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Mivacurium Arteriovenous Gradient during Steady State Infusion in Anesthetized Patients

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Background: **Mivacurium *cis trans* and *trans trans* isomers undergo rapid hydrolysis by plasma cholinesterase. As this enzyme is largely distributed, it cannot be excluded that these isomers might undergo peripheral elimination. This hypothesis was investigated in patients by measuring the difference between arterial and venous concentrations under a constant-rate continuous infusion of mivacurium.**

Methods: **During propofol–remifentanil anesthesia, eight adult consenting patients received an intravenous bolus dose of 0.2 mg/kg mivacurium, followed by a constant infusion (3, 5, or 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$) into the brachial vein. One hour after starting the infusion, arterial (radial artery) and venous (contralateral brachial vein) blood samples were drawn simultaneously at 15-min intervals for 45 min. Mivacurium isomers and metabolite plasma concentrations were determined by stereospecific high-performance liquid chromatography. Using the corresponding arterial and venous concentrations, the tissue extraction coefficient as well as total body clearance were calculated.**

Results: **During steady state conditions, the venous concentrations of the *trans trans* and *cis trans* isomers were 34 ± 13% and 42 ± 11% (mean ± SD) lower than the corresponding arterial concentrations ($P < 0.05$), respectively. For the *cis cis* isomer, the difference between venous and arterial concentrations was 3 ± 4% ($P = 0.063$). Total body clearances of the *trans trans* and *cis trans* isomers were greater when based on venous sampling ($P < 0.05$).**

Conclusion: **Pharmacokinetic parameters derived from a constant infusion of mivacurium depend heavily on the sampling site (arterial or venous) for the rapidly hydrolyzed isomers. These results strongly suggest a significant metabolism of mivacurium within muscle tissue that may account for the large interpatient variability in response to mivacurium.**

PHARMACOKINETIC studies dealing with mivacurium indicate that the active isomers *trans trans* (57% w/w) and *cis trans* (36% w/w) have a rapid half-life (< 3 min), whereas the *cis cis* isomer (6%) has a 30-min half-life.[1–3] An ester linkage renders this member of the benzylisoquinolinium family susceptible to metabolism by plasma cholinesterase (pseudocholinesterase or butyrylcholinesterase), resulting in extremely rapid clearance from the systemic circulation.[4] This enzymatic metabolism pertains to the two active isomers of mivacurium but not to the less potent one, *cis cis* mivacurium, because it is eliminated by several pathways, of which cholinesterase metabolism represents but one (perhaps minor) component.[5,6] Mivacurium hydrolysis produces two types of inactive metabolites, namely, the quaternary amino alcohols (*cis* and *trans*) and the quaternary monoesters (*cis* and *trans*). The latter may, in turn, undergo further hydrolysis into their respective alcohols.[7]

Plasma cholinesterase is distributed throughout the body, particularly in the liver, lung, intestines, muscle,[8] and end-plate (mice).[9] The enzyme is not necessarily localized intracellularly since it has recently been shown to be present in the cerebrospinal fluid of monkeys and pigs.[10] Mivacurium, whose distribution is mainly extracellular, may therefore undergo peripheral elimination in muscle tissue, which represents the effect compartment. Accordingly, as mivacurium transits from an arterial to a venous site across the forearm, hydrolysis by plasma cholinesterase may occur not only within the vascular space, but also in the extravascular space. We therefore hypothesized that a large difference would exist between arterial and venous concentrations of mivacurium under steady state conditions for the rapidly hydrolyzed isomers but not for the *cis cis* isomer. This, in turn, would imply that the derived pharmacokinetic and also pharmacokinetic–pharmacodynamic parameters for the rapidly hydrolyzed isomers would depend on sampling site.

The purpose of this study was to investigate whether mivacurium undergoes peripheral elimination in muscle. The arteriovenous gradient of mivacurium was measured in the forearm under steady state conditions in anesthetized patients undergoing elective surgery.

Materials and Methods

Chemicals

The three isomers of mivacurium chloride, the monoester and quaternary alcohol metabolites, as well as laudanosine were kindly supplied by GlaxoWellcome (Stevenage, Hertfordshire, United Kingdom). All organic solvents were high-performance liquid chromatography grade (Anachemia, Montreal, Québec, Canada).

Clinical Protocol

The study protocol was approved by the ethics review board of the Center Hospitalier de l'Université de Montréal, and all participants gave informed written consent before participating in the study. Eight adult patients classified as American Society of Anesthesiologists phys-

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ical status I or II and scheduled to undergo elective surgery in which the insertion of an arterial cannula was indicated were recruited for the study. Patients were 20–65 yr old and within 30% of their ideal body weight. Those with cardiovascular, pulmonary, psychiatric, neurologic, or neuromuscular disease as well as significant renal or liver impairment were excluded. A history of malignant hyperthermia, unusual sensitivity to neuromuscular blocking agents or intake of medications known or suspected to affect neuromuscular function, constituted additional exclusion criteria.

Monitoring included electrocardiography, continuous blood pressure determination, and pulse oximetry. Inspired and expired carbon dioxide, oxygen, and nitrous oxide concentrations were also monitored. Anesthesia was induced with remifentanil (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), propofol (1.5–2.5 mg/kg), and mivacurium (0.2 mg/kg) and maintained with propofol (80–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$), remifentanil (0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and 70% nitrous oxide in oxygen. The trachea was intubated, and mechanical ventilation was adjusted to maintain normal end-tidal carbon dioxide. For neuromuscular monitoring, the ulnar nerve was stimulated supramaximally at the wrist using the train-of-four pattern (2 Hz for 2 s) every 15 s. The response of the adductor pollicis muscle was recorded by accelerometry. A catheter was inserted into the brachial (the antecubital fossa) vein and used for injection of drugs and fluid replacement. On the same arm, the radial artery was used for arterial blood sampling while a catheter was placed in the brachial vein of the contralateral arm for venous blood sampling.

Mivacurium chloride (Mivacron®; Abbott Laboratories, Saint-Laurent, Québec, Canada) was supplied in vials, each milliliter containing the equivalent of 2 mg mivacurium. Patients received an intravenous bolus dose of 0.2 mg/kg. After recovery of at least one twitch in the train-of-four, an infusion rate that would keep the first twitch (T1) within 5–15% of the control value was chosen for each patient. This was achieved with constant infusion rates of 3 (n = 1), 5 (n = 4), and 7 (n = 3) $\mu g \cdot kg^{-1} \cdot min^{-1}$. Arterial and venous blood samples (3 ml) were drawn before drug administration, 1 h after starting the infusion, and 15, 30, and 45 min thereafter. Blood samples were collected simultaneously into heparin-prepared Vacutainer tubes (Becton Dickinson, Oakville, Ontario, Canada) containing 0.1 mg ecothiophate to inhibit degradation of mivacurium and kept on ice until centrifugation at 1,600*g* for 5 min. The decanted plasma was stored at −70°C until analysis.

Analytical Method

Plasma concentrations of mivacurium isomers and metabolites were determined simultaneously using a specific high-performance liquid chromatography assay coupled with fluorescence detection. This method was adapted from that previously reported for cisatracurium and its metabolites in human urine.[11] The lower limit of quantification of the assay was 4.9 ng/ml. The assay was linear up to 2,500 ng/ml for mivacurium isomers and up to 6,000 ng/ml for the metabolites. The method proved to be reproducible for each analyte with within- and between-assay coefficients of variation of less than 10% over the linear range.

Parameter Calculation

All arterial and venous plasma samples were analyzed in duplicate. As the difference between duplicate analyses was less than 10%, the mean of the two values was used. To verify that each patient was studied under steady state conditions, arterial and venous plasma concentrations obtained at different times during the 45-min collection period following the 1-h infusion were compared using the Friedman repeated measures analysis of variance on ranks. After statistical confirmation of steady state conditions, the arterial concentrations obtained at each collection time in a given patient were pooled and averaged. Venous samples were treated similarly. For each patient, the arteriovenous extraction ratio (E) of mivacurium was then calculated by using the mean arterial (Cp_{ssa}) and venous (Cp_{ssv}) steady state plasma concentrations in the following formula:

$$E(\%) = \frac{Cp_{ssa} - Cp_{ssv}}{Cp_{ssa}} \times 100$$

Because of the large range of infusion rates used in patients (3–7 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and to allow for parameter calculations, the plasma concentration for each isomer was normalized to an infusion rate of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of mivacurium. The infusion rate was corrected for the percentage of each isomer in the racemic mixture. Then, the corresponding total body clearance was estimated by dividing the infusion rate by either the mean arterial or venous steady state concentration.

Statistical Analysis

Data are represented as mean values ± SD. For each patient, a Wilcoxon signed rank test was used to compare arterial and venous parameters. The threshold for statistical significance (α) was set at 0.05.

Results

The six male and two female patients had a mean age of 52 ± 18 yr, mean height of 175 ± 12 cm, and mean weight of 85 ± 12 kg, corresponding to a mean body mass index of 27. Patients were scheduled for total hip replacement (n = 3), discoidectomy (n = 3), and total

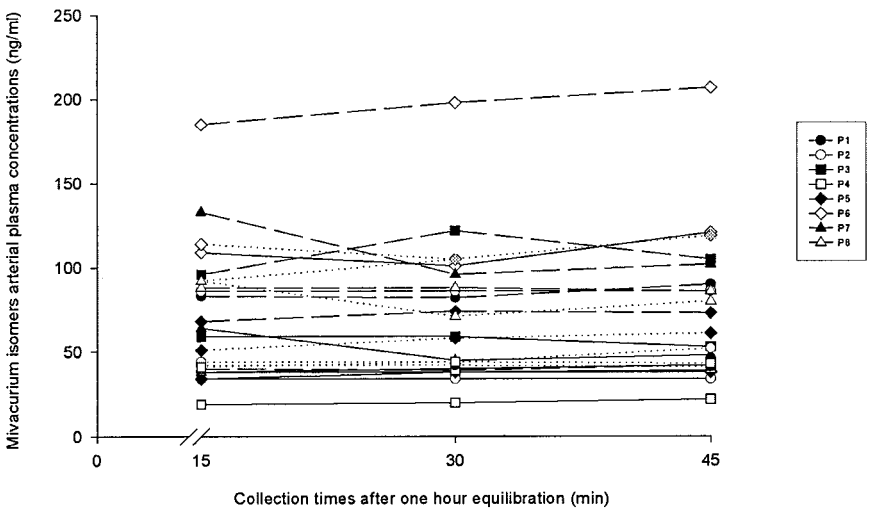

Fig. 1. Steady state arterial concentrations for *cis trans* (—), *trans trans* (- -), and *cis cis* mivacurium (...) at different collection times in each patient. Infusion rates were 3 (patient 1), 5 (patients 2, 4, 7, 8), and 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (patients 3, 5, 6).

knee replacement (n = 2). The infusion rate was not altered, and neuromuscular recordings remained stable for at least 1 h before and during the sampling period.

One hour after starting mivacurium infusion, arterial concentrations for the *trans trans* and *cis trans* isomers were stable in all patients during the sampling period (fig. 1). Therefore, steady state was considered to be achieved. Venous concentrations were found to be consistently lower than their corresponding arterial concentrations (table 1). For the *trans trans* isomer, mean venous steady state concentrations amounted to 66 ± 13% of the mean arterial concentrations ($P = 0.008$), representing a 34% gradient across the forearm (table 1 and fig. 2A). The estimated total body clearance was different depending on the sampling site. The clearance calculated using venous concentrations was 60% higher than that calculated using arterial concentrations ($P = 0.008$). For the *cis trans* isomer (table 2 and fig. 2B), mean venous steady state concentrations represented 58 ± 11% of the mean arterial concentrations, corresponding to an arteriovenous gradient of 42% across the forearm ($P = 0.008$). The estimated clearance was 1.9-fold higher when calculated using mean venous concentrations ($P = 0.004$). Steady state concentrations were reached for the *cis cis* isomer in all patients except in patient 3, for whom we retained only the last-period arterial and venous concentrations. Arterial and venous concentrations for the *cis cis* isomer were virtually identical ($P = 0.063$; table 1 and fig. 2C), with no difference in clearance estimates.

In table 2, arterial and venous plasma steady state concentrations for mivacurium metabolites are presented for 7 patients only because of insufficient volume of blood samples from patient 3. There were no significant arteriovenous differences for the *cis* monoester ($P = 0.144$), *trans* monoester ($P = 0.640$), *cis* alcohol ($P = 0.080$), and *trans* alcohol ($P = 0.958$) metabolites of mivacurium.

Discussion

This study reveals an important arteriovenous gradient for the two rapidly hydrolyzed isomers of mivacurium during constant intravenous infusion of the drug in humans, suggesting a high extraction across the forearm. In contrast, no extraction was observed for the less potent *cis cis* isomer. Assuming that the three isomers of mivacurium have similar physicochemical properties, the arteriovenous concentration difference observed for the *cis trans* and *trans trans* isomers would result from intravascular degradation or tissue hydrolysis in the forearm.

In our study, particular attention was paid to the experimental design to reach steady state conditions and minimize *ex vivo* degradation of mivacurium. Steady state conditions were ensured by allowing a long time of equilibration (1 h) before drawing the first samples. The infusion rate was not altered during that time, and twitch response remained stable throughout. No inhalational agents, which might have potentiated the blockade, were given. The lack of significant variation of mivacurium concentrations over time in a given patient confirmed that steady state was achieved. Dead space was minimized in the intravenous tubing by infusing or collecting the drug as close as possible to the intravenous or arterial access site. Blood was drawn from both sites at approximately the same speed, and the transfer of blood into ecothiophate-containing tubes was completed within 5 s. As withdrawing blood (and drug) from the arterial circulation might have affected venous concentrations, arterial and venous samples were drawn from different arms. We therefore assumed that the arterial concentrations in both arms were identical.

Under steady state conditions, no difference should be measured between the arterial and venous concentrations of a drug across an organ that is not involved in its metabolism or elimination, since net tissue uptake is

Table 1. Steady State Pharmacokinetic Parameters for Mivacurium Isomers

Patient	Infusion Rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Normalized Steady State Plasma Concentrations* (ng/ml)		Total Body Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)		Arteriovenous Extraction (%)
		Arterial	Venous	Arterial	Venous	
			trans trans-mivacurium			
1	3	28 ± 1.5	14 ± 2.5	20	41	51
2	5	17 ± 0.0	8 ± 0.8	33	74	55
3	7	15 ± 1.9	11 ± 1.3	37	53	31
4	5	8 ± 0.3	7 ± 0.4	71	85	17
5	7	10 ± 0.5	7 ± 0.2	56	79	29
6	7	28 ± 1.6	18 ± 0.8	21	31	34
7	5	22 ± 4.0	15 ± 2.6	26	38	31
8	5	17 ± 0.2	13 ± 0.9	33	43	24
Mean	—	18.4	11.6†	37	56†	34
SD	—	7.5	4.2	18	21	13
			cis trans-mivacurium			
1	3	13 ± 0.7	7 ± 1.5	27	54	50
2	5	7 ± 0.0	3 ± 0.3	53	129	59
3	7	8 ± 0.5	4 ± 0.8	44	84	47
4	5	4 ± 0.3	2 ± 0.3	89	164	46
5	7	5 ± 0.3	4 ± 0.2	69	98	30
6	7	16 ± 1.4	10 ± 1.1	24	35	32
7	5	10 ± 2.0	6 ± 1.3	34	56	38
8	5	8 ± 0.1	5 ± 0.5	47	68	30
Mean	—	8.9	5.2†	48	86†	42
SD	—	4.0	2.6	22	43	11
			cis cis-mivacurium			
1	3	14 ± 0.2	13 ± 1.0	4	5	8
2	5	9 ± 0.9	9 ± 0.0	6	6	−1
3	7	6	6	10	10	0
4	5	9 ± 0.3	8 ± 0.5	7	7	4
5	7	8 ± 0.7	8 ± 1.1	7	7	−1
6	7	16 ± 1.0	15 ± 1.5	4	4	6
7	5	16 ± 2.1	15 ± 0.3	4	4	6
8	5	15 ± 0.2	15 ± 0.5	4	4	2
Mean	—	11.7	11.2	6	6	3
SD	—	3.8	3.7	2	2	4

* Each value represents the mean concentration obtained for the three periods ± SD after normalization to an infusion rate of 1 $\mu \cdot kg^{-1} \cdot min^{-1}$. † $P < 0.05$.

zero.[12] This was confirmed in the current study for the *cis cis* isomer of mivacurium, where only a 3% arteriovenous difference was found across the forearm. Conversely, we found that the forearm venous concentrations of the *trans trans* and *cis trans* isomers were almost twofold lower than their corresponding arterial concentrations. This is consistent with published data demonstrating that the elimination of *cis trans* and *trans trans* mivacurium depends largely on plasma cholinesterase, while the *cis cis* isomer is eliminated mainly by renal excretion.[6]

Mivacurium is the first neuromuscular blocking agent for which an arteriovenous gradient is established during constant intravenous infusion. Similar findings have been observed for other short-acting ester-containing compounds largely distributed throughout the body.[13–16] This arteriovenous difference was attributed to an irreversible loss of the drug as it passes through the microcirculation of the forearm, most probably because of rapid elimination by tissue esterases. For mivacurium, the arteriovenous gradient may result from intravascular degradation or tissue hydrolysis in the forearm, but the exact localization of the enzyme remains to be clarified. As mivacurium, a biquaternary ammonium, is almost exclusively distributed in the extracellular fluid, fat was excluded *a priori* as a potential site of metabolism in the forearm. Connective tissue was also excluded because it represents a very small fraction of the total mass of the forearm, and no report indicates butyrylcholinesterase or "plasma cholinesterase" activity. Although as much as 50–70% of the resting blood flow to the forearm goes to the skeletal muscle in conscious humans,[17] muscle is made up of 1% blood only.[18] If one assumes that the average blood flow in the forearm of anesthetized patients[19] is 27 $ml \cdot kg\ tissue^{-1} \cdot min^{-1}$, venous concentrations would be expected to lag by only 21 s. Hence, degradation by plasma cholinesterase may occur within the intravascular space, although to a negligible extent (< 10%

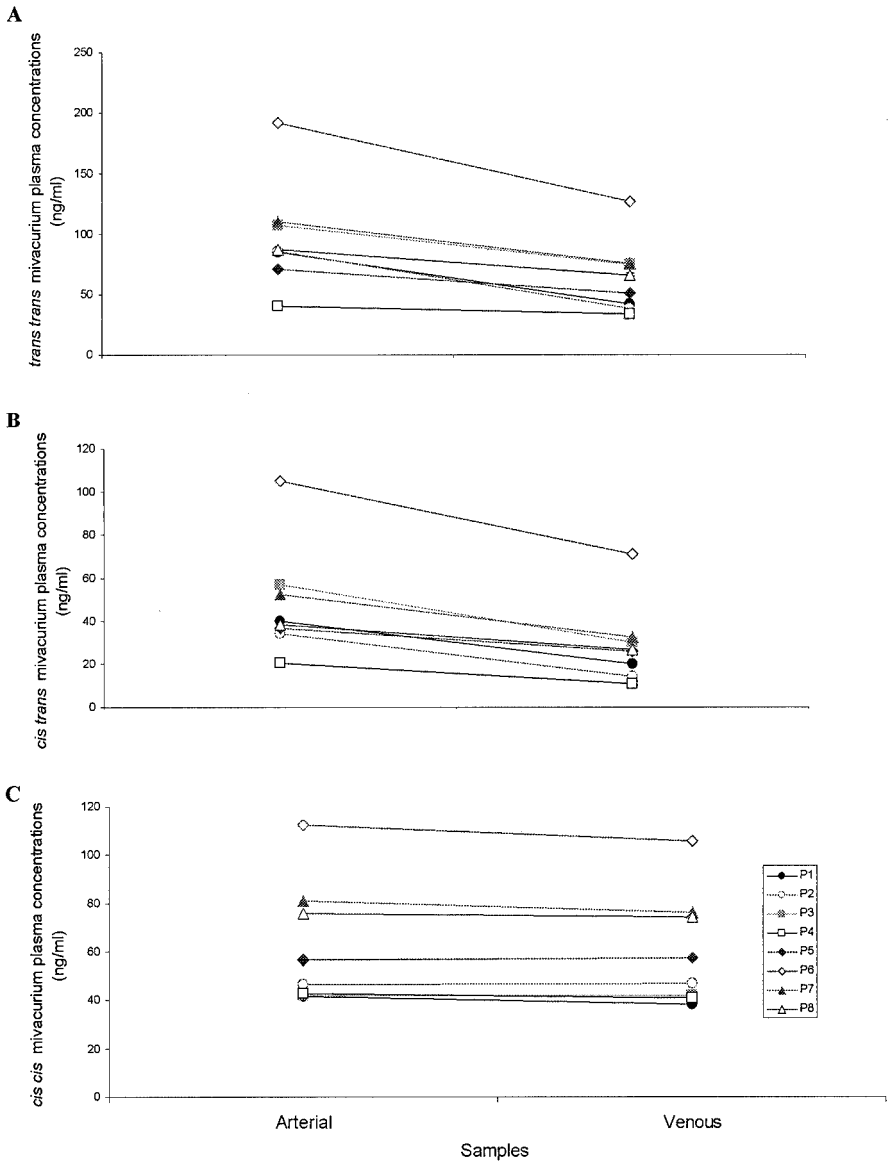

Fig. 2. Mean arterial and venous steady state concentrations for (*A*) *trans trans*, (*B*) *cis trans*, and (*C*) *cis cis* mivacurium in eight anesthetized patients.

if one assumes an elimination half-life of 2.3 min).[2] Therefore, extravascular hydrolysis of *cistrans* and *trans trans* mivacurium may contribute to the significant arteriovenous difference of the two active isomers. In view of the extracellular distribution of mivacurium, it would be reasonable to infer that butyrylcholinesterase may be present in the interstitial fluid of the muscle tissue and play an important role in the extravascular hydrolysis of mivacurium.

To estimate the potential contribution of the muscle tissue to the overall elimination of mivacurium, we estimated muscle tissue clearance grossly by multiplying the extraction ratio obtained for each patient by the average muscle blood flow multiplied by 40% (the percentage of the muscular mass in the body) corrected for plasma fraction (60%). Under these premises, muscle tissue clearance would represent as much as 16% of the total body clearance in most patients. Therefore, although muscle tissue extraction is relatively high for mivacurium (40%), its contribution to the overall clearance seems less important because muscle blood flow represents only 15% of the cardiac output.[18]

As mivacurium undergoes elimination in the muscle tissue, we would expect the concentrations of its primary metabolites to be higher in venous than in arterial blood during steady state conditions. However, the concentrations of the *cis* and *trans* monoesters and of the *trans* alcohol were found to be similar in arterial and venous blood. This finding is not surprising when one considers the long elimination half-lives of the metabolites (100 min)[2] and given that steady state conditions were not reached for the metabolites even after a 2-h infusion of mivacurium. Also, the rate of formation of the metabolites is approximately 50 times faster than their *in vivo* rate of elimination, meaning that during constant

Table 2. Arteriovenous Plasma Concentrations for Mivacurium Metabolites

Patient	Infusion Rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Plasma Concentrations (ng/ml)*		Arteriovenous Extraction (%)
		Arterial	Venous	
		cis monoester		
1	3	879 ± 67	930 ± 169	−6
2	5	527 ± 101	531 ± 100	−1
3†	7	—	—	—
4	5	916 ± 89	838 ± 112	9
5	7	730 ± 79	710 ± 62	3
6	7	885 ± 51	797 ± 45	3
7	5	853 ± 32	793 ± 12	7
8	5	782 ± 16	720 ± 135	−2
Mean	—	796	780	2
SD	—	135	129	5
		trans monoester		
1	3	326 ± 20	343 ± 56	−5
2	5	204 ± 32	207 ± 36	−1
3†	7	—	—	—
4	5	362 ± 201	305 ± 38	−8
5	7	288 ± 84	246 ± 17	2
6	7	269 ± 13	269 ± 13	0
7	5	30 ± 3	277 ± 2	10
8	5	224 ± 38	255 ± 12	−3
Mean	—	270	272	−1
SD	—	41	43	6
		cis alcohol		
1	3	8 ± 1	9 ± 0.2	−14
2	5	6 ± 1	6 ± 0.7	−5
3†	7	—	—	—
4	5	15	15	4
5	7	7 ± 0.2	7 ± 0.5	−11
6	7	4 ± 0.4	4 ± 0.6	0
7	5	5 ± 0.1	5 ± 0.1	0
8	5	3 ± 0.2	3 ± 0.1	0
Mean	—	7	7	−4
SD	—	4	4	7
		trans alcohol		
1	3	193 ± 16	204 ± 31	−5
2	5	123 ± 25	125 ± 29	−2
3†	7	—	—	—
4	5	129 ± 20	115 ± 17	11
5	7	92 ± 6	89 ± 3	3
6	7	97 ± 6	95 ± 10	2
7	5	117 ± 5	117 ± 4	0
8	5	116 ± 2	116 ± 3	1
Mean	—	124	123	1
SD	—	33	38	5

* Each value represents the mean concentration obtained for the three periods ± SD after normalization to an infusion rate of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. † Metabolites were not available.

infusion of mivacurium, extensive formation of metabolites overrides their elimination.

It is well recognized that arterial blood provides the most reliable pharmacokinetic parameters.[13,15,16,20,21] The use of venous blood for studying mivacurium kinetics would lead to substantial overestimation of mivacurium clearance and volume of distribution. This was clearly demonstrated in our study since mivacurium arterial body clearance was as much as 34 and 44% lower than venous clearance for the *trans trans* and *cis trans* isomers, respectively. Such a difference was not observed with the *cis cis* isomer. It is worth emphasizing that the arterial clearances observed herein are similar to those reported by Lacroix *et al.*,[2] who used arterial blood, but 50% lower than those reported by other investigators when venous blood was used.[1,5,6] Likewise, plasma clearance calculated using venous data are in close agreement with previous published data.[1,5,6] Theoretically, for mivacurium and other ultra–short-acting drugs eliminated in peripheral tissue, infusion regi-

mens based on arterial rather than venous concentrations would be more appropriate, especially in patients with a high arteriovenous gradient.

The sampling site not only affect pharmacokinetic parameters, but also pharmacokinetic–pharmacodynamic estimates. This is particularly true for a drug such as mivacurium that is rapidly eliminated within the sampling tissue itself. Several investigators[13,16,20,22,23] pointed out the implications of an arteriovenous gradient on the concentration–effect relation. Parameters such as the EC_{50}, k_{eo} (the rate constant describing the lag time between concentration and effect), and γ (the slope factor) have been shown to differ for atracurium. A 40% higher EC_{50} value and a 47% lower k_{eo} were observed for atracurium when arterial data were used instead of venous data.[22] To our knowledge, the concentration–effect relation of the two active isomers of mivacurium has not been characterized in patients using a traditional model with a link to the central compartment although a model with a link to the peripheral compartment has been proposed.[24] Modeling difficulties are certainly attributable to the inherent complexity of this drug, although the presence of peripheral elimination may also contribute as the extraction of mivacurium across the forearm varies considerably between patients. This observation is in support of the large interindividual variability in the infusion rates required to obtain a stable neuromuscular blockade[25,26] and in the time required to obtain spontaneous recovery from mivacurium neuromuscular blockade.[26–29]

Such a high interindividual variability in tissue metabolism is not surprising because mivacurium is hydrolyzed by plasma cholinesterase, an enzyme known to exhibit genetic polymorphism. Approximately 24% of the white population carries at least one genetic variant allele of the plasma cholinesterase enzyme.[30] Patients with plasma cholinesterase deficiency exhibited slow hydrolysis of mivacurium and, consequently, a prolonged neuromuscular block.[26,28,31–34] Muscle tissue hydrolysis of mivacurium may complicate the situation because butyrylcholinesterase activity may differ between plasma and tissue. Such variability warrants monitoring of neuromuscular blockade in patients receiving mivacurium.

In conclusion, the major finding of our study is that significant extraction of the two active isomers of mivacurium occurs during their transit through the forearm, confirming the presence of an important elimination in peripheral tissue. This fact added to the known genetic polymorphism of plasma cholinesterase may account for the large intersubject variability in infusion rates and pharmacologic response of mivacurium. Therefore, arterial samples should be preferred to venous samples in studies designed to characterize the concentration–effect relation of such drugs; otherwise, conclusions may be wrong.

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