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The Pharmacokinetics and Pharmacodynamics of the Stereoisomers of Mivacurium in Patients Receiving Nitrous Oxide/Opioid/Barbiturate Anesthesia

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Background: **Mivacurium consists of a mixture of three stereoisomers: *cis-trans* (34–40%), *trans-trans* (52–60%), and *cis-cis* (4–8%). These isomers differ in potency (the *trans-trans* and the *cis-trans* isomers are equipotent and the *cis-cis* isomer is 1/13th as potent a neuromuscular blocking agent) and in rates of *in vitro* hydrolysis (*in vitro* half-lives are less than 2 min for the *cis-trans* and *trans-trans* isomers and 276 min for the *cis-cis* isomer). The current study was undertaken to determine the pharmacokinetic profile of the individual stereoisomers of mivacurium, to evaluate the dose-proportionality of the more potent *trans-trans* and *cis-trans* isomers, and to evaluate the pharmacodynamics of mivacurium in healthy adult patients receiving a consecutive two-step infusion of mivacurium.**

Methods: **Eighteen ASA physical status 1 or 2 adult male patients undergoing elective surgery under nitrous oxide/oxygen/fentanyl anesthesia were studied. Neuromuscular function was monitored using a mechanomyograph at a frequency of 0.15 Hz. An infusion of mivacurium was begun at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Sixty minutes later, the infusion rate was doubled to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and, 60 min after that, the infusion was discontinued. All patients were allowed to recover spontaneously from mivacurium-induced neuromuscular block. Venous blood samples were drawn for the determination of the plasma concentrations of each isomer of mivacurium by a stereospecific high performance liquid chromatographic method. Pharmacokinetic parameters were determined using noncompartmental analysis.**

Results: **During the 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion, patients developed 83.2 ± 13.6% neuromuscular block. Increasing the infusion to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased the depth of block to 99.0 ± 2.0%. After discontinuation of the infusion, patients returned to 25% of their baseline muscle strength in 9.3 ± 3.7 min and had 25–75% and 5–95% recovery indexes of 7.2 ± 1.8 and 16.8 ± 3.7 min, respectively. The volumes of distribution (V_β) of the *cis-trans*, *trans-trans*, and *cis-cis* isomers were 0.29 ± 0.24, 0.15 ± 0.05, and 0.34 ± 0.08 l/kg, respectively. During the 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion, the steady-state clearances of the potent *cis-trans* and *trans-trans* isomers were 106 ± 67 and 63 ± 34 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively; the clearance of the less potent *cis-cis* isomer was 4.6 ± 1.1 $ml \cdot min^{-1} \cdot kg^{-1}$. The elimination half-lives of the *cis-trans* and *trans-trans* isomers were 1.8 ± 1.1 and 1.9 ± 0.7 min, respectively, and that of the *cis-cis* isomer was 52.9 ± 19.8 min. Clearance of the *cis-trans* and *trans-trans* isomers did not vary with infusion rate.**

Conclusions: **The short elimination half-lives and high metabolic clearances of the potent *cis-trans* and *trans-trans* isomers are consistent with the short duration of action of mivacurium. The *cis-cis* isomer does not appear to produce significant neuromuscular block as evident by the return of twitch height to baseline despite persistent *cis-cis* isomer concentrations. (Key words: Pharmacodynamics, neuromuscular relaxants: mivacurium. Pharmacokinetics: stereoisomers.)**

MIVACURIUM chloride is a new short-acting nondepolarizing neuromuscular blocking agent consisting of a mixture of three stereoisomers: *cis-trans, trans-trans,* and *cis-cis*. As geometric isomers, these are three distinct compounds with the same structural formula; they do not interconvert *in vivo* or *in vitro*. The *trans-trans* isomer constitutes 52–62% of the mivacurium mixture, the *cis-trans* isomer 34–40% of the mixture, and the *cis-cis* isomer 4–8% of the mixture.** In anes-

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thetized cats, the three isomers of mivacurium differ in potency. The *trans-trans* and *cis-trans* isomers are equipotent in terms of their neuromuscular blocking potential with their ED_{95} values being 42 ± 3 and 45 ± 3 μg/kg, respectively. The *cis-cis* isomer is approximately 1/13th as potent in cats as the other two isomers, with an ED_{95} of 592 μg/kg.[1]

Mivacurium is a substrate for plasma cholinesterase and is metabolized at a rate of approximately 70–88% that of succinylcholine at comparable multiples of the Michaelis-Menten constant (Km).[2] A study of the hydrolysis of the individual isomers using pooled human plasma showed that the mean *in vitro* half-life for the disappearance of the less potent *cis-cis* isomer was 276 min, whereas the mean *in vitro* half-lives of the more potent *cis-trans* and *trans-trans* isomers were 1.30 and 0.83 min, respectively.††

Pharmacokinetic studies of mivacurium in patients have yielded terminal half-life estimates of approximately 20 min.[3] ‡‡ In these studies, however, the assay used to determine the plasma concentration of mivacurium was not stereospecific and, therefore, could not distinguish the individual isomers. Hence, the 20-min terminal half-life of mivacurium calculated in these studies most likely represents slow elimination of the *cis-cis* isomer. The current study was undertaken to determine the pharmacokinetic profile of the individual stereoisomers of mivacurium, to evaluate the dose proportionality of the *trans-trans* and *cis-trans* isomers, and to evaluate the pharmacodynamics of mivacurium in healthy adult patients receiving a consecutive two-step infusion of mivacurium.

Methods and Materials

Patient Selection

The study protocol was approved by the Human Rights and Research Committee of Cornell University Medical College–New York Hospital. Informed consent was obtained from 18 ASA physical status 1 or 2 patients between the ages of 33 and 55 yr who were scheduled to undergo lengthy minor surgical procedures. Patients with neuromuscular, cardiovascular, hepatic, renal, neurologic, or pulmonary disease were excluded from the study. In addition, those taking any medication known to affect neuromuscular transmission were not included in the study.

Anesthetic Management

In the operating room, electrocardiograms, pulse oximeters, blood pressure cuffs, capnographs, and esophageal temperature probes were applied for routine monitoring. After preoxygenation, anesthesia was induced with intravenous midazolam (20–80 μg/kg), fentanyl (2–12 μg/kg), and thiopental (2–10 mg/kg). Ventilation with oxygen and nitrous oxide (30:70 mixture) was controlled using an anesthesia face mask. The patients' tracheas were intubated before mivacurium administration, and anesthesia was maintained with oxygen (30%) and nitrous oxide (70%) and additional doses of fentanyl, midazolam, and thiopental intravenously as required to maintain stable heart rate and arterial pressure and to permit mechanical ventilation. Ventilation was adjusted to maintain normocapnia.

Esophageal temperature was maintained between 35°C and 37°C with warmed intravenous fluids, blankets, and gas humidifiers. After induction of anesthesia, a second intravenous catheter was inserted for blood sampling, and blood was obtained for determination of the patient's dibucaine number and plasma cholinesterase activity. Plasma cholinesterase activity was determined colorimetrically using butyrylthiocholine as the substrate.

Neuromuscular Monitoring

The ulnar nerve was stimulated at the wrist through 23-G steel needle electrodes with a supramaximal square-wave impulse of 0.2 ms duration. The stimulus was delivered at a frequency of 0.15 Hz from a Grass (Quincy, MA) S88 stimulator in conjunction with a Grass stimulus isolation unit. Response to stimulation was measured with a force displacement transducer (Grass model FT-10) applied to the thumb and recorded on a Grass model 7 polygraph.

Onset and recovery from neuromuscular block were determined by the mechanical response elicited from a single twitch stimulus. Onset and maximum block were determined using the initial baseline response to stimulation. Recovery was determined using the maximal, stable twitch height after discontinuation of mivacurium administration as the baseline for comparison.

†† Croft-Harrelson J: Personal communication. 1993.

‡‡ deBros F, Basta SJ, Ali HH, Wargin W, Welch R: Pharmacokinetics and pharmacodynamics of BW B1090U in healthy surgical patients receiving N_2O/O_2 isoflurane anesthesia (abstract). ANESTHESIOLOGY 67:A609, 1987.

Muscle Relaxant Administration

After at least a 10-min stable baseline of neuromuscular response to stimulation, an infusion of mivacurium was begun at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (infusion rate 1). After 60 min, the infusion rate of mivacurium was increased to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (infusion rate 2). Sixty minutes later, the infusion was discontinued, and the patient was allowed to recover spontaneously from mivacurium-induced neuromuscular block. Once recovery from mivacurium block was complete, if further muscle relaxation was required, vecuronium was administered in bolus doses of 10–20 $\mu g/kg$ as clinically indicated. If necessary, residual neuromuscular block due to vecuronium was antagonized with neostigmine (20–50 $\mu g/kg$) and atropine (10–30 $\mu g/kg$) at the end of the surgical procedure.

Determination of Mivacurium Plasma Concentrations

Blood samples (5 ml each) were collected before the start of the infusion and at 1, 2, 3, 4, 6, 10, 15, 20, 30, 45, and 60 min after the initiation of infusion rate 1. Samples were drawn at identical times after the initiation of infusion rate 2. In addition, blood samples were collected at 1, 2, 3, 4, 6, 8, 12, 20, 30, 45, 60, 90, 120, and 240 min after discontinuation of the second infusion of mivacurium. A second intravenous catheter, not located in the extremity being used either to deliver the mivacurium infusion or to monitor neuromuscular block, was used for blood sampling.

Immediately after collection, the blood was transferred into a Vacutainer (Becton Dickinson, Franklin Lakes, NJ) containing EDTA (ethylenediaminetetraacetic acid) as an anticoagulant and 400 μl of the cholinesterase inhibitor phospholine iodide (0.25%) and mixed thoroughly. This process was completed within 15 s from the beginning of sample collection. The blood samples were then centrifuged, and the plasma was decanted and frozen. Later, the plasma samples were thawed and analyzed using a stereospecific high performance liquid chromatographic method with fluorometric detection of the isomers of mivacurium. The accuracy and precision of the assay, expressed as the percent deviation of measured values from the true values and the percent coefficient of variation, respectively, were 10% or less at all concentrations except for the lower limit of quantitation ($\leq$16% at 5 ng/ml). The extraction efficiencies for the *trans-trans, cis-trans*, and *cis-cis* isomers were 54%, 54%, and 56%, respectively.[4]

Pharmacodynamics

The maximum degree of neuromuscular block (twitch inhibition) at each of the infusion rates and the times to 5%, 25%, 50%, 75%, and 95% recovery after the discontinuation of the mivacurium infusion were recorded. The 5–25%, 25–75%, and 5–95% recovery indexes, or time required from 5% to 25%, 25% to 75%, and 5% to 95% recovery of baseline muscle strength, respectively, were determined.

Pharmacokinetics

Individual mivacurium isomer plasma concentration-time data were analyzed using noncompartmental methods. Noncompartmental modeling assumes that mivacurium is eliminated from the central compartment. The exact percentage of each isomer administered, as measured within 1 month of the date of the patient study, was used to calculate the doses in the determination of pharmacokinetic parameters. Because of their short half-lives, the *trans-trans* and *cis-trans* isomers achieved steady-state (C_{ss}) during each of the 60-min infusions. Their C_{ss} values, therefore, were estimated by averaging three to five concentration values obtained 15–60 min after the beginning of each infusion rate. The plasma clearance ($CL = K_0/C_{ss}$, where K_0 is the infusion rate of the isomer), the volume of distribution ($V_\beta = K_0/C_{ss} \cdot \beta$, where β is the elimination rate constant) and the elimination half-life ($t_{1/2}\beta = 0.693/\beta$) of these isomers were calculated. The concentration of the *cis-cis* isomer did not reach steady-state by the end of each infusion period. Therefore, its CL could not be calculated using this approach.

The volume of distribution at steady-state (Vd_{ss}) was not calculated because an accurate estimation of the area under the plasma concentration-time curve (AUC) and the area under the first moment curve was not possible because of transient problems, lasting 2–5 min, with the infusion pump early during the infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Because concentrations of *cis-trans* and *trans-trans* isomers in the plasma decrease so rapidly, these isomers were not detectable when these pump malfunctions occurred. Problems with the calculations of AUC were only magnified when the value was squared for the calculation of Vd_{ss}. Because of these methodologic problems, the V_β was calculated for each compound. While V_β does not describe a physiologic entity, as does Vd_{ss}, and is influenced by elimination of the compound, it more closely approximated predictions of the true volume of distribution than Vd_{ss} in this study.

Table 1. Demographics (n = 18)

	Mean ± SD	Range
Age (yr)	40.9 ± 8.4	27–55
pChE activity (units/l)*	13.9 ± 3.6	7.8–20.5
Weight (kg)	82.3 ± 11.0	51–98
ABW/IBW†	1.07 ± 0.13	0.79–1.39

* Range of normal plasma cholinesterase (pChE) values is 8–18 units/l.

† Actual body weight (ABW) divided by ideal body weight (IBW).

The AUC, CL (Dose/AUC, where dose is the amount of isomer given), and V_β (V_β = Dose/(AUC · β)) were calculated for the *cis-cis* isomer. The observed maximum concentration (C_{max}) for this isomer was identified at each infusion rate.

All results, unless otherwise specified, are presented as the mean ± SD. Clearance values were compared at each infusion rate using the paired *t* test for samples with unequal variances. $P < 0.05$ was considered statistically significant.

Results

Demographics

The 18 patients studied were male. As can be seen in table 1, patients ranged in age from 33 to 55 yr with an average age of 41 yr. As also can be seen in table 1, all patients were within 20% of their ideal body weights, and all had normal plasma cholinesterase activity.

Pharmacodynamics

During the initial mivacurium infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, patients developed maximum neuromuscular block ranging from 50% to 100%, with a mean of 83.2 ± 13.6%. Doubling the infusion rate to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased the depth of neuromuscular block, with 13 of 17 patients achieving 100% block.

Table 2. Pharmacodynamics (n = 18)

	Time (min)	
Recovery Index	Mean ± SD	Range
5–25%	3.9 ± 0.9	2.4–5.9
25–75%	7.2 ± 1.8	4.5–10.5
5–95%	16.8 ± 3.7	11.7–23.5

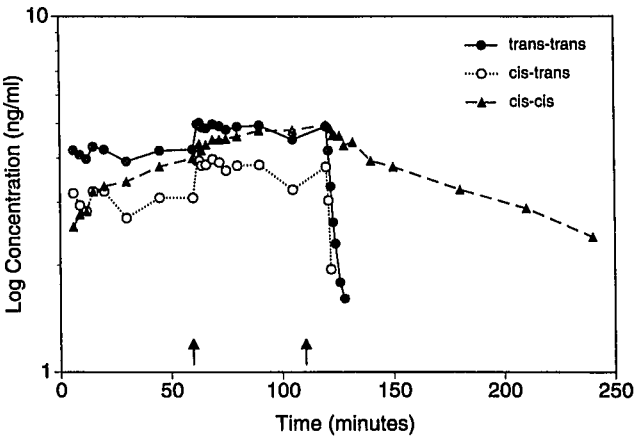

Fig. 1. The plasma concentrations of each of the isomers over time in a single patient. The plasma concentration of the *cis-trans* isomer is denoted by ○ · · · ○, that of the *trans-trans* isomer by ●——●, and that of the *cis-cis* isomer by ▲– – –▲.

The range of maximum block at this infusion rate was 93–100% with a mean of 99.0 ± 2.0%.

The 5–25%, 25–75%, and 5–95% recovery indexes are reported in table 2, with a mean 25–75% recovery index of 7.2 ± 1.8 min and a mean 5–95% recovery index of 16.8 ± 3.7 min.

After discontinuation of the infusion, patients returned to 5% of their baseline twitch height in 2.0–13.3 min, with a mean (±SD) of 6.3 ± 3.1 min. Patients returned to 25% of their baseline muscle strength within 4.4–17.5 min (mean ± SD 9.3 ± 3.7 min) and to 95% of their baseline in 15–35 min (mean ± SD 22.1 ± 5.9 min).

Pharmacokinetics

The plasma concentrations of each of the isomers over time for an individual patient are shown in figure 1.

Table 3. Pharmacokinetics Dose Proportionality

	cis-trans Isomer	trans-trans Isomer
C_{ss} (ng/ml)		
5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	21 ± 10	59 ± 25
10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	44 ± 18	125 ± 44
Cl (ml · min^{-1} · kg^{-1})		
5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	106 ± 67	63 ± 34
10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	105 ± 63	56 ± 26
V_β (l/kg)	0.29 ± 0.24	0.15 ± 0.05

Data are mean ± SD.

C_{max} values for the cis-cis isomer were 121 ± 24 ng/ml.

After initiation of each of the infusion rates (5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the plasma concentrations of the *cis-trans* and *trans-trans* isomers plateaued or reached steady-state rapidly (within 10 min). Within 8–10 min after discontinuation of the infusion, these isomers became undetectable in the plasma. In contrast, the *cis-cis* isomer did not achieve steady-state during either infusion period and, after discontinuation of the infusion, the plasma concentration of this isomer decreased slowly.

Table 3 summarizes the plasma concentrations at steady-state, CL, and V_β values for the *cis-trans* and *trans-trans* isomers at 5 and at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The paired *t* test demonstrated no significant difference in CL for the *cis-trans* isomer or the *trans-trans* isomer at the two infusion rates. The elimination half-lives of the *cis-trans* and *trans-trans* isomers were 1.8 ± 1.1 and 1.9 ± 0.7 min, respectively.

In contrast to the high CLs and short elimination half-lives of the cis-trans and trans-trans isomers, the CL of the cis-cis isomer was 4.6 ± 1.1 $ml \cdot min^{-1} \cdot kg^{-1}$, and its elimination half-life was 52.9 ± 19.8 min. Its V_β was 0.34 ± 0.08 l/kg.

Figure 2 illustrates the relationship between plasma cholinesterase activity and the CL of the *trans-trans, cis-trans,* and *cis-cis* isomers. The CLs of the *trans-trans* and *cis-trans* isomers are highly dependent on the plasma cholinesterase activity. In contrast, the CL of the *cis-cis* isomer is not related to plasma cholinesterase activity.

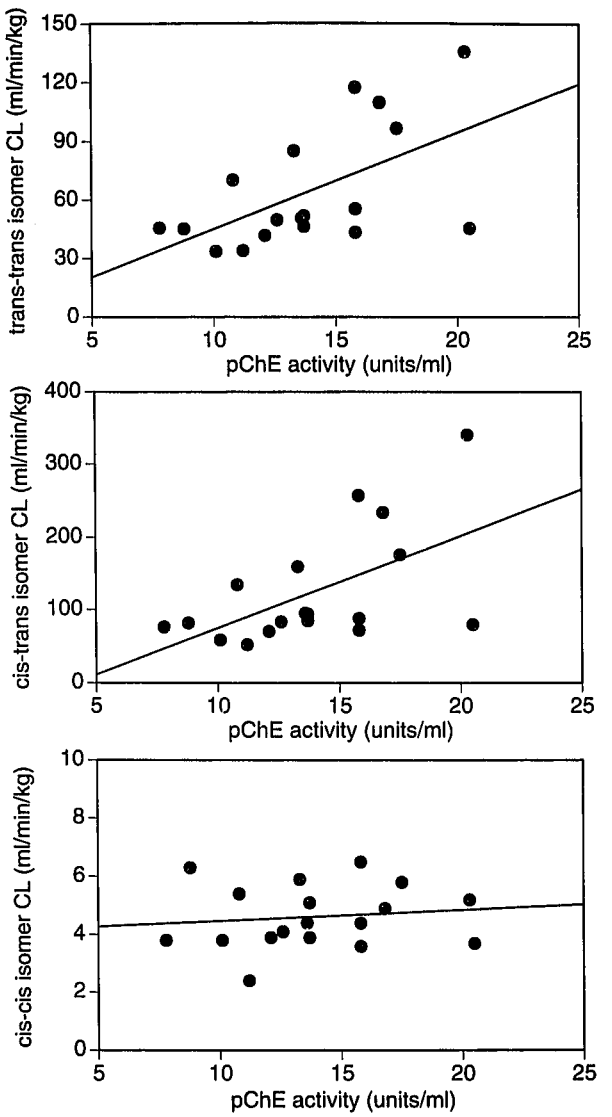

Fig. 2. The clearance (CL) of each of the isomers as a function of plasma cholinesterase (pChE) activity. While the CL of the *cis-trans* and *trans-trans* isomers is dependent on plasma cholinesterase activity (r^2 is 0.323 and 0.326, respectively; $P < 0.05$), there is no relationship between the CL of the *cis-cis* isomer and plasma cholinesterase activity ($r^2 = 0.016$, $P = 0.62$).

Discussion

The three isomers of mivacurium differ in terms of their pharmacokinetic profiles. The short elimination half-lives and high metabolic CLs of potent *cis-trans* and *trans-trans* isomers are consistent with the short duration of action of mivacurium. The less potent *cis-cis* isomer does not appear to produce significant neuromuscular block, as evident by the return of twitch height to baseline despite persistent *cis-cis* isomer concentrations.

To fully understand the nature of the mixture and to predict the time course of neuromuscular block after various doses of mivacurium, one needs to understand the contribution of each stereoisomer to the overall duration of action of mivacurium. The *cis-trans* and *trans-trans* isomers comprise 92–96% of mivacurium and are about 13 times more potent than the less potent *cis-cis* isomer in cats.[1] In humans, the very high CL values of the *cis-trans* and *trans-trans* isomers (105–106 and 56–63 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively) are far greater than cardiac output, glomerular filtration rate, and liver blood flow, reflecting the extensive metabolism of these compounds by plasma cholinesterase. The volume of distribution of the compounds is very small, reflecting limited tissue distribution secondary to the

polarity of the isomers and their large molecular weight. The high CLs and small volumes of distribution are associated with short elimination half-lives of 1.8 and 1.9 min for the *cis-trans* and *trans-trans* isomers, respectively, which are very similar to the half-lives found *in vitro*. The short elimination half-lives and high metabolic CLs of the *cis-trans* and *trans-trans* isomers are consistent with the short duration of action of mivacurium.

The increased depth of neuromuscular block with doubling of the infusion rate from 5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is consistent with the increased plasma concentrations of the *cis-trans* and *trans-trans* isomers. The CLs of the *trans-trans* and *cis-trans* isomers are not affected by a change in the infusion rate of mivacurium. Therefore, the pharmacokinetics of the *trans-trans* and *cis-trans* isomers are linear or dose-proportional within the range of infusion rates studied.

Because of limitations imposed by the Institutional Review Board at The New York Hospital–Cornell Medical Center, the study was undertaken using venous blood. There is no data on the simultaneous determination of mivacurium pharmacokinetics in arterial and venous blood. Donati *et al.*,[5] however, reported that atracurium concentrations were higher in arterial blood than in venous blood; for the first 3 min, the difference was greater than 50%. By 20 min, venous concentrations were approximately 90% of arterial concentrations. Because our CL estimates are based on steady-state concentrations and because half-lives were estimated after termination of a 2-h infusion, the difference between arterial and venous concentrations should be minimized. The arteriovenous differences would be more substantial if the pharmacokinetics were estimated after administration of a bolus dose.

Because of the rapid CL and short elimination half-life of each of the more potent isomers, spontaneous recovery from mivacurium-induced neuromuscular block is rapid. In this study, all patients received a 2-h infusion of mivacurium. The majority of patients (87%) had 100% neuromuscular block at infusion rate 2 for at least 45 min before discontinuing the infusion. Despite this apparent overdose of muscle relaxant, patients recovered to 5%, 25%, and 95% of their baseline twitch height in 6.3 (range 2.0–13.3), 9.3 (range 4.4–17.5), and 22.1 (range 15–35) min, respectively, after discontinuation of the infusion. The 25–75% recovery index of approximately 7 min reported in this study is similar to the 6.5–7-min recovery index reported previously.[6,7] The 5–95% recovery index of 16–17 min is only about 2 min longer than the 14–15-min recovery indexes reported previously.[6,7] In patients receiving infusions lasting 30–324 min, recovery indexes in other studies were not related to the size of the dose of mivacurium or to the duration of the infusion.[6,7]

The CL of the *cis-cis* isomer of 4.6 $ml \cdot min^{-1} \cdot kg^{-1}$ is similar to CLs reported for the intermediate-acting muscle relaxants atracurium and vecuronium.[8–11] The elimination half-life of the *cis-cis* isomer of 52.9 min determined in this study is substantially shorter than the *in vitro* value reported previously of 276 min.[††] Therefore, in addition to slow hydrolysis by plasma cholinesterase, the *cis-cis* isomer may be eliminated unchanged through the kidney and the liver.

In the current study, the *cis-cis* isomer does not appear to contribute significantly to neuromuscular block. Twitch height returned promptly to baseline despite persistent plasma concentrations of the *cis-cis* isomer. In addition, if one assumes that the *cis-cis* isomer is 1/10th to 1/13th as potent as the other two isomers, the EC_{50} for the potent isomers is 67.3 ± 30.4 $ng \cdot ml^{-1}$.[12] Based on this model, one would predict that the maximum plasma concentration of the *cis-cis* isomer observed in this study (172 ng/ml) would be associated with less than 5% block.

What may happen to the plasma concentration of the *cis-cis* isomer during even longer infusions? If the infusion is given, as in this study, at a predetermined rate without regard for degree of neuromuscular block, the plasma concentration of this isomer presumably will increase and reach a steady-state only after the infusion has continued for at least 5–6 h (*i.e.*, five half-lives).

The likelihood of the *cis-cis* isomer contributing to significant neuromuscular block in healthy patients in the clinical setting is remote because of its low potency, especially if neuromuscular block is monitored properly. Because mivacurium is a benzylisoquinolinium diester, even if the *cis-cis* isomer were to increase to a plasma concentration that might cause neuromuscular block, in the worst case, recovery should occur over a similar time course as it does after the intermediate-acting benzylisoquinolinium atracurium, because the CLs are similar. Significant neuromuscular block due to the *cis-cis* isomer has not been demonstrated in patients receiving infusions of mivacurium lasting many hours with monitoring of neuromuscular block and appropriate dosing.[6,7]

Mivacurium and its metabolites are eliminated to a small extent in the urine.[7] The limited data regarding the use of mivacurium in patients with renal disease

suggests that the pharmacodynamics of mivacurium are altered in this patient population.[3,13,14] The pharmacokinetics of mivacurium in patients with end-stage renal disease have not yet been fully characterized through the use of a stereospecific assay. Because of the likely possibility that the *cis-cis* isomer, whose CL is unrelated to plasma cholinesterase activity, is excreted renally, there is the potential for it to accumulate in patients with end-stage renal disease.

In conclusion, mivacurium is comprised of three stereoisomers: two potent isomers, *cis-trans* and *trans-trans*, that comprise the major portion of the relaxant mixture, and one less potent isomer, *cis-cis*, that comprises approximately 6% of the product. The *cis-trans* and *trans-trans* isomers have very short elimination half-lives of 1.8 and 1.9 min, respectively, and very high CLs of 105–106 and 56–63 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively. The less potent *cis-cis* isomer has a slower CL of 4.6 $ml \cdot min^{-1} \cdot kg^{-1}$, similar to those of vecuronium and atracurium, and a longer elimination half-life of 52.9 min, which is similar to that of vecuronium. In this study, even in the presence of persistent *cis-cis* isomer concentrations, spontaneous recovery of twitch to baseline height occurred approximately 20 min after discontinuation of a 2-h infusion of mivacurium. The more potent *trans-trans* and *cis-trans* isomers constitute about 95% of the mivacurium mixture and appear to be responsible for its unique pharmacodynamic profile.

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