thiopental and/or morphine as necessary. Group II consisted of seven patients who received halothane, 0.5–0.7 per cent, end-tidal, and N_2O, 70 per cent. Group III received halothane, 1.0–1.2 per cent, end-tidal, and N_2O, 70 per cent.

Ventilation was controlled to maintain arterial blood P_{CO_2} between 34 and 40 torr. Distal esophageal temperature was maintained between 34.5 and 36.8 C. Twenty minutes following induction of anesthesia, each patient received a rapid intravenous infusion of *d*Tc, 16.8 μg/kg/min, over 10 min, followed immediately by a slower infusion of 1.2 μg/kg/min that was maintained until the end of the surgical procedure (70–240 min). The *d*Tc infusion rates were decreased 30–50 per cent for Group III patients. This drug administration protocol resulted in an approximately constant plasma concentration of *d*Tc and degree of paralysis (effect) within 50–70 min. Samples of venous blood were obtained from the forearm opposite that used to administer the *d*Tc. Blood samples for drug analysis were obtained every minute during the initial 10-min rapid infusion, and at 2-min intervals for the first 15 min of the second infusion, after which samples were obtained every 15 min until the end of the operation. A total of 20–30 blood samples were obtained per patient. Concentrations of *d*Tc in plasma were assayed using a radioimmunoassay described by Horowitz and Spector.[5] The coefficient of variation of the assay at three different concentrations was 8 per cent, with a lower limit of sensitivity of 0.05 μg/ml.

Pharmacologic effect was determined by the force of thumb adduction, measured with a Grass (FT-10) force transducer, and recorded on a polygraph. The ulnar nerve was stimulated with a Grass S-44 stimulator through 27-gauge needle electrodes placed at the wrist. Single supramaximal stimuli of 0.1 msec duration at 0.15 pulse/sec were used. The drug effect was quantified by the degree of paralysis, with 0 effect representing no paralysis and 1.0 representing total paralysis.

The plasma concentration curves obtained for individual patients were fitted to a biexponential equation interpreted as a two-compartment mamillary model using nonlinear least-squares regression analysis.[6] When the same data were fit to a triexponential equation, or a three-compartment model, and statistical testing performed on the residual sum of squares,[7] a significant preference was demonstrated for the biexponential model. The resulting estimates of pharmacokinetic parameters for each individual were then used to fit their individual effect data to a pharmacodynamic model (see below). A weighting value of one was used in fitting plasma and effect data. The following parameters were derived for each patient using standard formulas[8]: $t\alpha_{1/2}$—apparent distribution half-life; $t\beta_{1/2}$—apparent elimination half-life; V_1—volume of the central compartment (plasma volume together with the volume of extracellular fluid of highly perfused tissues); $V_{D_{ss}}$—volume of distribution at steady state (volume in which the drug would have to be distributed in steady state, if the partition coefficient between blood and all tissues were one); and Cl—total plasma clearance.

The pharmacodynamic model previously described[4] characterizes the sensitivity and temporal components of a plasma concentration–pharmacologic effect relationship. The sensitivity component measures the steady-state plasma concentration that would result in 50 per cent pharmacologic effect ($C_{pss(50)}$). If plasma concentration and pharmacologic effect data are gathered when a steady state is not present, there occurs a dysequilibrium between the concentration of drug in plasma and the site of action, re-

TABLE 1. Clinical Data (Mean ± SD)

Patient Group	Age (Years)	Weight (kg)	Premedication (mg)		Induction (mg)				Maintenance (mg)	
			Diazepam	Morphine	Thiopental	Succinyl-choline	Diazepam	Morphine	Thiopental	Morphine
Nitrous oxide–narcotic	34 ± 10	65 ± 13	10.5 ± 1.4	9.8 ± 1.5	215 ± 139	70 ± 20	17.5 ± 5.1	19.8 ± 6.8	187 ± 179	4.0 ± 4.8
Halothane, 0.5–0.7 per cent	40 ± 13	68 ± 10	10.3 ± 3.2	6.5 ± 3.2	282 ± 88	66 ± 18	—	—	—	—
Halothane, 1.0–1.2 per cent	32 ± 6	76 ± 17	11.0 ± 2.4	11.0 ± 2.4	224 ± 67	83 ± 22	—	—	—	—

sulting in a plasma concentration–pharmacologic effect dysequilibrium. The pharmacodynamic model that has been developed models and adjusts for the temporal plasma concentration–pharmacologic effect dysequilibrium and allows one to calculate what would occur if a steady state were present.

In the pharmacodynamic model, a first-order rate constant (K_{eo}) characterizes the rate at which the effect site equilibrates with the plasma concentration. Mathematically the pharmacodynamic model is accomplished by postulating a "hypothetical" effect compartment, the dynamics of which are adjusted by the rate constant K_{eo}. The amount of drug in the effect compartment, A_e, is related to the observed effect with the Hill equation, a nonlinear form that characterizes a sigmoid concentration–response relationship. The model is portrayed in figure 1. Nonlinear least-squares regression analysis[6] is used to fit the effect data to the pharmacodynamic model and estimate the values of $C_{pss(50)}$ and K_{eo}. The half-time for C_p to equilibrate with effect can be calculated by dividing the estimate of the rate constant K_{eo} into the natural log of two.

Pharmacokinetic and pharmacodynamic mean parameter values for the three groups were compared with analysis of variance ($P = .05$) and Sheffe's multiple-contrast procedure ($P = .05$).[9]

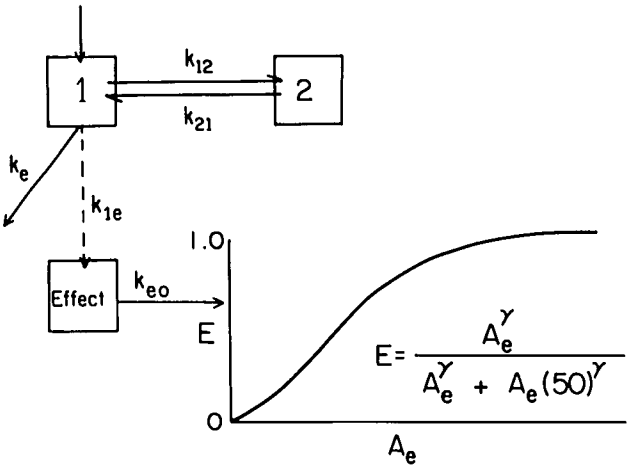

FIG. 1. The pharmacokinetic and pharmacodynamic model as applied to *d*Tc. Plasma concentration data are treated as a two-compartment mamillary model, with K_{21} and K_{12} being rate constants of drug transfer between compartments 1 and 2. K_e is the rate constant for drug elimination from the body. The Hill equation is used to relate A_e, the amount of drug in the hypothetical effect compartment, to the effect, E, and generate a sigmoid concentration–effect curve. Model parameters that are determined in the nonlinear regression are K_{eo}, the first-order rate constant that characterizes the plasma concentration–effect dysequilibrium, γ, a parameter of the Hill equation that allows sigmoidicity of response, and $A_{e(50)}$, a constant term in the Hill equation.

Results

The three groups of patients were comparable with respect to age, weight, premedication, and induction of anesthesia (table 1). In the N_2O–narcotic group, not all patients needed maintenance drug administration, which accounts for the large standard deviations of the doses of thiopental and morphine.

There was excellent agreement between the observed and fitted plasma concentrations using the two-compartment pharmacokinetic model and between observed and fitted effect data using the pharmacodynamic model for each patient in all three groups. Figure 2 displays data for one patient receiving halothane, 0.5–0.7 per cent. The plasma concentration of *d*Tc increased immediately; however the time to onset of detectable effect was approximately 5 min. Effect then began to parallel the plasma concentration curve, and peaked approximately 5 min later. Visually, this lag between plasma concentration and effect suggests the necessity for the equilibration parameter, K_{eo}, of our model. With use of a rapid, then slower, infusion rate, approximately constant plasma concentration and effect were obtained within 45–60 min of starting the slower infusion rate.

No significant difference in any of the pharmacokinetic parameters was found when the N_2O–narcotic group was compared with the halothane groups (table 2). The change in sensitivity to *d*Tc that occurred with halothane was due solely to altered pharmacodynamics. The mean $C_{pss(50)}$ of the halothane, 0.5–0.7 per cent, group was significantly decreased relative to the N_2O–narcotic group, which was further significantly decreased in the halothane, 1.0–1.2 per cent, group (figure 3; table 2). The absolute variability (standard deviation) for the $C_{pss(50)}$ of the N_2O–narcotic group was greater than that seen in either halothane group. When the standard deviation (SD) of each group is adjusted to the mean value (SD/mean × 100 per cent), the coefficient of variation or relative variability is derived. The N_2O–narcotic and halothane, 1.0–1.2 per cent, groups had coefficients of variation of 36 per cent, while that for the halothane, 0.5–0.7 per cent, group was 11 per cent.

The value of $t_{1/2}K_{eo}$ was shortest for the N_2O–narcotic group and progressively increased in the two halothane groups (figure 4; table 2). The N_2O–narcotic $t_{1/2}K_{eo}$ was significantly different from that for halothane, 1.0–1.2 per cent. Relative and absolute variabilities of the $t_{1/2}K_{eo}$ parameters were comparable among groups.

Discussion

In this study a two-compartment pharmacokinetic model was found to be adequate to characterize the

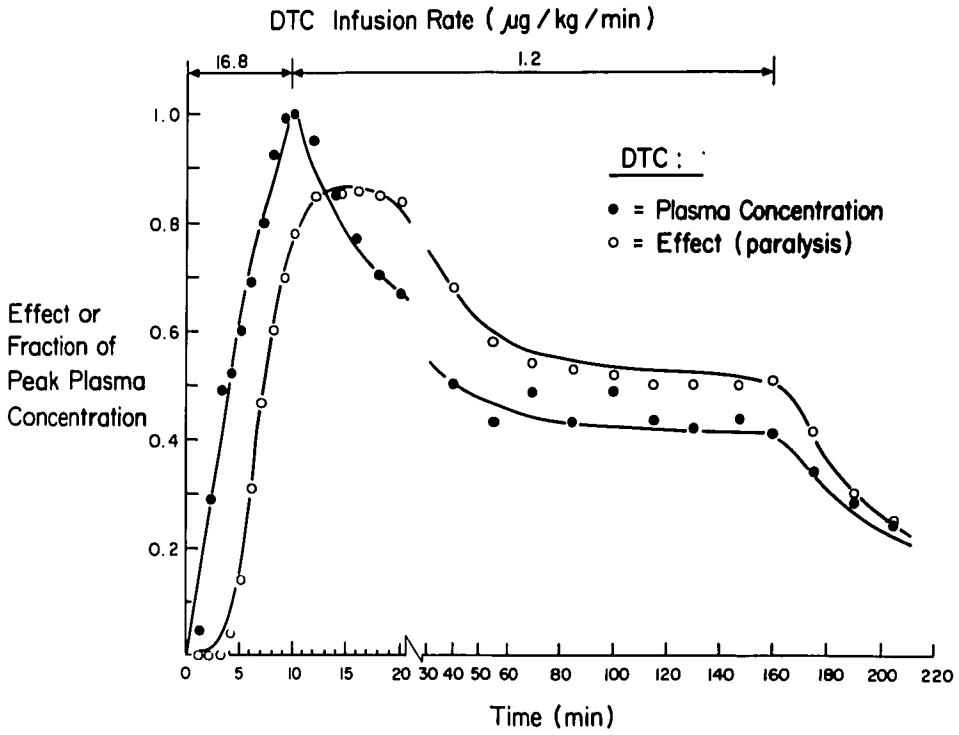

FIG. 2. Data from a patient in the halothane, 0.5–0.7 per cent, group. Plasma concentration is plotted as the fraction of the peak plasma concentration observed (1.29 μg/ml); effect is the extent of paralysis (0 = no paralysis, 1.0 = 100 per cent paralysis). The solid lines represent the fitted function as determined by nonlinear regression, while the circles represent the actual plasma concentration and effect.

behavior of *d*Tc where blood sampling did not exceed three to four hours. In contrast, Gibaldi *et al.*[10] found a three-compartment pharmacokinetic model necessary to characterize the 24-hour urinary excretion data of Kalow[11] and the plasma concentration data of Cohen *et al.*[12] While a long terminal elimination half-life and third "deep"peripheral compartment probably exist for *d*Tc, they have little pharmacokinetic or clinical significance when the drug is used for operative procedures the durations of which do not approach the six-hour terminal elimination half-life estimated by Gibaldi *et al.*

The pharmacodynamic model that has been developed accurately characterizes the relationship between plasma concentration and pharmacologic effect for *d*Tc. For most drugs, pharmacologic response is proportional to the concentration of drug at the site of action. At steady state, drug concentration is at an equilibrium in all parts of the body, including the site of drug action. Therefore, plasma concentration is directly proportional to drug concentration at the site of action. Thus, the $C_{pss(50)}$ of the model becomes an estimate of individual sensitivity to the drug. The $C_{pss(50)}$ is derived by gathering plasma concentration and pharmacologic effect data under non-steady-state conditions and mathematically characterizing the temporal dysequilibrium by the rate constant K_{eo}. The magnitude of the rate constant will depend on the perfusion of the active site, the rate of drug diffusion from capillary blood to site of action, the blood–tissue partition coefficient of the drug, the rate of drug–receptor association and dissociation, and the time course of subsequent pharmacologic response. If one assumes that diffusion, drug–receptor interaction, and pharmacologic response are instantaneous, then K_{eo} will be directly proportional to perfusion

TABLE 2. Pharmacokinetic and Pharmacodynamic Values (Mean ± SD)

Patient Group	No.	$t_{\alpha_{1/2}}$ (Min)	$t_{\beta_{1/2}}$ (Min)	V_1 (l/kg)	$V_{D_{ss}}$ (l/kg)	Cl (ml/kg/min)	$t_{1/2}K_{eo}$ (Min)	$C_{pss(50)}$ (μg/ml)
Nitrous oxide–narcotic	14	6.2 ± 3.7	119 ± 66	.099 ± .027	.297 ± .105	2.25 ± .70	4.7 ± 1.2*	.60 ± .22†
Halothane, 0.5–0.7 per cent	7	6.4 ± 2.4	104 ± 56	.101 ± .036	.289 ± .105	2.50 ± .60	6.0 ± 1.2	.36 ± .04†
Halothane, 1.0–1.2 per cent	7	4.8 ± 3.5	84 ± 69	.076 ± .031	.299 ± .098	2.60 ± .95	7.9 ± 2.5*	.22 ± .08†

See text for explanation of symbols.

* $t_{1/2}K_{eo}$: halothane, 1.0–1.2 per cent > N_2O–narcotic, $P = 0.05$.

† $C_{pss(50)}$: N_2O–narcotic > halothane, 0.5–0.7 per cent > halothane, 1.0–1.2 per cent, $P = 0.05$.

of the neuromuscular junction and inversely proportional to the blood–muscle drug partition coefficient. The dysequilibrium between plasma concentration and pharmacologic effect is maximal after bolus intravenous injection during the phase of drug distribution. The perfusion to the site of action is the determining factor for onset of pharmacologic effect. After drug distribution has been completed, during the terminal elimination phase, a pseudoequilibrium between plasma concentration and tissue concentrations exists, so that effect and plasma concentration decline in parallel as drug is eliminated.

The actual estimates of pharmacodynamic parameters obtained (table 2) for *d*Tc are plausible when compared with other available data. The $C_{pss(50)}$ of 0.36 μg/ml for the halothane, 0.5–0.7 per cent, group is similar to the mean plasma concentration of 0.45 μg/ml that produced 50 per cent effect in the data of Matteo *et al.*[13] The latter data do not represent a steady state but were obtained while plasma concentration was decreasing, and so should predict higher plasma concentrations relative to a steady-state value. The quantity K_{eo} should be equal to the ratio of perfusion of the tissue containing the active site to the partition coefficient of that tissue. Muscle perfusion is approximately 3 ml/100 g/min, while the muscle–blood partition coefficient for *d*Tc has been estimated to be 0.2.[12] This results in a theoretical $t_{1/2}K_{eo}$ of 4.6 min, not different from the values obtained in our three groups (table 2).

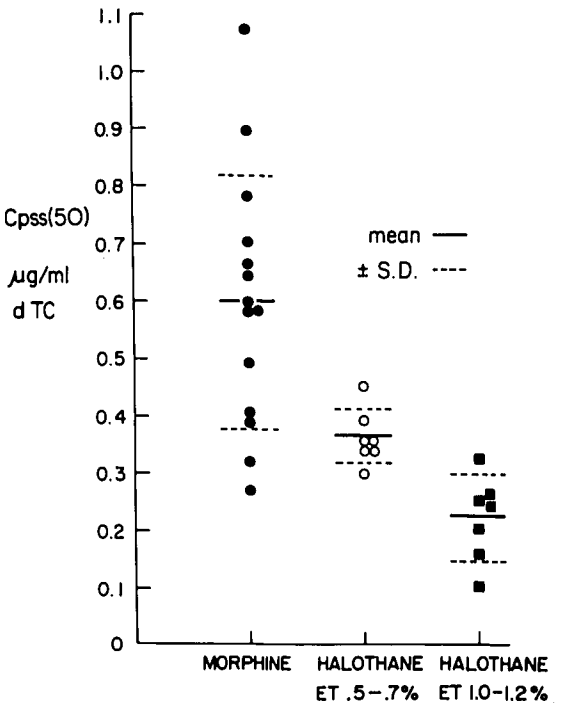

FIG. 3. Values of the sensitivity parameter of the pharmacodynamic model—$C_{pss(50)}$ (steady-state plasma concentration that produces 50 per cent effect) for the three patient groups.

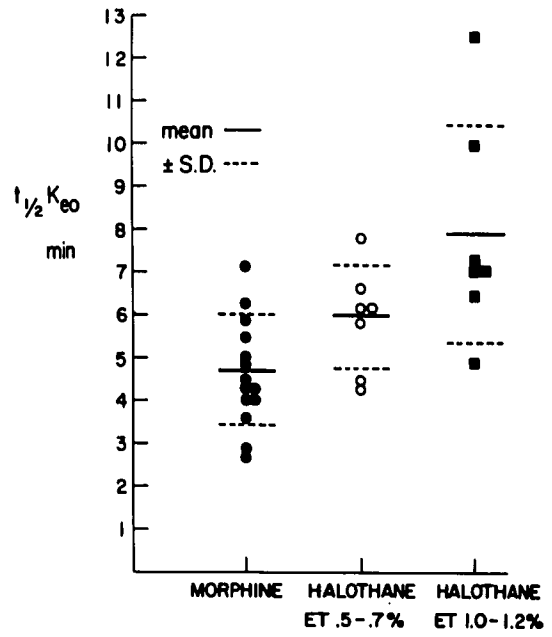

FIG. 4. Values of the temporal parameter of the pharmacodynamic model—$t_{1/2}K_{eo}$ (half-time for equilibration between plasma concentration–pharmacologic effect) for the three patient groups.

Gibaldi *et al.*[10] previously suggested that *d*Tc effect is proportional to the amount of drug present in the central compartment. This would imply instantaneous equilibration between plasma concentration and pharmacologic effect. In a previous publication[4] it was demonstrated with data from this study that much poorer data characterization occurred when the effect was made proportional to the amount of drug in the central compartment. The discrepancy between our findings and those of Gibaldi *et al.* arises in part from the nature of the data used. Gibaldi *et al.* used plasma concentration and effect data that were obtained following bolus drug administration during the terminal elimination phase. Thus, data were gathered during pseudoequilibrium between drug and tissue, and the lag between plasma concentration and drug in tissues (including muscle) was minimized. In contrast, most of our data were gathered during the upstroke and subsequent downstroke of a rapid drug infusion, when plasma concentration and effect are expected to be maximally out of phase.

In this study halothane anesthesia did not significantly affect the pharmacokinetics of *d*Tc when compared with N_2O–narcotic anesthesia. In man, the total plasma clearance is low, approximately 175 ml/70 kg/min, with 40 per cent renal elimination,[14] and 60 per cent non-renal elimination, the latter possibly being hepatic–biliary excretion of unmetabolized

*d*Tc.[15] In dogs, Cohen *et al.*[15] have shown that the hepatic and renal extraction ratios (fraction of drug removed on one pass through the eliminating organ) for *d*Tc are low. Thus, hepatic and renal elimination of *d*Tc may be capacity-limited processes and would not be expected to be influenced by organ perfusion, as would be the case if the eliminating organ's extraction ratios were high.[16] One would therefore predict that the significant decrease in hepatic and renal perfusion that halothane induces[17] would not affect the elimination of *d*Tc in a major way. The findings that the elimination half-life and total plasma clearance of *d*Tc do not change in the presence of halothane would tend to substantiate this prediction.

The potentiation of *d*Tc response by halothane is due to altered pharmacodynamics. The $C_{pss(50)}$ of 0.6 μg/ml for N_2O–narcotic anesthesia is significantly different from the value of 0.36 μg/ml for the halothane, 0.5–0.7 per cent, group. While *d*Tc sensitivities during the two different kinds of general anesthesia have been estimated by use of other approaches,[2,18,19] this is the first quantification of the magnitude of the alteration in *d*Tc response. As the halothane end-tidal concentration was increased from 0.5–0.7 per cent to 1.0–1.2 per cent, $C_{pss(50)}$ decreased from 0.36 μg/ml to 0.22 μg/ml. A similar increasing sensitivity to *d*Tc from increasing halothane concentration was obtained in previous dose–response studies.[2]

The larger absolute and relative variability of $C_{pss(50)}$ or drug sensitivity seen with N_2O–narcotic anesthesia relative to halothane, 0.5–0.7 per cent, would suggest that anesthesia with halothane, 0.5–0.7 per cent, would be preferable to N_2O–narcotic anesthesia when studies of muscle relaxants are being conducted. The decreased variability of response would mean fewer patients would need to be studied to detect differences among groups. Examination of previous studies that have used the cumulative dose–response technique[18] and single dose–response studies¶ with N_2O–narcotic anesthesia and recovery times after a fixed dose[19] with N_2O–narcotic and halothane anesthesia does not disclose any difference in the variabilities of responses with the two different anesthetics. Conceivably the characterization of pharmacokinetic behavior coupled with accurate characterization of the plasma concentration–effect relationship, as was done in this study, permits more accurate description of individual drug sensitivities.

For *d*Tc, the parameter $t_{1/2}K_{eo}$ in the model should be inversely proportional to perfusion at the neuromuscular junction. The assumptions necessary for this to be so are reasonable, since the large surface area of the capillaries and the ionized polar nature of *d*Tc allow ready diffusion of drug into the extracellular fluid of muscle. Also, the postsynaptic membrane receptor affinity for *d*Tc is high, resulting in a rapid pharmacologic response. Following bolus intravenous injection, when plasma and muscle *d*Tc concentrations are at maximal dysequilibrium, our model states that the onset of neuromuscular paralysis is proportional to muscle perfusion, and can be characterized by the half-time $t_{1/2}K_{eo}$. Recovery of paralysis during the terminal elimination phase of *d*Tc, however, will not be affected by muscle perfusion, since the decline of plasma concentration is so slow that plasma and muscle *d*Tc concentrations would be expected to maintain the same pseudoequilibrium over a considerable concentration range. Using an animal model and bolus injections of the drug gallamine, Goat *et al.*[20] found that the rate of onset and the extent of paralysis were greatly affected by muscle blood flow, while recovery from paralysis was not. They interpreted their data as confirmation that the predominant rate-controlling factor in the recovery of neuromuscular blockage is the rate of disruption of the drug–receptor union. Their results can also be explained more parsimoniously using the above-described pharmacokinetic principles embodied in our model, in which drug association and disassociation are assumed to be essentially instantaneous processes.

The $t_{1/2}K_{eo}$ was smallest for the N_2O–narcotic group and progressively increased as the halothane concentration was increased, implying decreased muscle blood flow with halothane anesthesia relative to N_2O–narcotic anesthesia. While an evaluation of blood flow during N_2O–narcotic and halothane anesthesia comparable to the conditions of our study is not available, it has been shown that halothane decreases muscle blood flow relative to thiopental–N_2O anesthesia.[21] Additional significant decreases of muscle blood flow occur, relative to the awake control state and administration of low concentrations of halothane, when halothane concentration is increased[22] and N_2O is added.[23] The significant difference in $t_{1/2}K_{eo}$ for halothane, 1.0–1.2 per cent, relative to N_2O–narcotic anesthesia is compatible with the expected decrease of muscle blood flow by the high concentration of halothane. The increasing $t_{1/2}K_{eo}$ as halothane concentration is increased would suggest a longer time to the onset of paralysis after the initial dose. This would be true only if the sensitivity of the neuromuscular junction remained unchanged. The decrease in $C_{pss(50)}$ that occurs with increasing halothane concentration counterbalances the increased time required to deliver drug to the neuromuscular junction, such

¶ Savarese JJ, Donlon JV, Ali HH: Human dose-response curves for neuromuscular blocking agents: A comparison of two methods of construction and analysis (Abstr). American Society of Anesthesiologists Annual Meeting, 1974, pp 121–122.

that the net result in our study was that times to onset of paralysis were similar in the three groups.

In summary, this study finds that halothane does not affect the pharmacokinetics of *d*Tc relative to N_2O–narcotic anesthesia. The increased response to *d*Tc that occurs with halothane is due to increased sensitivity. Halothane increases the mean sensitivity of an individual to *d*Tc relative to N_2O–narcotic anesthesia by a factor of 1.7 times at a concentration of 0.5–0.7 per cent and by a factor of 2.8 times at a concentration of 1.0–1.2 per cent. The half-time for equilibration between plasma concentration and muscle is prolonged with halothane, 1.0–1.2 per cent, relative to N_2O–narcotic anesthesia, probably because of decreased muscle perfusion with halothane.

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