The Pharmacokinetics and Steady State Pharmacodynamics of Mivacurium in Children

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Background: The authors previously showed that children require larger infusion rates of mivacurium than adults to maintain target twitch depression. Here, they determined whether there are differences between children and adults in mivacurium's pharmacokinetic and pharmacodynamic properties.

Methods: Twenty-seven patients aged 1–58 yr were anesthetized with nitrous oxide and isoflurane. Cholinesterase activity and adductor pollicis twitch tension in response to train-of-four stimuli were measured. Mivacurium was infused, targeting 90% twitch depression. When twitch was stably depressed 85%–95% for 10 min with no change in infusion rate for 15 min, plasma was sampled to determine concentrations of mivacurium's stereoisomers. Clearance of the *trans-trans* ($Cl_{trans-trans}$) and *cis-trans* ($Cl_{cis-trans}$) isomers was determined as the mivacurium infusion rate (adjusted for isomer composition) divided by the concentration of that isomer. Using the Hill equation, assuming equipotency of the *trans-trans* and *cis-trans* isomers, and ignoring the contribution of the nonpotent *cis-cis* isomer, the authors estimated the steady state plasma concentration yielding 90% twitch depression, C_{90}. The effect of age on cholinesterase activity, the infusion rate depressing twitch tension by 90% (IR_{90}), C_{90}, $Cl_{trans-trans}$, and $Cl_{cis-trans}$ was determined using linear regression.

Results: Cholinesterase activity, IR_{90}, and C_{90} did not vary with age. Both $Cl_{trans-trans}$ ($r^2 = 0.19$, $P = 0.01$) and $Cl_{cis-trans}$ ($r^2 = 0.19$, $P = 0.02$) decreased with age.

Conclusion: Clearance of mivacurium's potent isomers is larger in younger patients, consistent with the larger mivacurium infusion requirement in children than in adults reported previously. (Key words: Drug infusions; muscle relaxants; plasma cholinesterase; pseudocholinesterase.)

WE[1] previously showed that children aged 1–9 yr require approximately two times more mivacurium than adults to maintain 50% twitch depression, despite the fact that they have similar activity of plasma cholinesterase (the enzyme believed to degrade mivacurium[2]). At steady state, the quantity of mivacurium infused to maintain target twitch depression depends on two factors: plasma clearance of the drug and the concentration of drug required to produce target twitch depression. The larger mivacurium infusion requirement in children than in adults results from maturational differences in either plasma clearance, neuromuscular junction sensitivity, or both. To determine whether plasma clearance or neuromuscular junction sensitivity (or both) varies with age, we infused mivacurium to produce approximately 90% twitch depression at steady state and measured mivacurium isomer concentrations. We used the Hill equation to estimate the steady state plasma concentration producing 90% twitch tension depression (C_{90}). We also estimated plasma clearance of mivacurium's potent *trans-trans* and *cis-trans* isomers.

Methods

After obtaining approval from our institutional review board and informed consent from parents or patients, we studied 15 patients aged 1–12 yr and 14 patients aged 13–58 yr, all of them classified as American Society of Anesthesiologists physical status I or II, who were scheduled for elective surgery. Patients with neuromuscular, renal, or hepatic disease, and those with any condition or requiring any medications known to alter neuromuscular function were excluded. In children, anesthesia was induced by mask with nitrous oxide and

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halothane; in adults, anesthesia was induced with intravenous propofol (1–3 mg/kg) and fentanyl (5 μg/kg). Tracheal intubation was performed without the use of muscle relaxants. After tracheal intubation, anesthesia was maintained with 60% nitrous oxide and isoflurane. The end-tidal isoflurane concentration was maintained at 0.8% in patients <13 yr and at 0.64% in patients ≥13 yr for >20 min before mivacurium was infused and until the study was complete. Ventilation was controlled to maintain normocapnia. Electrocardiography, noninvasive blood pressure, and pulse oximetry were monitored continuously. Esophageal temperature was maintained between 35.5–37.9°C. After induction of anesthesia and before infusion of mivacurium, 3 ml venous blood was sampled to determine plasma cholinesterase activity and dibucaine inhibition photometrically using acetylthiocholine as a substrate (Smith-Kline Beecham Clinical Laboratories, Van Nuys, CA).

Train-of-four supramaximal stimuli were applied to the ulnar nerve *via* subcutaneous 27-gauge needles at the wrist. Mechanical twitch response of the adductor pollicis was measured using a calibrated force displacement transducer and amplified. Twitch tension was digitized, displayed, and recorded on-line. Evoked twitch tension was also recorded on a strip chart. The first twitch response of each train-of-four (T1) was stable for at least 20 min before mivacurium infusion.

Mivacurium was initially infused at $4\ \mu g \cdot kg^{-1} \cdot min^{-1}$ in patients <13 yr old and $2\ \mu g \cdot kg^{-1} \cdot min^{-1}$ in patients ≥13 yr old until twitch depression was stable for >10 min; the minimum duration of this infusion was 30 min. We assumed that twitch depression related to steady state mivacurium infusion rate by the Hill equation[3]:

$$\text{Twitch depression} = \frac{\text{Infusion rate}^\gamma}{(\text{Infusion rate}^\gamma + IR_{50}{}^\gamma)}$$

where IR_{50} is the infusion rate depressing twitch tension by 50% and γ is the Hill factor governing the sigmoidicity of the relation between infusion rate and twitch depression. Using the twitch depression produced by a given infusion rate of mivacurium and a previously reported[3] value of 2.6 for γ, we determined the mivacurium infusion rate predicted to depress twitch tension 90% [IR_{90} (predicted)]. Mivacurium was then infused at IR_{90} (predicted) until twitch tension was stable for >10 min. If twitch tension stabilized outside of the range 85%–95%, IR_{90}(predicted) was estimated again and mivacurium was infused at that rate to achieve twitch tension as close as possible to target 90%. Steady state infusion was defined as a constant infusion rate for at least 15 min with at least 10 min of stable twitch tension (<2% change in twitch tension). The infusate was sampled to determine the concentration of each of the mivacurium isomers.

Venous blood (5 ml/sample) was sampled 10 min and 1 min before and 2, 4, 6, and 8 min after discontinuing the mivacurium infusion; in three patients ages 1, 16, and 58 yr, arterial rather than venous blood was sampled. In one patient who was 35 yr old, vascular access was interrupted briefly after discontinuing the mivacurium infusion and venous blood was sampled at only 2 and 10 min. To prevent mivacurium from degrading *in vitro*, 1.25 mg phospholine iodide in 100 μl H_2O was added to each sample immediately; samples were iced within 1 min and separated and frozen within 1 h.

Plasma concentrations of the three mivacurium isomers were determined using liquid chromatography (model RF-551PC Fluorescence Detector, Shimadzu, Kyoto, Japan). The lower limit of detection of the assay was 5 ng/ml, its calibration was linear over a range of 5–200 ng/ml of each isomer, and the coefficient of variation for the three isomers was ≤16% at 5 ng/ml. Extraction coefficients for each of the mivacurium stereoisomers were >85%.

Plasma clearance of the *trans-trans* and *cis-trans* isomers ($Cl_{trans-trans}$ and $Cl_{cis-trans}$, respectively) was determined as the mivacurium infusion rate (adjusted for isomer composition) divided by the steady state concentration of that isomer. Using the Hill equation, we estimated the steady state plasma concentration that depressed twitch tension by 90% (C_{90}) for each patient, assuming that the *trans-trans* and *cis-trans* isomers were equipotent and ignoring any neuromuscular effect of the nonpotent *cis-cis* isomer. We also estimated the IR_{90} using the Hill equation, the final infusion rate, and the resulting twitch depression; γ was assigned the value 2.6.

The effect of (log) age on clearance of each of the potent mivacurium isomers, C_{90}, IR_{90}, and plasma cholinesterase, was determined by analysis of linear regression. These values were compared using Student's t test between patients younger and older than 13 yr. In addition, the effect of plasma cholinesterase on $Cl_{trans-trans}$ and $Cl_{cis-trans}$ was determined by analysis of linear regression.

Postinfusion concentrations of the *trans-trans* and *cis-trans* isomers of mivacurium were plotted against time. Because these plots failed to reveal the expected monoexponential decay of mivacurium concentrations (and there were insufficient data from each patient to

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Table 1. Values for Plasma Cholinesterase Activity, IR_{90}, Clearance of Mivacurium Isomers, C_{90}, and Time for Twitch Tension to Recover from 25% to 75% of Control

	Age Group	
	1–12 yr	13–58 yr
Plasma cholinesterase activity (IU/ml)	4.0 ± 0.9 (1.0)	4.7 ± 1.7 (11)
IR_{90} ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	6.1 ± 1.9 (14)	5.9 ± 2.2 (13)
$Cl_{trans\text{-}trans}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)*	132 ± 80 (14)	80 ± 32 (13)
$Cl_{cis\text{-}trans}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)*	230 ± 176 (13)	121 ± 31 (13)
C_{90} (ng/ml)	50 ± 18 (13)	71 ± 33 (13)
Time for twitch tension to recover from 25% to 75% of control (min)	7.3 ± 3.6 (13)	6.7 ± 1.8 (12)

Values are mean ± SD, N in parentheses. Clearance of the *cis-cis* isomer of mivacurium was not determined (see Discussion).

* Children differ from adults ($P < 0.05$) by Student's *t* test for unpaired data.

fit a polyexponential curve), it was not appropriate to quantify mivacurium washout by fitting exponential curves to these concentration values. Instead, postinfusion concentration values for the *trans-trans* isomer were divided by the average of the two concentration values obtained during the infusion for that patient. For each sampling time, ratios for each patient were plotted against (log) age and analyzed by linear regression. In addition, values for patients <13 yr were compared with those for older patients using Student's *t* test for unpaired data. Values for *cis-trans* isomer concentrations were not analyzed in a similar manner because, in most patients, this isomer could not be detected 2 min after the infusion was stopped. Time for twitch tension to recover from 25% to 75% of the control value was determined. These values were plotted against (log) age and analyzed by linear regression.

Values are reported as means ± SD. Probability values <0.05 were considered significant.

Results

Two patients had values for plasma cholinesterase activity outside the normal range (2.0–6.5 U/ml): one adult greater (8.6 U/ml) and one child less (1.5 U/ml) than normal bounds; these patients were excluded from all analyses. Values for dibucaine inhibition were within normal limits for all patients. For one patient who was 26 yr old, twitch depression was stable at 84%; for the remaining 26 patients, twitch depression was stable between 87–94%. The *trans-trans* isomer constituted 60

± 1% of the mivacurium infusate, the *cis-trans* isomer 34 ± 1%, and the *cis-cis* isomer the remaining 6 ± 1%.

In six patients aged 1, 2, 7, 11, 26, and 35 yr, we could not determine plasma cholinesterase activity. In the remaining 21, plasma cholinesterase activity did not vary with (log) age ($r^2 = 0.03$, $P = 0.23$; table 1). The infusion rate that depressed twitch tension by 90% (IR_{90}) did not vary with age ($r^2 < 0.01$, $P = 0.86$; fig. 1).

Clearance of the *trans-trans* isomer decreased with age ($r^2 = 0.19$, $P = 0.01$; fig. 2). For one patient who was 4 yr old, the concentration of the *cis-trans* isomer during the infusion was less than the limit of detection of the assay; $Cl_{cis\text{-}trans}$ was not calculated for this patient. For the remaining 26 patients, clearance of the *cis-trans* isomer decreased with age ($r^2 = 0.19$, $P = 0.02$; fig. 2). There was no relation between plasma cholinesterase activity and either $Cl_{trans\text{-}trans}$ ($r^2 = 0.08$, $P = 0.12$) or $Cl_{cis\text{-}trans}$ ($r^2 = 0.02$, $P = 0.26$). Both $Cl_{trans\text{-}trans}$ and $Cl_{cis\text{-}trans}$ were greater in patients younger than 13 yr compared with older patients.

C_{90} was not calculated for the patient in whom the *cis-trans* isomer was not detected during the infusion. For the remaining 26 patients, C_{90} was not related to (log) age ($r^2 = 0.08$, $P = 0.09$; fig. 3). C_{90} did not differ in patients younger than 13 yr compared with those who were 13 yr and older ($P = 0.06$).

Two minutes after the infusion was discontinued, the concentration of the *trans-trans* isomer averaged 37 ± 12% of the value during the infusion. There was no relation between these values and age (fig. 4, table 2). Similarly, these values at 4, 6, and 8 min after infusion
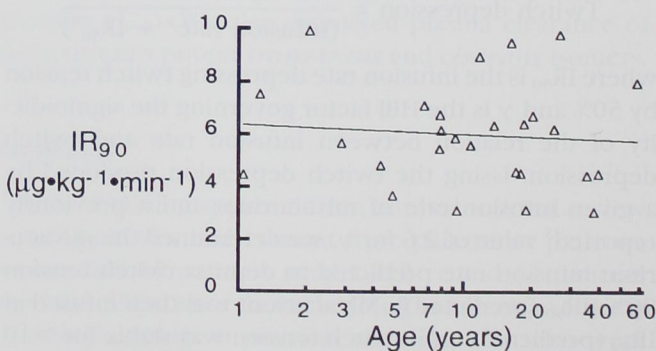

Fig. 1. The infusion rate expected to yield 90% twitch depression is plotted against (log) age; this value was calculated using the Hill equation from the infusion rate that yielded approximately 90% twitch depression and the resulting twitch depression. Triangles represent measured values; the line was obtained by analysis of linear regression ($r^2 < 0.01$, $P = 0.86$).
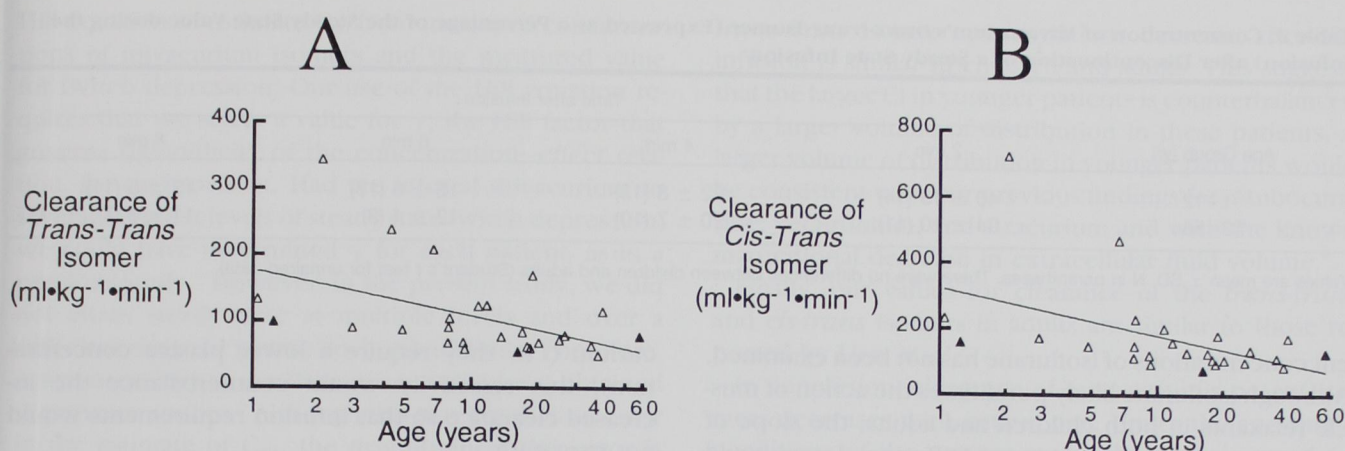
A

B

Fig. 2. Clearance of mivacurium's *trans-trans* isomer (*A*) and *cis-trans* isomer (*B*) are plotted against (log) age. Triangles represent measured values. Open symbols are based on venous samples, and closed symbols are based on arterial samples. The line was obtained by analysis of linear regression (*trans-trans:* $r^2 = 0.19$, $P = 0.01$; *cis-trans:* $r^2 = 0.19$, $P = 0.02$).

did not vary with age. In two patients, neuromuscular monitoring was discontinued before twitch tension recovered to 75% of the control value. In the remaining 25 patients, the time for twitch tension to recover from 25% to 75% of the control value did not vary with age ($r^2 = 0.10$, $P = 0.07$); the median value was 6.4 min.

Discussion

We previously showed that mivacurium infusion rates to produce the IR_{50} in children exceed values for adults.[1] In contrast, the present study did not demonstrate age-related changes in the IR_{90} infusion rate. We

consider two possible explanations for this discrepancy between studies. First, if the slope of the concentration-effect relation (γ) for mivacurium differed between children and adults, there might be maturational differences in IR_{50} (as in our previous study[1]) but not in IR_{90} (as in the present study). However, unpublished data from our previous studies[1,3] demonstrate that γ is similar for children and adults. Second, anesthetic conditions differed slightly among the studies. Although nitrous oxide and isoflurane were used in both studies, end-tidal isoflurane concentrations were larger in the previous study (1.2% in children and 1% in adults) than in the present study (0.8% in children and 0.64% in adults). The neuromuscular potentiating effect of these differ-
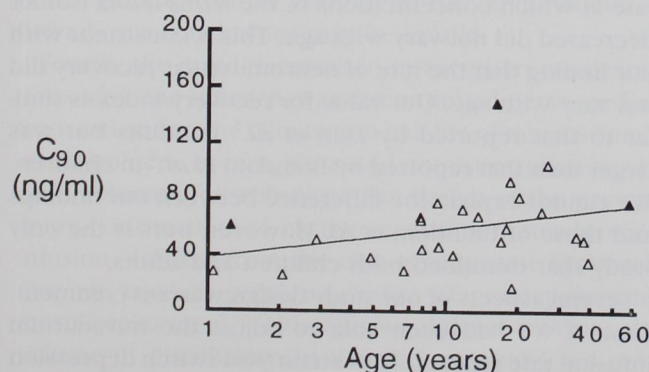

Fig. 3. Values for the plasma concentration of mivacurium producing 90% twitch depression (C_{90}) are plotted against (log) age. Triangles represent measured values. Open symbols are based on venous samples, and closed symbols are based on arterial samples. The line was obtained by analysis of linear regression ($r^2 = 0.08$, $P = 0.09$).
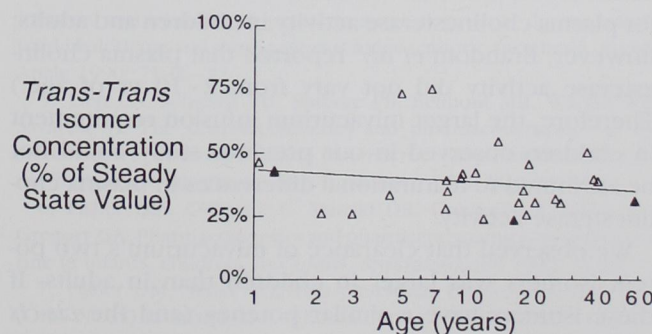

Fig. 4. Values for the concentration of the *trans-trans* isomer 2 min after the infusion was discontinued. Values are expressed as a percentage of the steady state value during the infusion and are plotted against (log) age. Triangles represent measured values. Open symbols are based on venous samples, closed symbols on arterial samples. The line was obtained by analysis of linear regression ($r^2 = 0.06$, $P = 0.12$).

Table 2. Concentration of Mivacurium's *trans-trans* Isomer (Expressed as a Percentage of the Steady State Value during the Infusion) after Discontinuation of a Steady State Infusion

Age Group (yr)	Time after Infusion			
	2 min	4 min	6 min	8 min
1–12	40 ± 13 (14)	22 ± 8 (13)	16 ± 6 (13)	12 ± 5 (11)
13–58	34 ± 10 (11)	20 ± 7 (10)	12 ± 4 (9)	11 ± 3 (7)

Values are mean ± SD, N in parentheses. There were no differences between children and adults (Student's *t* test for unpaired data).

ent concentrations of isoflurane has not been examined. Although isoflurane likely potentiates the action of muscle relaxants in both children and adults, the slope of such potentiation is unknown. Differing slopes could produce one effect at a certain multiple of minimum alveolar concentration and a different effect at a different multiple of minimum alveolar concentration. In turn, providing equal minimum alveolar concentration fractions of the potent inhaled anesthetic may not adjust for such a difference appropriately. Additional studies are needed to determine the influence of age on the potentiation produced by different minimum alveolar concentration fractions of potent inhaled anesthetics.

The present study was designed to explain whether the larger infusion requirement for mivacurium in children observed previously resulted from maturational changes in pharmacodynamics or in pharmacokinetics. Because mivacurium is believed to be eliminated predominantly by plasma cholinesterase,[2] this larger infusion requirement in children might result from greater enzymatic activity in those patients. However, in both the present study and our previous investigation,[1] plasma cholinesterase activity was comparable in children and adults. (No other study has obtained values for plasma cholinesterase activity in children and adults; however, Brandom *et al.*[4] reported that plasma cholinesterase activity did not vary from 2–10 yr of age.) Therefore, the larger mivacurium infusion requirement in children observed in our previous study could not be attributed to maturational differences in plasma cholinesterase activity.

We observed that clearance of mivacurium's two potent isomers was larger in children than in adults. If these isomers have a similar potency (and the *cis-cis* isomer is markedly less potent), then children will require a larger infusion rate to maintain plasma concentrations of mivacurium comparable to those in adults. In turn, if sensitivity to mivacurium did not vary with age, infusion requirements would be larger in younger patients. Conversely, if children were sensitive to miva-

curium (*i.e.*, they require a lower plasma concentration), this sensitivity would counterbalance the increased clearance so that infusion requirements would not vary with age.

Although maturational differences in neuromuscular junction sensitivity were not significant, the *t* test comparing C_{90} in children and adults and linear regression of C_{90} compared with age approached significance ($P = 0.06$, table 1; and $P = 0.09$, fig. 3, respectively). This suggests that, under the anesthetic conditions of the present study, there might be maturational changes in sensitivity to mivacurium and that these changes counterbalance the larger clearance of mivacurium's potent isomers in children. This is consistent with our finding in the present study that mivacurium's infusion rate did not change with age. In contrast, in our previous study, mivacurium's infusion rate was greater in children than in adults. This suggests that under the anesthetic conditions of that study, sensitivity to mivacurium did not change with age, so that the larger clearance of mivacurium's potent isomers resulted in a larger infusion requirement in children compared with adults.

After the mivacurium infusion was discontinued, the rate at which concentrations of the *trans-trans* isomer decreased did not vary with age. This is consistent with our finding that the rate of neuromuscular recovery did not vary with age. Our value for recovery index is similar to that reported by Lien *et al.*[5] in adults but was larger than that reported by Brandom *et al.*[4] in children. We cannot explain the difference between our findings and those of Brandom *et al.* However, ours is the only study that examined both children and adults.

Several aspects of our study design warrant comment. First, if we had been able to adjust the mivacurium infusion rate repeatedly to attain 90% twitch depression in each patient, measured values for mivacurium concentrations would represent those producing 90% twitch depression. However, time constraints prevented us from attaining exactly 90% twitch depression in most of our patients. As a result, we had to use the

Hill equation to estimate C_{90} from measured concentrations of mivacurium isomers and the measured value for twitch depression. Our use of the Hill equation requires that we select a value for γ, the Hill factor that governs sigmoidicity of the concentration–effect relation, for each patient. Had we infused mivacurium to several different levels of steady state twitch depression, we could have determined γ for each patient, as in a previous study.[3] However, in the present study, we did not attain steady state at multiple levels and over a sufficient range to permit such calculations. Therefore, it was necessary to use the average value for γ obtained in previous studies.[3] Although this may result in an error in the estimate of C_{90}, the magnitude of this error is probably small. For example, if we attained 85% twitch depression and the true value for γ were 3, using a value of 2.6 for γ would make our estimate of C_{90} incorrect by only 2.4%.

Second, we did not estimate clearance of the *cis-cis* isomer. Previous studies have shown that clearance of this isomer is markedly less than that of the remaining isomers and that the elimination half-life of this isomer exceeds 45 min. Therefore, our study design did not result in a sufficient period of constant mivacurium infusion to ensure steady state conditions for that isomer.

Third, we ignored any contribution of the *cis-cis* isomer to the neuromuscular effects of mivacurium. This was based on studies in cats# showing that the potency of this isomer is one tenth that of the remaining isomers. Although the *cis-cis* isomer represents only 6% of the administered drug, its low clearance (<one tenth that of the other isomers[5]) results in its concentration being similar to that of the *trans-trans* isomer. If this assumption regarding relative potency of the *cis-cis* isomer is flawed, our conclusions may be invalid.

Fourth, the rapid decrease in mivacurium concentrations after the infusion was discontinued prevented us from estimating the elimination half-life of mivacurium's stereoisomers. In turn, we could not estimate mivacurium's volume of distribution. The design of the present study — estimation of clearance during a steady state infusion — differs from the non–steady state approach that we used in previous studies of nondepolarizing muscle relaxants.[6-8] Although we did not estimate the volume of distribution in the present study, we note that Cl is larger in younger patients but the rate at which

trans-trans isomer concentrations decrease after the infusion is similar in children and adults. This suggests that the larger Cl in younger patients is counterbalanced by a larger volume of distribution in these patients. A larger volume of distribution in younger patients would be consistent with our previous findings for *d*-tubocurarine, vecuronium, and atracurium and with the known maturational decrease in extracellular fluid volume.[9]

Finally, our values for clearance of the *trans-trans* and *cis-trans* isomers in adults are similar to those reported by Lien *et al.*[5]

In conclusion, clearance of mivacurium's potent isomers decreases with patient age. Under the anesthetic conditions of the present study, there was a trend toward a change in neuromuscular junction sensitivity with age. These maturational changes in mivacurium's clearance and neuromuscular junction sensitivity to mivacurium counterbalance so that, under these anesthetic conditions, the infusion rate to maintain 90% twitch depression does not vary with age. The latter finding differs from that of a previous study from our institution.

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