

Time-dependent Increase in Sensitivity to d-Tubocurarine during Enflurane Anesthesia in Man

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

The pharmacokinetics of *d*-tubocurarine (*d*Tc) during enflurane and during halothane anesthesia were compared in man. Seven patients received enflurane (1.3–1.4 per cent end-tidal) with nitrous oxide (70 per cent), while seven patients received an equipotent anesthetic concentration of halothane (0.5–0.7 per cent end-tidal) with nitrous oxide (70 per cent). Force of thumb adduction was used to assess paralysis. Using a rapid followed by a slower infusion of *d*Tc, relatively constant plasma concentrations were obtained within an hour and were maintained for one to two hours. To determine the effect of enflurane with nitrous oxide on force of thumb adduction, a control group of four patients did not receive *d*Tc while thumb adduction was monitored for two to three hours. In the halothane-treated group, a constant plasma concentration of *d*Tc resulted in a constant degree of paralysis. With enflurane, however, a constant plasma concentration resulted in a time-dependent increase of paralysis, indicating an increased sensitivity of the neuromuscular junction to *d*Tc. In the control group, enflurane alone did not decrease the force of thumb adduction.

The increase in paralysis in the enflurane-treated group was linear over a one to two hour period, with a mean increase of 9.0 per cent per hour. Evaluating only the first hour of enflurane anesthesia, the steady-state plasma concentration that caused 50 per cent paralysis ($C_{p(50)}$) was $.52 \pm .13 \mu\text{g/ml}$ (mean \pm SD), while the $C_{p(50)}$ for halothane was significantly lower, $.36 \pm .04 \mu\text{g/ml}$. Thus, during the first hour of enflurane anesthesia, larger amounts of *d*Tc will be needed to initiate paralysis in comparison with halothane anesthesia. As the duration of enflurane anesthesia increases, sensitivity to *d*Tc will progressively increase, and subsequent maintenance doses of *d*Tc needed will be smaller, relative to equipotent halothane anesthesia. (Key words: Anesthetics, volatile: enflurane; halothane. Neuromuscular relaxants: *d*-tubocurarine. Pharmacokinetics: kinetics. Pharmacology: pharmacodynamics.)

PREVIOUS STUDIES of enflurane and nondepolarizing muscle relaxants have shown greater potentiation of the paralysis response for enflurane compared with

equipotent anesthetic concentrations of halothane,¹ diethyl ether, or Innovar®–nitrous oxide anesthesia.^{2,3}

We have evaluated the relative contribution of altered pharmacokinetics and pharmacodynamics to the potentiation of the response to *d*Tc during enflurane relative to halothane anesthesia. Pharmacokinetic and pharmacodynamic models were used to characterize the plasma concentration–paralysis relationships during anesthesia with the two general anesthetics. A time-dependent increase in sensitivity of the neuromuscular junction to the paralysis resulting from *d*Tc was found to occur with enflurane anesthesia. This phenomenon was not seen with halothane anesthesia.

Methods and Materials

Eighteen patients (ASA I) aged 38 ± 12 years (mean \pm SD) and weighing 70 ± 14 kg, undergoing elective surgical procedures involving the ear, nose, and throat or genitourinary tract were studied. Approval of the local Committee on Human Research and informed patient consent were obtained. Diazepam, 0.15 mg/kg, orally, and morphine, 0.15 mg/kg, im, were given an hour prior to operation. After administration of thiopental, 3–4 mg/kg, iv, the trachea was intubated with the aid of succinylcholine, 1 mg/kg. The 18 patients were divided into three groups. One group of seven patients received enflurane, 1.3–1.4 per cent end-tidal concentration, and N₂O, 70 per cent, while a second group of seven patients received an equipotent anesthetic concentration of halothane, 0.5–0.7 per cent end-tidal, and N₂O, 70 per cent. The data from the latter group have been reported.⁴ A third (control) group of four patients received enflurane, 1.3–1.4 per cent, with N₂O, 70 per cent, without *d*Tc, to determine the effect of this concentration of enflurane on the force of thumb adduction.

Ventilation was controlled to maintain PaCO₂ 34–40 torr. Distal esophageal temperature was maintained between 34.5 and 36.8 C. Twenty minutes after induction of anesthesia, patients in the enflurane and halothane experimental groups received rapid intravenous infusions of *d*Tc, 11.8 to 16.8 $\mu\text{g/kg/min}$, followed by slower infusions at 0.9–1.2 $\mu\text{g/kg/min}$, maintained until the end of the operative procedure (80–240 min). This drug administration protocol was designed to result in an approximately constant plasma concentration of *d*Tc within an hour of starting the first infusion.

* Clinical Pharmacology Fellow, Departments of Anesthesia and Medicine.

† Assistant Professor, Department of Anesthesia.

‡ Professor, Department of Anesthesia and Pharmacology.

§ Associate Professor, Laboratory Medicine and Medicine.

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

TABLE 1. Pharmacokinetic and Pharmacodynamic Values (Mean \pm SD)

	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_1 (l/kg)	$V_{d_{ss}}$ (l/kg)	Cl (ml/kg/min)	$t_{1/2}K_{eo}$ (min)	$Cp_{ss(50)}$ (μ g/ml)
Enflurane, 1.3–1.4 per cent (n = 7)	5.4 \pm 2.6	101 \pm 48	0.081 \pm 0.074	0.248 \pm 0.074	2.05 \pm 0.33	4.9 \pm 1.8	0.52 \pm 0.13*
Halothane, 0.5–0.7 per cent (n = 7)	6.4 \pm 2.4	104 \pm 56	0.101 \pm 0.036	0.289 \pm 0.105	2.5 \pm 0.60	6.0 \pm 1.2	0.36 \pm 0.04*

See text for explanation of symbols.

* Significantly different, $P < 0.05$.

Venous blood samples were obtained from the forearm opposite that used to administer dTc . Blood samples for drug analysis were obtained every minute during the initial ten-minute rapid infusion, and at two-minute intervals for the first 15 minutes of the second infusion, after which samples were obtained every 15 minutes until the end of the surgical procedure. Totals of 20–30 blood samples per patient were obtained.

Concentrations of dTc in plasma were determined by radioimmunoassay.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 μ g/ml. The drug effect (degree of paralysis) was quantified by the depression of the force of thumb adduction (Grass FT-10 force transducer), with 0 effect representing no paralysis and 1.0 representing 100 per cent paralysis. A Grass S-44 stimulator delivered single supramaximal stimuli of 0.1-msec duration at 0.15 Hz to the ulnar nerve through 27-gauge needle electrodes inserted at the wrist.

The plasma concentration data of individual patients were fitted, using nonlinear least-squares regression analysis,⁶ to a biexponential equation interpreted as a two-compartment mammillary pharmacokinetic model. The central compartment of this model represents plasma and highly perfused, rapidly equilibrating tissues, while the peripheral compartment represents less well perfused and slower-equilibrating tissues. The resulting estimates of pharmacokinetic values for each individual were then used to fit their individual effect data to a pharmacodynamic model previously described.⁷ A weighting value of 1 was used in fitting plasma and effect data. The following pharmacokinetic parameters were derived for each patient by use of

standard formulas⁸: $t_{1/2\alpha}$, apparent distribution half-life; $t_{1/2\beta}$, apparent elimination half-life; V_1 , volume of the central compartment (plasma volume together with the extracellular fluid of highly perfused tissues); $V_{d_{ss}}$, volume of distribution (volume in which the drug would have to be distributed in a steady state, if the partition coefficient between blood and all tissues were 1); Cl, total plasma clearance.

The pharmacodynamic model characterizes the sensitivity and temporal components of a plasma concentration–pharmacologic effect relationship. The sensitivity component measures the steady-state plasma concentration that results in 50 per cent pharmacologic effect ($Cp_{ss(50)}$). When plasma concentration and pharmacologic effect data are gathered when a steady state is not present, a disequilibrium between the concentration of drug in plasma and the site of action occurs, resulting in a plasma concentration–pharmacologic effect disequilibrium.⁹ This model adjusts for the temporal plasma concentration–pharmacologic effect disequilibrium and allows calculation of the degree of pharmacologic response from a given plasma concentration if steady-state conditions were present. A first-order rate constant (K_{eo}) is used to characterize the rate at which the effect site equilibrates with the plasma concentration. Nonlinear least-squares regression analysis⁶ is used to fit the effect data to the pharmacodynamic model and to estimate the values of $Cp_{ss(50)}$ and K_{eo} . The half-time for plasma concentration to equilibrate with the effect ($t_{1/2}K_{eo}$) is calculated by dividing the estimate of the rate constant K_{eo} into the natural log of 2.

Two analyses were performed on the data. The first examined the changes in sensitivity to dTc as time progressed with the two anesthetics. As indicated previously, after an hour of the second infusion, a constant plasma concentration of dTc was achieved. This constant plasma concentration was maintained for an additional one to two hours in four of the seven patients in the halothane-treated group and five of the seven patients in the enflurane-treated group. In the remainder of the patients, it was not possible to maintain a constant plasma concentration of dTc for longer than one hour because of termination of the surgical procedures; therefore, these patients were not included in the first analysis. A constant plasma

ABBREVIATIONS

$Cp_{ss(50)}$	= steady-state plasma concentration of d -tubocurarine (dTc) that results in 50 per cent paralysis (μ g/ml)
$t_{1/2}K_{eo}$	= half-time for equilibration between plasma concentration of dTc and paralysis (min)
$t_{1/2\alpha}$	= apparent distribution half-life (min)
$t_{1/2\beta}$	= apparent elimination half-life (min)
V_1	= volume of the central compartment (l/kg)
$V_{d_{ss}}$	= volume of distribution at steady-state (l/kg)
Cl	= total plasma clearance (ml/kg/min)

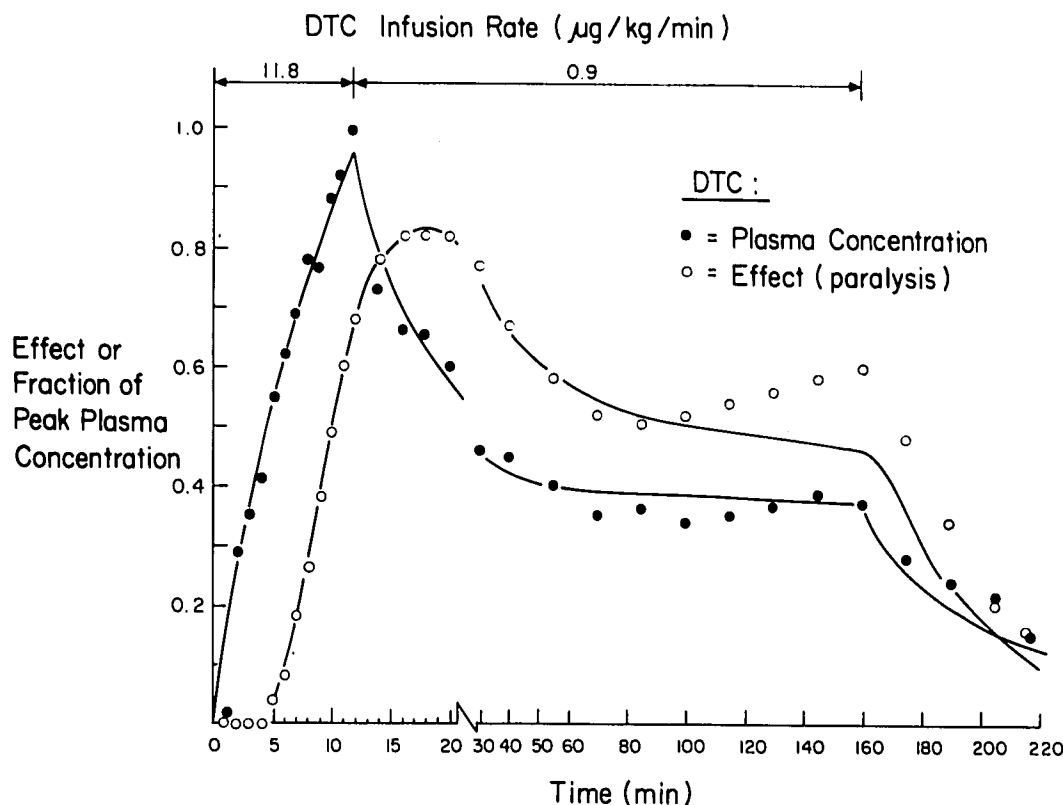


FIG. 1. Data from a patient in the enflurane group. Plasma concentration is plotted as the fraction of the peak plasma concentration observed ($1.24 \mu\text{g/ml}$); effect is the degree of paralysis (0 = no paralysis, 1.0 = 100 per cent paralysis). The circles represent the actual plasma concentration and effect data, while the solid lines represent the fitted function to the pharmacokinetic and dynamic models. Since only the first 60 min of effect data was fitted to the pharmacodynamic model, the predicted degree of paralysis after 60 min is much lower than that actually observed, because sensitivity to dT_c progressively increased with time.

concentration of dT_c should give a constant degree of paralysis if sensitivity is constant. To examine this, the degree of paralysis during the constant plasma concentration in each patient was related to time with linear regression. The slope of the regression line represents the change in sensitivity to dT_c , and by examining the 95 per cent confidence limits of the slope, one can determine whether the slope could be zero (*i.e.*, no change in sensitivity with time).

The second analysis used the previously described models to quantitate the pharmacokinetic and pharmacodynamic differences in dT_c during administration of the two anesthetics. All the plasma concentration *vs.* time data from the seven patients in each group were fitted to the pharmacokinetic model. The pharmacodynamic model used assumes that sensitivity to the drug remains constant throughout the period of study. This proved to be the case for halothane, but not for enflurane. In fitting the paralysis data to the pharmacodynamic model to estimate $C_{p_{ss(50)}}$ and $t_{1/2}K_{eo}$, all the paralysis data for the seven patients in the halothane-treated group were used; however, because sensitivity to dT_c was constantly changing in the enflurane-treated

group, only the first 60 min of paralysis data from these seven patients were used. Pharmacokinetic and pharmacodynamic mean values for the two patient groups were compared with a two-tailed nonparametric Mann-Whitney test, with a significance level of $P < 0.05$ being used.¹⁰

Results

The two groups were comparable with respect to age, weight, premedication, induction of anesthesia, and type of operative procedure. As demonstrated previously,^{4,7} the dT_c plasma concentration *vs.* time data were well characterized using a two-compartment pharmacokinetic model. No significant difference in the pharmacokinetics of dT_c was found when the halothane and enflurane experimental groups were compared (table 1).

In the first analysis, once steady-state plasma concentrations were achieved, there was a marked difference between the two anesthetics in the relationships of plasma concentrations and degrees of paralysis. In the halothane-treated group, a constant plasma concentration resulted in a constant degree of paraly-

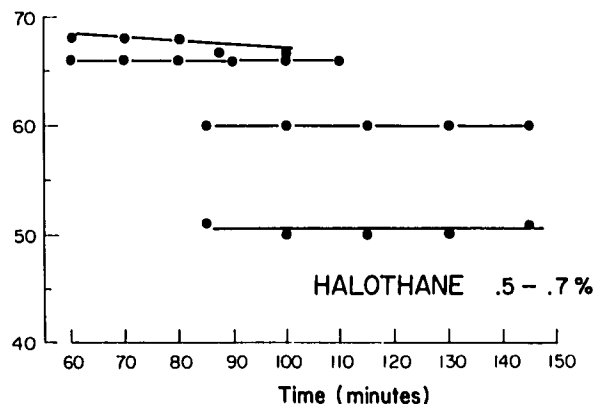
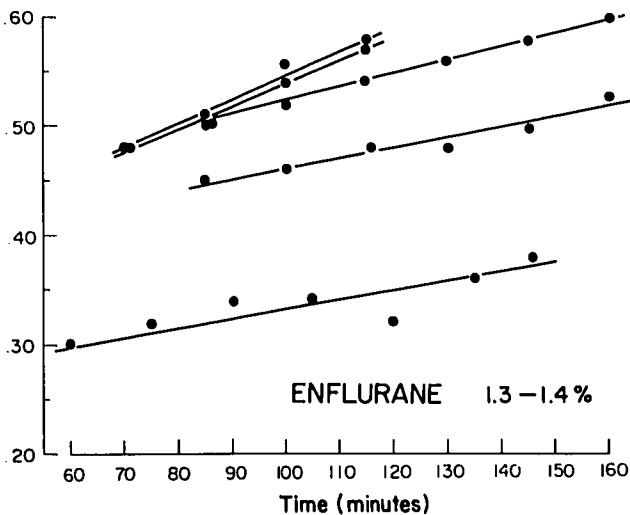
Steady State
EffectSteady State
Effect

FIG. 2. The steady-state effect (0 = no paralysis of thumb, 1.0 = 100 per cent paralysis) resulting after achievement of a constant plasma concentration of dTc is plotted against the time after beginning the first infusion for those patients who had constant dTc concentrations for one to two hours (see text). The circles represent the observed effects (paralysis), while the solid lines represent the linear regression lines for individual patients.

sis that was maintained for the duration of study. With enflurane, in spite of a constant plasma concentration, paralysis did not remain constant, but rather, increased with time. This can be seen in figure 1, representing data obtained from a patient in the enflurane-treated group. After an hour, when plasma concentrations of dTc were relatively constant, paralysis progressively increased.

Figure 2 shows the relationship of steady-state paralysis to time in the patients whose plasma concentrations were maintained constant for one to two hours. In the halothane-treated group, the paralysis minimally varied with time, and the 95 per cent confidence limits of each individual regression line slope included zero. In the enflurane-treated group, however, the increase in paralysis was 9.0 ± 4.0 per cent paralysis per hour

(mean \pm SD), with a range of 4.3 to 13.8 per cent per hour. For each patient in the enflurane experimental group, the 95 per cent confidence limits for the slope of the regression line did not include zero, indicating a statistically significant difference from the halothane experimental group.

Since sensitivity to dTc is constantly increasing with time during enflurane anesthesia, the $Cp_{ss(50)}$ will also be constantly varying. By using only the first 60 min of paralysis data to estimate the pharmacodynamics of the enflurane experimental group, the derived $Cp_{ss(50)}$ represents the average sensitivity over the one-hour period. While the pharmacodynamic model used is not able to quantitate the changing sensitivity to dTc , the average $Cp_{ss(50)}$ that it calculates is accurate. This can be seen by observing in figure 1 how well the fitted function (solid line) from which the $Cp_{ss(50)}$ is calculated parallels the raw paralysis data (open circles) for the first hour.

There was no significant difference between the values for $t_{1/2}K_{e0}$ obtained for the enflurane and halothane experimental groups (table 1). The index of sensitivity, or $Cp_{ss(50)}$, showed significantly greater sensitivity for enflurane than for halothane. This indicates that, at least for the first hour of enflurane administration, patients were less sensitive to dTc than during administration of an equipotent anesthetic concentration of halothane. In the four control patients receiving enflurane without dTc , there was no decrease in the force of thumb adduction over a two to three hour period.

Discussion

The difference between responsivenesses to dTc with enflurane and with halothane is due not to alterations in drug distribution or elimination (pharmacokinetics), but rather to altered neuromuscular junction sensitivity to dTc (pharmacodynamics). With halothane, neuromuscular junction sensitivity to dTc remains constant for the duration of the anesthesia. With enflurane, however, there is a time-dependent increase in neuromuscular sensitivity to the paralyzing action of dTc . This increase in sensitivity appears to be a linear phenomenon, at least for the first two to three hours of enflurane anesthesia, with depression of the force of thumb adduction increasing at approximately 9.0 per cent per hour.

While this study did not determine the mechanism of the time-dependent increase in neuromuscular junction sensitivity that occurs with enflurane, the two anesthetic agents do have some similar and also some different electrophysiologic effects. In general, potent inhalational anesthetics have minimal effects on nerve conduction velocity, transmitter release from the nerve terminal, the agonist-neuromuscular receptor dissociation rate constant, or acetylcholinesterase activ-

ity.¹¹⁻¹³ They induce a "depolarization-like" block of the postjunctional receptor by several mechanisms. The depolarizing effect of agonists such as acetylcholine, succinylcholine, or carbachol is inhibited by inhalational anesthetics, possibly by alterations of sodium-potassium conductance channels in the receptor.^{11,12} This results in an alteration of the endplate potential generated by an agonist. Additionally, a change in the threshold necessary for an endplate potential to trigger a muscle action potential and subsequent muscle contraction also occurs.^{11,12} These impairments of neuromuscular transmission become additive to the effect of a nondepolarizing muscle relaxant, resulting in an overall potentiation of the paralysis when potent inhalational agents are present.

Enflurane markedly increases the threshold of the muscle fiber for propagation of an endplate potential to a muscle action potential, while halothane has minimal effect on this threshold.¹² Muscle paralysis coincides with the failure of the propagation of an endplate potential to a muscle action potential. This difference in effects on the muscle fiber with enflurane relative to halothane may account for the time-dependent increase in sensitivity to dTc seen with enflurane. The equilibration time of enflurane between muscle and blood is relatively long, due to the high solubility of enflurane in muscle. The half-time for equilibration of enflurane from blood to muscle is approximately 40 min. Thus, muscle concentrations of enflurane slowly increase with time, reaching a steady-state concentration in five or six half-lives, or 200–240 min.¹⁴ The slow increase of enflurane muscle concentration coupled with its effect on the muscle action potential may account for the time-dependent increase in sensitivity to dTc found in this study. Enflurane alone did not produce time-dependent depression of the force of thumb adduction when administered for as long as three hours to four control patients. Previous studies have shown that concentrations of enflurane greater than that used in this study are necessary for a direct enflurane-induced depression of the force of thumb adduction.^{2,3} The decrease of the neuromuscular junction safety margin by dTc may be necessary to uncover the time-dependent effect of enflurane on muscle action potential.¹⁵

Since neuromuscular junction sensitivity to dTc during administration of enflurane is constantly changing, the $Cp_{ss(50)}$ will be decreasing with time. When only the first hour of enflurane's effect on the neuromuscular junction was evaluated using our previously described model,⁸ the average $Cp_{ss(50)}$ was found to be significantly higher than the $Cp_{ss(50)}$ of an equipotent anesthetic concentration of halothane, that is, the neuromuscular junction was less sensitive to dTc with enflurane than with halothane. This finding is opposite to the findings of Fogdall and Miller¹; however, their

study was performed after several hours of exposure of the patients to enflurane; thus, it is likely that their patients would show greater sensitivity relative to halothane. The time-dependent increase in sensitivity might also explain the nonparallelism of the single dose versus response curves of halothane and enflurane found by Fogdall and Miller.¹

During the first hour of enflurane anesthesia, the initial paralyzing dose of dTc necessary is larger relative to that needed during halothane anesthesia. However, as the duration of anesthesia progresses, sensitivity to dTc will progressively increase. Subsequent maintenance doses need to be decreased more with enflurane than with halothane, or the time intervals between doses increased. Additionally, because of the constant change in sensitivity, enflurane is probably a poor choice of an anesthetic to use for future studies of muscle relaxants intended to evaluate dose or plasma concentration-paralysis relationships.

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