

# Potential of Mivacurium Blockade by Low Dose of Pancuronium

## A Pharmacokinetic Study

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**Background:** Mivacurium is potentiated by pancuronium to a much greater extent than other relaxants. In a previous investigation we suggested that this potentiation could be due to the ability of pancuronium to inhibit plasma cholinesterase activity, but we did not measure plasma concentrations of mivacurium. In the current study we performed a pharmacokinetic analysis by measuring the plasma concentration of mivacurium when preceded by administration of a low dose of pancuronium.

**Methods:** After induction of general anesthesia with propofol and fentanyl and orotracheal intubation, 10 patients (pancuronium-mivacurium group) received 15 µg/kg pancuronium followed 3 min later by 0.1 mg/kg mivacurium, whereas 10 other patients (mivacurium group) received saline followed by 0.13 mg/kg mivacurium 3 min later. Plasma cholinesterase activity was measured before and 3 and 30 min after pancuronium dosing in the pancuronium-mivacurium group and was measured before and after administration of saline in the mivacurium group. Arterial plasma concentrations of mivacurium and its metabolites were measured at 0.5, 1, 1.5, 2, 4, 10, 20, and 30 min after injection. Neuromuscular blockade was assessed by mechanomyography.

**Results:** Plasma cholinesterase activity decreased by 26% in the pancuronium-mivacurium group 3 min after injection of pancuronium ( $P < 0.01$ ) and returned to baseline values 30 min later; however, no significant variation was observed in the mivacurium group. The clearances of the two most active isomers (Cis-Trans and Trans-Trans) were lower in the pancuronium-mivacurium group ( $17.6 \pm 5.1$ ,  $14.7 \pm 5.3$  ml · min<sup>-1</sup> · kg<sup>-1</sup>, respectively) than in the mivacurium group ( $32.4 \pm 20.2$ ,  $24.8 \pm 13.5$  ml · min<sup>-1</sup> · kg<sup>-1</sup>;  $P < 0.05$ ).

**Conclusions:** A subparalyzing dose of pancuronium decreased plasma cholinesterase activity and the clearance of the two most active isomers of mivacurium. Pancuronium potentiates mivacurium more than other neuromuscular blocking agents because, in addition to its occupancy of postsynaptic acetylcholine receptors, it slows down the hydrolysis of mivacurium.

PANCURONIUM potentiates mivacurium to a much greater extent than other muscle relaxants.<sup>1-5</sup> Pancuronium differs from other neuromuscular blocking agents by its ability to inhibit plasma cholinesterase (Bche).<sup>6,7</sup> Because mivacurium is rapidly hydrolyzed by Bche, potentiation of mivacurium by pancuronium could also result from an inhibition of mivacurium hydrolysis rather than from an interaction at the acetylcholine receptor of the neuromuscular junction. After a previous investigation, in which we used the isolated arm technique, we suggested that potentiation of mivacurium by pancuronium could be most likely explained by an increase in the plasma concentration of mivacurium.<sup>8</sup> However, because we did not measure the plasma concentration of mivacurium, our explanation remained speculative.

Another reason for the interaction between mivacurium and pancuronium could be a pharmacodynamic synergism at the neuromuscular junction. In the present study we explored the pancuronium-mivacurium interaction by measuring the plasma concentration of mivacurium and of its metabolites.

## Materials and Methods

The study protocol was approved by the ethics committee of Joffre Dupuytren University Hospital, Limoges, France, and written informed consent was obtained from each patient. The 20 patients enrolled in the study were 18-65 yr old and were to undergo elective major vascular and orthopedic surgery during general anesthesia with tracheal intubation, necessitating an arterial line to continuously monitor the blood pressure. Patients with histories of renal, hepatic, or neuromuscular disease, those taking medication known to interfere with neuromuscular function or Bche activity, and those with anticipated airway difficulties were excluded from the study. Premedication was at the discretion of the anesthetist.

After placement of an intravenous line and a radial artery catheter for invasive monitoring of the blood pressure, anesthesia was induced with fentanyl (3-4 µg/kg) and propofol (2-3 mg/kg). Orotracheal intubation was performed without muscle relaxants and anesthesia was maintained with the inhalation of 60% nitrous oxide and isoflurane (0.7% end-tidal) in oxygen delivered by con-

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trolled ventilation and the repeated administration of 1–2  $\mu\text{g/kg}$  fentanyl. Patients randomly received either an intravenous 15- $\mu\text{l/kg}$  injection of saline, followed 3 min later by a single slow (10-sec) intravenous 130- $\mu\text{g/kg}$  injection of mivacurium (mivacurium group) or an intravenous 15- $\mu\text{g/kg}$  injection of pancuronium followed 3 min later by a slow intravenous 10-sec injection of 100  $\mu\text{g/kg}$  mivacurium (pancuronium-mivacurium group). Esophageal temperature was measured in all patients and maintained by surface air-warming between 36 and 37°C.

#### *Monitoring of Neuromuscular Function*

The ulnar nerve of the arm opposite the radial artery cannula was stimulated supramaximally (60 mA) with train-of-four stimulation every 12 sec. The evoked thumb response was measured with a force transducer (Entran®, Les Clayes-sous-Bois, France) with a preload of 300 g and was recorded continuously on a polygraph. After a delay of 5 min of stabilization, the following parameters were recorded: the maximum degree of neuromuscular blockade ( $E_{\text{max}}$ ), the time from injection to reaching  $E_{\text{max}}$  (onset time), and the times to spontaneous return of the evoked twitch to 25%, 75%, and 90% of control response (TH 25, TH 75, and TH 90).

#### *Sampling*

Arterial blood samples were withdrawn with 5-ml heparinized syringes prefilled with 50  $\mu\text{l}$  solution (2 mg/ml echothiophate, a potent plasma cholinesterase inhibitor). The arterial cannula was connected directly to a three-way stopcock. Blood samples for Bche measurement were collected before induction of anesthesia in both groups and also at 3 and 30 min after pancuronium dosing in the pancuronium-mivacurium group and 3 and 30 min after the saline dosing in the mivacurium group. For the mivacurium assay, blood samples were collected and at 30, 60, and 90 sec and 4, 10, 20, and 30 min after mivacurium injection. All sampling was performed before skin incision.

Samples were transferred in plastic tubes, kept on ice, and centrifuged at 5,000  $t/\text{min}$  at 4°C for 7 min. The plasma was stored at –75°C until liquid chromatographic analysis. Bche activity was measured by a colorimetric method (Sigma Diagnostics, St. Louis, MO); the normal range of Bche was 3,000–10,000 IU/l, and the coefficient of variation was of 5%. The dibucaine number was measured from blood samples collected before induction of anesthesia. Dibucaine numbers for carriers of the usual gene were greater than 83.<sup>9</sup>

#### *Mivacurium Assay*

Plasma concentrations of the three mivacurium isomers (Cis-Trans, Trans-Trans, and Cis-Cis) and the four metabolites (Cis141 alcohol, Trans 141 alcohol, Cis 879 ester, and Trans 879 ester) were measured by means of

high-performance liquid chromatography coupled with fluorometric detection.<sup>10</sup> The lower limit of detection of mivacurium isomers was 10 ng/ml, and the coefficient of variation was 10%.

#### *Pharmacokinetic Analysis*

The plasma concentration *versus* time data were analyzed with use of the Kinetica® program (V 200–200; Inna Phase, Philadelphia, PA). The dose of each isomer administered was considered to be 57%, 36%, and 6% of the total dose of mivacurium for the Trans-Trans, Cis-Trans, and Cis-Cis isomers, respectively, as previously described.<sup>11</sup> A noncompartmental approach was used. The total plasma area-under-the curve concentration-time curve (AUC) of mivacurium isomers and its metabolites was calculated on the basis of the theory that the plasma concentration of mivacurium isomers and metabolites was zero at time zero and was normalized to a dose of 100  $\mu\text{g/kg}$  mivacurium. The elimination half-life ( $t_{1/2}$ ) of mivacurium isomers was determined by linear regression analysis. Plasma concentrations of 10 ng/ml or less were excluded from the linear regression analysis. The plasma clearance of the mivacurium isomers was obtained by dividing the equivalent dose of each isomer by the AUC of each isomer. The total apparent volume of distribution in the body ( $V_d\beta$ ) was calculated as follows:  $V_d\beta = \text{Cl} \times t_{1/2}/0.693$ , where Cl is plasma clearance. The maximum concentration of mivacurium isomers and metabolites ( $C_{\text{max}}$ ) was determined.

#### *Statistical Analysis*

Sample size was determined from the data of our previous investigation,<sup>8</sup> which detected a statistically significant difference ( $P < 0.05$ ) greater than 15 min in clinical duration of action, with an SD of 5 min and a power of 0.8.

Results are presented as mean  $\pm$  SD and/or median (range), as appropriate. The data were compared between the two groups with use of the Student  $t$  test or Mann-Whitney rank sum test for unpaired data. Bche values before and after muscle relaxant administration and recovery of muscle relaxation were compared with one-way ANOVA for repeated measurements and paired  $t$  tests. Data were analyzed with StatView for Windows (version 4.5.7; Abacus, Berkeley, CA).

## **Results**

Demographic data are presented in table 1. For all patients Bche activity was within the normal range and was phenotypically normal, as indicated by the dibucaine number (table 2). There was no difference in preoperative Bche between the two groups. In the pancuronium-mivacurium group, Bche significantly decreased, by 26%, 3 min after pancuronium dosing ( $P <$

**Table 1. Characteristics of Patients**

	Mivacurium	Pancuronium-Mivacurium
Age, yr	58 ± 7	53 ± 6
Weight, kg	70 ± 11	74 ± 14
Height, cm	165 ± 8	171 ± 9
Sex, n (male/female)	(4/6)	(3/7)

n = 10 for mivacurium; n = 10 for pancuronium-mivacurium. Values for age, weight, and height shown as mean ± SD.

0.01) and was lower than in the mivacurium group ( $P < 0.05$ ); this difference was no longer detected after 30 min. In the mivacurium group, Bche at 3 and 30 min after saline did not differ from preoperative values.

#### Pharmacokinetic Data

The evolution of the mean plasma concentration *versus* time of the mivacurium isomers is shown in figure 1A-C. The plasma concentrations are expressed as normalized to a dose of 100 µg/kg mivacurium. The plasma concentrations of the Trans-Trans and Cis-Trans isomers in the mivacurium group were lower at 1.5, 2, 4, and 10 min than those in the pancuronium-mivacurium group ( $P < 0.05$ ). The calculated clearance of the two most active isomers was significantly lower in the pancuronium-mivacurium group than in the mivacurium group (table 3) ( $P < 0.05$ ). The maximum concentration of mivacurium metabolites ( $C_{max}$ ) was observed early after the administration of mivacurium, because it corresponded with the blood sample withdrawn at 0.5 or 1 min from almost all patients (table 4). The  $C_{max}$  of metabolites Cis 141 alcohol, Trans 141 alcohol, Cis 879 ester, and Trans 879 ester were significantly lower in the pancuronium-mivacurium group than in the mivacurium group ( $P < 0.05$ ). The dose-normalized AUC values of the metabolites in the pancuronium-mivacurium group were 20% or less than those of the mivacurium group ( $P < 0.05$ ).

**Table 2. Plasma Cholinesterase Activity and Dubicaine Numbers**

	Mivacurium (0.13 mg/kg)	Pancuronium-Mivacurium (15 µg/kg + 0.1 mg/kg)
Dubicaine numbers	86	86
Range	84-88	85-87
Bche, before induction	7500 ± 1000	8500 ± 1200
Range	6000-9000	7000-10000
Bche, 3 min after pancuronium or saline	7700 ± 1200	6300 ± 1300†‡
Range	5500-9500	4800-9000
Percentage of variation	+3 ± 2%	-26 ± 10%*
Bche, 30 min after pancuronium or saline	7600 ± 1200	7800 ± 1000
Range	5500-9200	5800-10000
Percentage of variation	+2 ± 1%	-9 ± 4%

n = 10 for mivacurium; n = 10 for pancuronium-mivacurium.

\*  $P < 0.01$  versus group mivacurium, †  $P < 0.05$  versus group mivacurium, ‡  $P < 0.01$  versus before induction.

Bche = plasma cholinesterase activity.

#### Pharmacodynamic Data

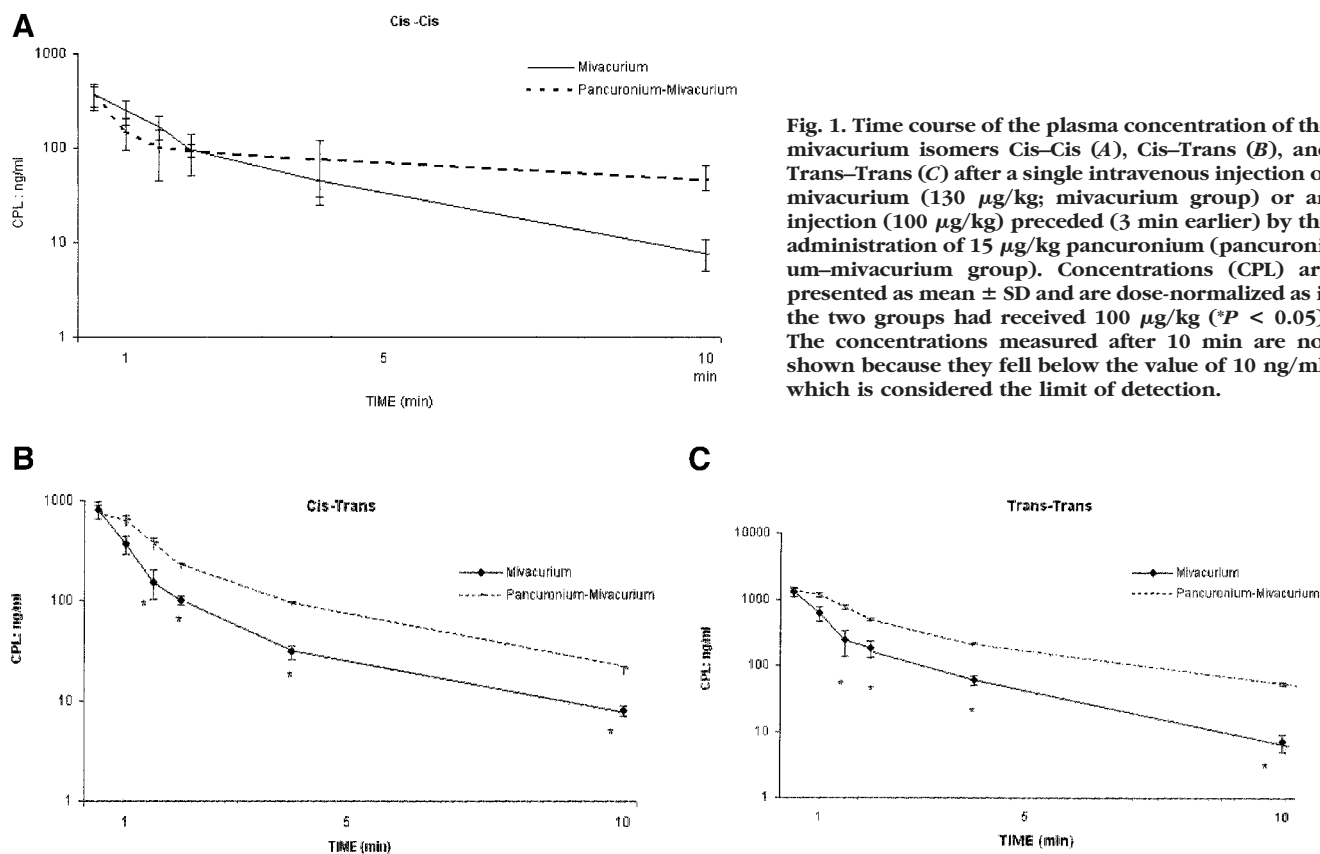
As shown in table 5, the  $E_{max}$  was greater in the pancuronium-mivacurium group than in mivacurium group ( $P < 0.05$ ). Onset of maximum blockade was shorter in the pancuronium-mivacurium group ( $P < 0.05$ ). Duration of neuromuscular blockade was longer in the pancuronium-mivacurium group than in the mivacurium group ( $P < 0.05$ ).

#### Discussion

This study shows that inhibition of Bche by pancuronium contributed to the potentiation of mivacurium by decreasing its plasma clearance.

Several studies have demonstrated that pancuronium potentiates mivacurium to a much greater extent than other nondepolarizing blocking agents.<sup>1-5</sup> Subparalyzing doses of pancuronium potentiate mivacurium by shortening the onset time, increasing the maximum initial depression of twitch height and the duration of action of a single bolus dose,<sup>1,2</sup> or decreasing the dose of mivacurium necessary to maintain a fixed degree of blockade during a continuous infusion.<sup>3</sup> In the present study, a low dose (15 µg/kg) of pancuronium potentiated the effect of a single bolus dose of mivacurium. These results are similar to those we reported after a previous study<sup>8</sup> and those of most other studies exhibiting a potentiating effect of low doses of pancuronium on the neuromuscular blocking effect of mivacurium.<sup>1-3</sup>

In the present study, we choose to administer an equipotent dose of a single muscle relaxant to the combined mixture, although we agree that for a sole pharmacokinetic analysis the administration of the same dose of mivacurium would be preferred. The 100-µg/kg dose of mivacurium with 15 µg/kg pancuronium and the 130-µg/kg dose of mivacurium alone were also used in our previous study.<sup>8</sup> On the basis of the  $ED_{50}$  values of



**Fig. 1.** Time course of the plasma concentration of the mivacurium isomers Cis-Cis (A), Cis-Trans (B), and Trans-Trans (C) after a single intravenous injection of mivacurium (130  $\mu\text{g}/\text{kg}$ ; mivacurium group) or an injection (100  $\mu\text{g}/\text{kg}$ ) preceded (3 min earlier) by the administration of 15  $\mu\text{g}/\text{kg}$  pancuronium (pancuronium-mivacurium group). Concentrations (CPL) are presented as mean  $\pm$  SD and are dose-normalized as if the two groups had received 100  $\mu\text{g}/\text{kg}$  (\* $P < 0.05$ ). The concentrations measured after 10 min are not shown because they fell below the value of 10 ng/ml, which is considered the limit of detection.

58  $\mu\text{g}/\text{kg}$  for mivacurium and 38  $\mu\text{g}/\text{kg}$  for pancuronium reported by Rautoma *et al.*,<sup>12</sup> we assume that the pancuronium-mivacurium combination would be nearly equipotent to the sole dose of mivacurium used in our study if there were no synergy between these two muscle relaxants. Compared with the single 130- $\mu\text{g}/\text{kg}$  dose of mivacurium, the pancuronium-mivacurium combination caused an overall doubling in the duration of action. In addition, the onset time was shorter and the degree of maximum blocking effect was greater in the pancuronium-mivacurium group than in the mivacurium group.

The simultaneous measurement of the plasma concentration of mivacurium isomers and its neuromuscular effect may have permitted the development of a combined pharmacokinetic-pharmacodynamic analysis. Nevertheless, we preferred to limit our analysis to the present data, because mivacurium consists of several isomers with different potencies that necessitate too many extrapolations for a proper pharmacokinetic-pharmacodynamic analysis.

There are at least two theories to explain the synergism between mivacurium and pancuronium. First, at the level of the two  $\alpha$  subunits of the acetylcholine receptor of the neuromuscular junction, more receptors may be occupied when structurally different muscle relaxants are given simultaneously.<sup>13</sup> In this respect, pancuronium is known to exhibit a particularly large difference in affinity for the two  $\alpha$  subunits.<sup>13</sup> Second,

pancuronium is known to inhibit plasma Bche, which hydrolyzes mivacurium.<sup>6,7</sup> Although the inhibitory effect of pancuronium on Bche is clearly documented by *in vitro* experiments,<sup>6,7</sup> the *in vivo* effect has been considered insignificant at a low dose of pancuronium<sup>12</sup> comparable to the dose used in our study. The inhibition of Bche that we observed in the current study was only 26% and was transient: it was detected 3 min but not 30 min after pancuronium administration.

Inhibition of Bche may potentiate the effect of mivacurium two ways. First, the decreased plasma clearance will slow down the plasma decay curve and therefore increase the duration of action. The greatest drug-induced prolongation of action of mivacurium was reported by Østergaard *et al.*<sup>14</sup> after bambuterol dosing, which caused almost complete inhibition of Bche. The mild inhibitory effect of metoclopramide on Bche also caused a significant increase in duration of action<sup>15,16</sup> of mivacurium. In the present study a 26% transient decrease in Bche led to a 50% decrease in plasma clearance of the most active isomers. Cook *et al.*<sup>17</sup> showed that the rate of mivacurium hydrolysis by Bche *in vitro* followed a first-order kinetic, but in the same study, they showed that the relationship between Bche activity and mivacurium *in vitro* half-life is not linear but hyperbolic. Therefore, it is conceivable that there is no linear relationship *in vivo* between Bche and mivacurium clearance.



Table 3. Pharmacokinetics Data

	Mivacurium (0.13 mg/kg)	Pancuronium- Mivacurium (15 $\mu$ g/kg + 0.1 mg/kg)
T <sub>1/2</sub> , min	—	—
Cis-Cis	26 $\pm$ 5	28 $\pm$ 4
Cis-Trans	1.5 $\pm$ 0.7	2.4 $\pm$ 0.7*
Trans-Trans	1.2 $\pm$ 0.6	2.3 $\pm$ 7*
Cl, ml $\cdot$ min <sup>-1</sup> $\cdot$ kg <sup>-1</sup> )	—	—
Cis-Cis	7 $\pm$ 4	6 $\pm$ 3
Cis-Trans	32.4 $\pm$ 20.2	17.6 $\pm$ 5.1*
Trans-Trans	24.8 $\pm$ 13.5	14.7 $\pm$ 5.3*
AUC total, ng $\cdot$ min $\cdot$ ml <sup>-1</sup> )	—	—
Cis-Cis	1000 $\pm$ 620	1000 $\pm$ 600
Cis-Trans	1400 $\pm$ 870	2236 $\pm$ 696*
Trans-Trans	2400 $\pm$ 1150	4306 $\pm$ 1539*
Vd $\beta$ (l/kg)	—	—
Cis-Cis	0.26 $\pm$ 0.01	0.24 $\pm$ 0.01
Cis-Trans	0.07 $\pm$ 0.03	0.06 $\pm$ 0.02
Trans-Trans	0.05 $\pm$ 0.03	0.05 $\pm$ 0.03

Values are shown as mean  $\pm$  SD or median (range) as appropriate. n = 10 for mivacurium; n = 10 for pancuronium-mivacurium. Estimated clearance, T<sub>1/2</sub>, total AUC normalized to a dose of 100  $\mu$ g/kg mivacurium, and the total apparent volume of distribution Vd $\beta$ .

\*  $P < 0.05$  versus group mivacurium.

AUC = area under the curve; T<sub>1/2</sub> = terminal half-life.

A second mechanism by which inhibition of Bche may potentiate mivacurium is an increase in the fraction of the dose reaching the neuromuscular junction; most of the dose of mivacurium administered is hydrolyzed on its way to the neuromuscular junction.<sup>10</sup> In patients with inherited Bche deficiency, mivacurium becomes a highly potent agent because its ED<sub>95</sub> decreases by a factor of 5 (from 75 to 15  $\mu$ g/kg).<sup>18</sup> To test the hypothesis that inhibition of Bche may increase the amount of mivacurium delivered to the neuromuscular junction, we performed early arterial blood sampling after mivacurium

Table 5. Pharmacodynamic Data

	Mivacurium	Pancuronium-Mivacurium
Onset, sec	192 $\pm$ 33	127 $\pm$ 42*
E <sub>max</sub> , %	96 $\pm$ 4	100*
T <sub>25</sub> %, min	16 $\pm$ 5	41 $\pm$ 9*
T <sub>75</sub> %, min	25 $\pm$ 6	61 $\pm$ 8*
T <sub>90</sub> %, min	29 $\pm$ 7	69 $\pm$ 9*

Values are mean  $\pm$  SD versus group mivacurium. n = 10 for mivacurium; n = 10 for pancuronium-mivacurium.

\*  $P < 0.05$ .

injection. Because of the rapid hydrolysis of mivacurium in the plasma and probably in the skeletal muscles,<sup>19</sup> it is important to perform early arterial sampling.<sup>11</sup> We observed that the peak plasma concentration of the two potent (Trans-Trans and Cis-Trans) isomers was within the same range in both groups, although the dose of mivacurium was lower in the pancuronium-mivacurium group. Therefore, inhibition of Bche resulted in an increase in the initial plasma concentration of mivacurium, although this effect was of a lesser magnitude than we expected from our previous study in which we used the isolated arm technique.<sup>8</sup>

The analysis of the appearance of the mivacurium metabolites in plasma also provides information about the rate of hydrolysis of mivacurium by Bche. The dose-normalized AUC values of the metabolites in the pancuronium-mivacurium group were 20% lower than the AUC values of the metabolites in the mivacurium group. This further suggests that mivacurium *in vivo* hydrolysis is slowed down by pancuronium.

In summary, we have found that pancuronium at a subparalyzing dose decreases the plasma clearance of the two most active mivacurium isomers. This effect is due to an inhibition of Bche and contributes to the potentiation of mivacurium by pancuronium.

Table 4. Maximum Concentration of Mivacurium Metabolites

	T <sub>max</sub> , min	C <sub>max</sub> , ng/ml	AUC, ng $\cdot$ min $\cdot$ ml <sup>-1</sup>
Cis 141 alcohol	—	—	—
Mivacurium	0.5 (0.5–1)	90 (28–241)	219 (163–600)
Pancuronium-Mivacurium	0.5 (0.5–4)	59* (42–114)	103 (84–160)*
Trans 141 alcohol	—	—	—
Mivacurium	0.5 (0.5–1)	550 (309–746)	8200 (5600–17000)
Pancuronium-Mivacurium	1 (0.5–4)	331* (260–640)	6100 (4600–12800)*
Cis 879 monoester	—	—	—
Mivacurium	0.5 (0.5–4)	460 (200–600)	7600 (3600–10200)
Pancuronium-Mivacurium	1 (0.5–4)	276* (121–440)	5900 (4300–12000)*
Trans 879 monoester	—	—	—
Mivacurium	1 (0.5–4)	1166 (400–2000)	15360 (4070–22100)
Pancuronium-Mivacurium	1 (0.5–4)	294* (160–550)	11960 (4300–21000)*

Time to maximum concentration (T<sub>max</sub>), maximum plasma concentration (C<sub>max</sub>), and area under the curve (AUC) of the mivacurium metabolites are normalized to a dose of 100  $\mu$ g/kg mivacurium. Values are shown as median (range in parentheses).

\*  $P < 0.05$  versus group mivacurium.

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