The Influence of Drug-induced Low Plasma Cholinesterase Activity on the Pharmacokinetics and Pharmacodynamics of Mivacurium

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Background: The short duration of action of mivacurium results from its rapid hydrolysis by plasma cholinesterase. Bambuterol, an oral bronchodilator, has an inhibiting effect on plasma cholinesterase. The purpose of this study was to evaluate the effect of bambuterol-induced low plasma cholinesterase activity on the pharmacokinetics and pharmacodynamics of mivacurium.

Methods: Fourteen patients received 20 mg bambuterol and 14 patients received placebo orally 2 h before induction of anesthesia. During anesthesia the neuromuscular block was monitored at the thumb using train-of-four nerve stimulation every 12 s and mechanomyography. The times to different levels of neuromuscular recovery after 0.2 mg/kg mivacurium were measured. The concentrations in venous blood of the three isomers and the metabolites of mivacurium were measured using high-performance liquid chromatography.

Results: Plasma cholinesterase activity was inhibited a median of 90% (range, 67–97%) after bambuterol. The time to first response to train-of-four nerve stimulation was 15 min (range, 9–21 min) and 59 min (range, 32–179 min) in patients receiving placebo and bambuterol, respectively. The estimated clearances of the isomers were significantly lower and the elimination half-lives of all three isomers significantly prolonged in patients receiving bambuterol. No difference was seen in elimination half-lives of the metabolites. The elimination rate constant from the effect compartment and the potency of mivacurium was not affected by bambuterol.

Conclusion: A 90% inhibition of plasma cholinesterase activity significantly reduced clearance of the isomers of mivacurium. Correspondingly, the duration of action of 0.2 mg/kg mivacurium was prolonged three- to fourfold, compared with patients not administered bambuterol. (Key words: Butyrylcholinesterase; enzymes; metabolites; neuromuscular relaxants; pseudocholinesterase; stereoisomers.)

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MIVACURIUM has a short duration of action because of its rapid hydrolysis by plasma cholinesterase (pChe).[1,2] In patients with phenotypically normal pChe or with renal or hepatic failure, an inverse relationship exists between enzyme activity and duration of action of mivacurium,[3–5] indicating that patients with very low enzyme activity might have a very prolonged neuromuscular block following mivacurium. In patients with low pChe resulting from renal or hepatic failure, clearance of the active isomers also are decreased.[4,6] No studies have investigated the effect of drug-induced low pChe activity on the pharmacokinetics and pharmacodynamics of mivacurium.

Bambuterol (the bis-dimethylcarbamate prodrug of terbutaline) is a bronchodilator with a prolonged duration of action intended for oral use.[7] The drug itself is inactive, but in the body it is metabolized enzymatically by pChe or active oxidative processes in the liver to the active compound terbutaline. The two carbamate groups in the molecule inhibit pChe; hence, the metabolism is slow and the duration of action of bambuterol is prolonged. This reversible inhibition is dose-dependent and maximal 2 h after oral administration of bambuterol.[8] A significant decrease in pChe activity is found after bambuterol administration, 20 or 30 mg administered orally, and this causes a three- to fourfold pro-

longed neuromuscular block after normal clinical doses of succinylcholine.[9-11]

The purpose of the current study was to evaluate the pharmacokinetics and pharmacodynamics of 0.2 mg/kg mivacurium in patients with low pChe activity after 20 mg oral bambuterol administration 2 h before induction of anesthesia.

Materials and Methods

Twenty-eight adult patients, classified as American Society of Anesthesiologists physical status I or II, scheduled for elective surgery to the ear or nose were enrolled in the study. All patients had a normal phenotype and low to normal pChe activity, according to the reference values of the Danish Cholinesterase Research Unit.[12] These values were determined from a blood sample taken 2 h before induction of anesthesia. Patients with histories of neuromuscular, cardiovascular, renal, or hepatic disorders were excluded from the study, as were women of childbearing potential and patients prescribed drugs that might affect the neuromuscular transmission. The patients gave informed consent, and the Copenhagen County Ethics Committee approved the study.

Originally, the study was designed to be double-blind, and the patients were randomized to receive either bambuterol or placebo. Because duration of action was extremely prolonged in two of the first five patients enrolled in the study, the ethics committee was informed. Subsequent unblinding of the study showed these patients received bambuterol. The study design was changed to an open study, for ethical reasons, and only patients scheduled for surgical procedures 2 to 3 h in duration were administered bambuterol.

Two hours before induction of anesthesia, the patients were administered bambuterol, 20 mg, or placebo orally, together with diazepam, 0.2 mg/kg. A new blood sample was taken before induction of anesthesia to measure pChe activity after bambuterol or placebo. This sample was sent immediately for analysis because the inhibition of pChe caused by bambuterol diminishes with time. Anesthesia was induced with 1-3 μg/kg fentanyl, 0.05-0.1 mg/kg diazepam, and 1.5-2.5 mg/kg propofol and maintained with 66% nitrous oxide in oxygen, 5-10 mg · kg^{-1} · h^{-1} propofol, and supplementary doses of fentanyl.

During surgery the patients were monitored continuously using electrocardiography, pulse oximetry, and capnography. Blood pressure was measured every minute for the first 3 min after administration of miva-

curium, and every 5 min thereafter. The blood pressure cuff and the intravenous line used for administration of anesthetics and fluid were on the same arm. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide pressure, 4.5-5.6 kPa). The rectal and peripheral skin temperature were measured and maintained above 35 and 32°C, respectively.[13] After induction of anesthesia a second intravenous catheter was inserted for blood sampling in the arm used for monitoring.

The mechanical twitch was recorded using a Myograph 2000 (Biometer International, Odense, Denmark). The ulnar nerve was stimulated at the wrist using surface electrodes and 1-Hz single-twitch stimulation. After supramaximal stimulation was achieved and the response to stimulation was stable for 5 min, the stimulation pattern was changed to train-of-four (TOF) stimulation every 12 s and a single bolus dose of mivacurium 0.2 mg/kg was administered over 30 s. Tracheal intubation was performed at 100% twitch (first response in the TOF response [T_1]) suppression. The neuromuscular block was allowed to recover spontaneously at the end of the surgical procedure, but if necessary residual neuromuscular block was antagonized with neostigmine 0.04 mg/kg preceded by atropine. If neostigmine was administered, the patient was excluded from the pharmacokinetic part of the study.

Pharmacodynamics

Onset (time from beginning of injection of mivacurium to 95% T_1 supression) and recovery data were determined using start control values, and monitoring was continued at least until 90% T_1 recovery and a TOF ratio of 0.75 were obtained. The period of no twitch response (from 100% T_1 depression to first response to TOF stimulation) and the duration to 10, 25, and 90% T_1 recovery and a TOF ratio of 0.75 were determined.[13] The interval from 25 to 75% twitch height recovery and the times to reappearance of twitches number 2, 3, and 4 in the TOF response also were calculated.[13] After reversal, the time from administration of neostigmine to 90% T_1 recovery and to a TOF ratio of 0.75 were measured.

Plasma Concentrations of Mivacurium

Venous blood samples (5 ml) were collected immediately before the administration of mivacurium and 1, 2, 5, 10, 20, 30, 60, 120, 240, and 360 min after the start of injection. In fewer than 10 s the blood was transferred into a vacutainer containing a cholinesterase inhibitor (phospholine iodide). The samples were centrifuged and the plasma was separated and frozen at −70°C. The ratio

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Table 1. Demographic and Biochemical Data

| Group | Number of Patients | Males/ Females | Age (yr) | Weight (kg) | Plasma Cholinesterase Activity U/l | | Dibucaine Number |
					Before Bambuterol/Placebo	After Bambuterol/Placebo	
Placebo	14	12/2	47	75	744	738	85
			(24–71)	(64–87)	(508–960)	(498–950)	(84–86)
Bambuterol	13	5/9	43	71	824	57*	84
			(27–77)	(55–96)	(474–1107)	(14–362)	(82–85)

Medians (ranges) are given.

* Significant difference between groups. Reference values of the Danish Cholinesterase Research Unit for plasma cholinesterase activity and dibucaine number are 660–1620 U/l and 79–87, respectively.[12]

of cis– cis, cis–trans, and trans–trans isomers in the clinical trial material used were approximately 5.7, 36.9, and 60.5%, respectively (data from the certificate of analysis by Glaxo Wellcome, Beckenham, UK). The concentration of each isomer and metabolite of mivacurium was determined by a stereospecific high-performance liquid chromatographic method with fluorometric detection and a stepped gradient. The drug assay was automated (ASPEC; Gilson). The coefficient of variation was 10% at all concentrations except for the lowest level of quantification (5 ng/ml), at which it was 14%. Extraction efficiency was 75%. Calibration was linear in the range between 5 and 1,000 ng/ml. The relative error was less than 6% for the isomers and the metabolites, except for the lowest concentration of the cis-141 metabolite (11%).

Pharmacokinetics

A two-compartment model was fitted to the plasma concentrations of each isomer separately. The fitting was performed by the ADAPT II[14] program using numeric integration of differential equations and the inverse of the calculated plasma concentration of mivacurium as weight factor. The following parameters were fitted: initial volume of distribution (V_1) and rate constants (k_e, k_{12}, and k_{21}). The goodness of fit was evaluated by visual inspection and from plots of residuals. The following secondary parameters were calculated: clearance, $V_1 \times k_e$; volume of distribution at steady state, $V_1 \times (k_{21} + k_{12})/k_{21}$; and terminal slope and half-life λ_z according to the following equation:

$$\lambda_z = \frac{1}{2} \left[k_{12} + k_{21} + k_{10} - \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4\, k_{21}k_{10}} \right]$$

Statistical Analysis

All pharmacokinetic and pharmacodynamic results are presented as the median and range. Data from patients receiving bambuterol were compared with those receiving placebo using the nonparametric Mann-Whitney U test. $P < 0.05$ was considered to be significant.

Results

Table 1 summarizes the demographic and biochemical data. All patients were within 20% of ideal body weights and were phenotypically normal, as indicated by normal dibucaine numbers. There was no difference in preoperative pChe activity in the two groups. The time between administration of bambuterol or placebo and mivacurium varied between 90 and 120 min. Bambuterol caused a 90% (range, 67–97%) decrease in pChe activity in all patients but one, in whom pChe activity only decreased from 851 to 694 U/l; i.e., by 18%. The data from this patient are not included in the tables or figure 1.

In the bambuterol group, one patient was excluded from the pharmacodynamic part of the study because of equipment failure, and four patients were excluded from the pharmacokinetic analysis in accordance with the protocol because it was necessary to administer neostigmine at the end of the procedure. In the placebo group, one patient received atracurium after complete recovery from mivacurium, and in three patients blood sampling was impossible or insufficient. These four patients were excluded from the pharmacokinetic analyses in this group.

Pharmacodynamic Data

Onset time was significantly shorter in patients receiving bambuterol than in those receiving placebo ($P < 0.01$), and the duration of action and recovery period were significantly prolonged in all patients administered bambuterol (table 2). In the patient in whom only a

A

cis-cis

B

trans-trans

C

cis-trans
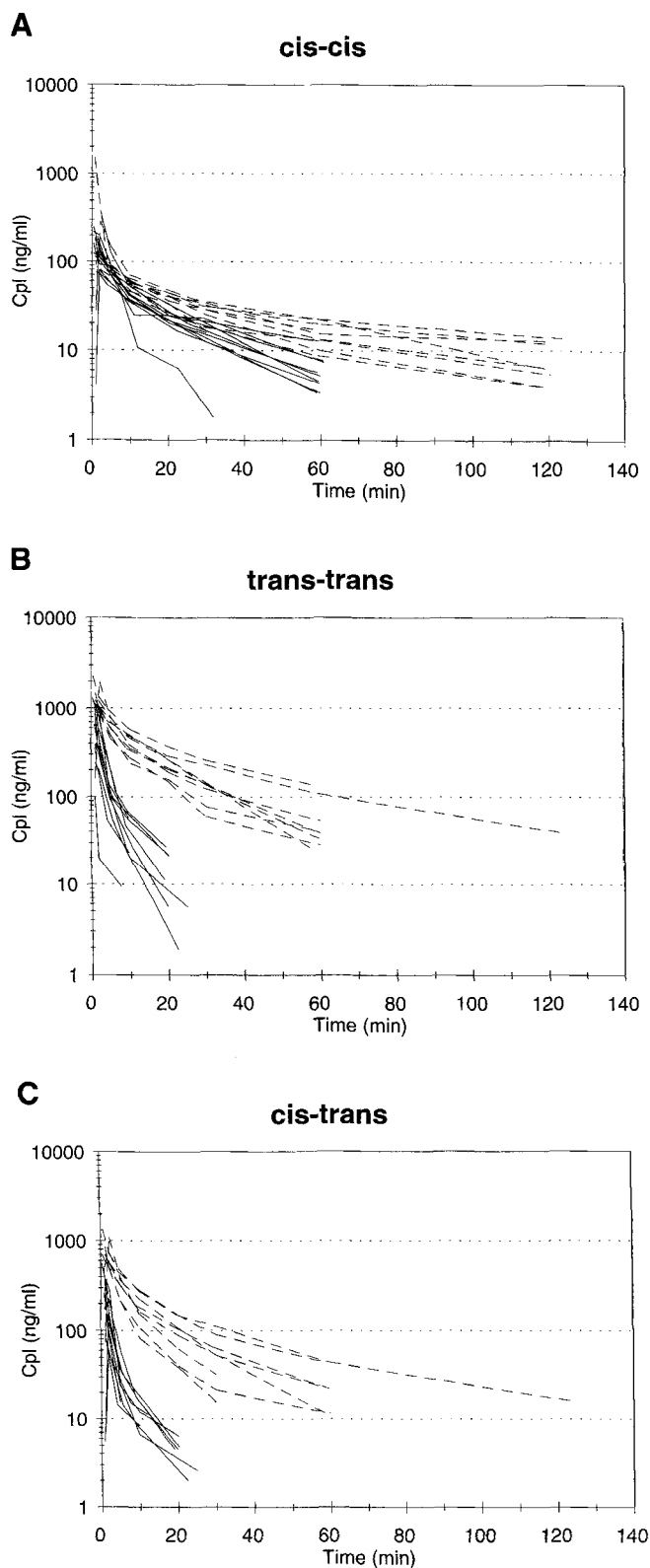
moderate decrease (18%) was seen in pChe activity after bambuterol, the recovery data were similar to those in patients not administered bambuterol.

There was an inverse relation between the postbambuterol pChe activity and the time to first response to TOF. In patients administered placebo, the time to recovery of T_1 was always less than 21 min, compared with 32 min or more (range, 32–179 min) in all patients administered bambuterol. The second, third, and fourth responses appeared 3.0, 4.6, and 5.5 min after recovery of the first evoked response to TOF stimulation in patients administered placebo, and 8.2, 20.0, and 23.1 min after in patients administered bambuterol. The neuromuscular block recovered spontaneously in all patients in the placebo group. In four patients administered bambuterol, residual neuromuscular block was antagonized with neostigmine. All patients were able lift their heads for 5 s before leaving the operation room and at discharge from the recovery room.

Adverse reactions that might be related to mivacurium were observed in three patients. Injection of mivacurium caused cutaneous flushing in one patient and in another mild bronchospasm, treated with terbutaline. Hypotension developed in one patient and was treated successfully with ephedrine.

Pharmacokinetic Data

Figure 1 shows the individual plasma concentrations of each of the three isomers progressively. Plasma concentrations were higher and the isomers were detectable for a longer period of time in patients who were administered bambuterol.

The pharmacokinetic data for the three isomers are summarized in table 3. Patients administered bambuterol had significantly lower clearance and elimination rate constants for all three isomers, indicating longer elimination half-lives. Clearance of the cis-cis isomer was affected less than those of the two active isomers by bambuterol. The elimination rate constant and hence the terminal half-lives of the cis-trans and trans-trans isomers were more affected relatively than those of the cis-cis isomer. The volumes of distribution at steady state were small in both groups of patients, and no statistically significant difference was found.

The plasma concentration of the cis quarternary alcohol metabolite was too low to allow for reliable esti-

Fig. 1. Plasma concentrations (ng/ml) of the cis–cis, cis–trans, and trans–trans isomers over time (min) in patients administered placebo (unbroken line) and bambuterol (broken line).

Table 2. Onset Time, Duration of Action, and Recovery Data following Mivacurium 0.2 mg/kg in Patients Receiving Bambuterol or Placebo

Group	Onset Time	T_1	Duration			Duration TOF 0.75	Interval (25–75%)
			10%	25%	90%		
Placebo	2.0 (1.0–3.2)	15.3 (9.1–20.8)	18.8 (11.4–24.3)	21.8 (13.6–27.5)	34.5 (20.1–44.0)	31.5 (21.0–40.5)	9.5 (4.7–11.9)
n	14	13	14	14	14	14	14
Bambuterol	1.2* (0.9–2.0)	58.9* (31.7–179.0)	71.2* (37.6–238.2)	86.9* (41.1–249.3)	122.1* (56.1–199.5)	121.6* (67.0–202.0)	26.7* (11.1–40.4)
n	13	12	11	11	7	8	9

Values given are minutes (medians and ranges) and n = number of observations. T_1 = time to reappearance of the first response to TOF (train of four ratio) stimulation. Data are presented according to the GCRP rules for pharmacodynamic studies in neuromuscular blocking agents.[13]
* Significant difference between groups ($P < 0.01$).

mates of the half-life or area-under-curve data. For the three other metabolites, the times to maximum concentration were significantly longer and the maximum concentrations significantly lower in patients receiving bambuterol than in those receiving placebo (table 4). The plasma concentrations of the cis and trans monoesters were measurable for 2 to 3 h, whereas those of the trans alcohol only were measurable for 1 to 2 h. No significant difference in the elimination half-lives of the three individual metabolites was found between the two groups of patients (table 4).

Discussion

The main findings of this study are that low pChe activity after 20 mg bambuterol administered orally significantly reduced the clearance and prolonged the elimination half-lives of the three isomers of mivacurium, causing a significantly prolonged duration of action and recovery time of mivacurium. No difference in concentration–effect relation was found, indicating that the prolonged duration of action seen in patients adminis-

tered bambuterol is a result of pharmacokinetic differences only.

Plasma Cholinesterase Activity

The dose of bambuterol administered (20 mg) is the dose recommended for clinical use. The 67–97% decrease in pChe activity is consistent with the findings of Fisher et al.[9] and Bang et al.[10] In one patient administered bambuterol, the pChe activity decreased only slightly. This might be because of slow absorption of the bambuterol tablet, meaning that the inhibition of pChe activity had not reached its maximum at the sampling time.

The clinical significance of decreased pChe activity for the duration of action of mivacurium has been described in healthy patients[3] and in patients with hepatic or renal failure.[4-6] In none of those studies, however, was the pChe activity as low as in the current study. Because of the very low pChe activity after bambuterol, more mivacurium reaches the neuromuscular receptor, and 0.2 mg/kg might be regarded as an overdose in these patients. Therefore, after two patients showed very pro-

Table 3. Estimated Clearance, Rate Constants (k_e, k_{12}, k_{21}), Terminal Half-life ($T_{1/2\lambda z}$) Initial Volume of Distribution (V_1), and Volume of Distribution at Steady State (VDss) in Patients Receiving Bambuterol or Placebo

Isomer	Clearance $ml \cdot kg^{-1} \cdot min^{-1}$	ke min^{-1}	k_{12} min^{-1}	k_{k21} min^{-1}	$T_{1/2\lambda z}$ min	V_1 l/kg	VDss l/kg
Cis–Cis							
Placebo	6.0 (4.2–9.8)	0.110 (0.070–0.203)	0.110 (0.042–0.224)	0.077 (0.053–0.101)	22.6 (16.9–38.4)	0.05 (0.02–0.14)	0.16 (0.06–0.22)
Bambuterol	3.7* (2.0–7.0)	0.065* (0.024–0.546)	0.105 (0.062–0.651)	0.065 (0.041–0.022)	37.3* (13.3–84.0)	0.07 (0.01–0.09)	0.16 (0.06–0.25)
Cis–Trans							
Placebo	50.3 (36.8–175.5)	0.647 (0.372–1.226)	0.218 (0.066–0.376)	0.147 (0.060–0.210)	6.7 (5.4–12.7)	0.08 (0.04–0.47)	0.18 (0.10–0.94)
Bambuterol	10.6* (5.7–18.5)	0.116* (0.056–0.263)	0.089 (0.039–0.164)	0.087 (0.035–0.146)	20.3* (8.7–39.9)	0.09 (0.05–0.10)	0.18 (0.14–0.22)
Trans–Trans							
Placebo	27.6 (22.2–96.0)	0.635 (0.328–1.028)	0.195 (0.049–0.469)	0.149 (0.077–0.273)	7.2 (3.8–11.8)	0.05 (0.02–0.29)	0.12 (0.06–0.36)
Bambuterol	7.5* (4.1–9.9)	0.091* (0.048–0.161)	0.129 (0.053–0.275)	0.104 (0.047–0.562)	19.4* (11.3–40.4)	0.08 (0.05–0.10)	0.16 (0.12–0.21)

Medians and ranges are given.
* Statistically significant difference ($P < 0.05$).

Table 4. Time to Maximum Concentration (t_{max}), Maximum Plasma Concentration (C_{max}), and Elimination Half-life ($t_{1/2\beta}$) of the Three Major Metabolites of Mivacurium

	t_{max} (min)	C_{max} (ng/ml)	$t_{1/2\beta}$ (min)
Cis 879 (monoester)			
Placebo	2 (1–5)	466 (299–779)	86 (68–113)
Bambuterol	20* (10–30)	159* (97–263)	78 (60–109)
Trans 879 (monoester)			
Placebo	2 (1–5)	619 (408–1091)	55 (23–91)
Bambuterol	20* (10–30)	227* (149–366)	79 (29–116)
Trans 141 (alcohol)			
Placebo	2 (1–5)	687 (458–1372)	27 (12–46)
Bambuterol	10* (5–20)	190* (140–297)	35 (22–55)

Medians and ranges are given.
* Statistically significant difference ($P < 0.05$).

longed responses to 0.2 mg/kg mivacurium, the study design was changed, and patients included in the bambuterol group were selected from groups of patients undergoing long-duration surgical procedures. Accordingly, patients administered bambuterol were anesthetized for a longer period of time than were patients who were administered placebo. The possibly potentiating effect of a higher total dose of intravenous anesthetics, however, was considered to be small compared with the effect of decreased pChe activity.

Pharmacodynamic Data

A statistically significant shorter onset time was seen in patients administered bambuterol, most probably because mivacurium 0.2 mg/kg represents a relative overdose in these patients. Less mivacurium is hydrolyzed in plasma initially, and a larger number of molecules reaches the neuromuscular endplate.

The recovery data in patients receiving placebo are consistent with the findings of Caldwell et al.[15] and Østergaard et al.[3] The neuromuscular block after mivacurium was significantly prolonged in all patients administered bambuterol compared with those administered placebo. The times to recovery of the second, third, and fourth responses in patients administered placebo is consistent with the findings of Kopman et al.[16] In patients administered bambuterol, these recovery times were four- to fivefold longer. The duration of the interval between recovery of the first and third responses to the TOF response has been found to be a useful indicator of the time to full clinical recovery. Time to a TOF ratio of 0.7 was estimated to be three to four times longer than the duration of this interval.[16] The same relation was seen in this study, both in patients administered placebo and in those administered bambuterol.

Pharmacokinetics

Patients administered bambuterol had a significantly slower elimination of mivacurium. Consequently, mivacurium plasma concentrations were higher at any administered time in the bambuterol group than in patients administered placebo. In each group of patients the clearance of the cis-trans isomer was higher than the clearance of the trans-trans isomer. The cis-cis isomer had the lowest clearance. This finding is in accordance with reported data.[4,6,9,17,18]

The clearances of the cis-trans and the trans-trans isomers in our placebo group are comparable to data of Lacroix et al.[18] and slightly lower than after both a short and a long infusion of mivacurium.[4,6,17,19] The clearance of the cis-cis isomer is also comparable to the data of Lacroix et al.,[18] but higher than reported previously, $3.8-5.4$ ml $\cdot$ kg$^{-1} \cdot$ min^{-1}.[4,6,17] Different administration techniques, sampling procedures, and pharmacokinetic models may explain this. We used venous sampling, and only a few samples were taken immediately after the injection of mivacurium. The initial part of the area under the plasma concentration-time curve may be estimated too low.[20] The hydrolysis of mivacurium in plasma is fast and starts immediately after the injection. Plasma concentrations based on relatively sparse venous sampling may not be representative of the changes in arterial plasma concentrations, especially in the initial distribution phase.

The clearances are significantly lower for all three isomers in patients administered bambuterol than in those administered placebo. The clearances of the cis-cis, cis-trans, and trans-trans isomers are approximately three fifths, one fifth, and one quarter, respectively, of the corresponding clearances in the placebo group. This indicates that the elimination of the cis-cis isomer is less influenced by low pChe activity than the active isomer is influenced. Most probably, the clearance of the cis-cis isomer is predominantly renal because a 50% reduction in clearance is seen in patients with end-stage renal failure.[4] In patients with hepatic failure, the elimination of the cis-cis isomer also was influenced, but less than that of the cis-trans and trans-trans isomers.[6] Most probably, the cis-cis isomer is eliminated by several pathways,[4] of which hydrolysis by pChe and renal elimination represent only two.

The clearances of the active isomers in patients administered bambuterol were lower than the clearances estimated in patients with renal or hepatic failure,[4,6] most probably because of lower pChe activity.

The mean elimination half-life of the cis-cis isomer

was 23 min in patients administered placebo, which is comparable to data from Lacroix et al.[18] but 50% shorter than reported by Lien et al.[17] and Head-Rapson et al.[4,6] The elimination half-lives of the cis–trans and the trans–trans isomers were, however, threefold longer in our study than reported previously after a continuous infusion[6,17] and a bolus dose.[4,18] Again, this might be explained by different techniques and sampling procedures. A significantly longer elimination half-life was seen for all three isomers in patients administered bambuterol, again longer than reported in patients with hepatic failure.[6]

Significant differences in time to maximum concentration and maximum concentration of the metabolites was found between patients receiving bambuterol and those receiving placebo. No difference in elimination half-life of the metabolites was found. In both the placebo and the bambuterol groups the elimination half-life of the trans alcohol was approximately one third, and that of the cis monoester four fifths, of the elimination half-life reported by Lacroix et al.,[18] whereas the half-life of the trans monoester in patients receiving placebo was three quarters of that reported by Lacroix et al. These differences might be a result of more frequent sampling in the study by Lacroix et al.

In conclusion, 20 mg bambuterol administered orally 2 h before induction of anesthesia caused a marked decrease in pChe activity, leading to reduced clearance and prolonged elimination half-life of mivacurium. This in turn prolonged the duration of action of mivacurium three- to fourfold.

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