

Anesthesiology

1998; 89:707-14

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Inhibition of the Enzymic Degradation of Suxamethonium and Mivacurium Increases the Onset Time of Submaximal Neuromuscular Block

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Background: The factors that influence the onset time of submaximal (<100%) neuromuscular block are not fully known. The authors hypothesized that differences in the rate of decrease in the plasma concentration result in differences in the rate of equilibration between plasma and biophase and thus in different onset times. If this hypothesis is valid, inhibition of the enzymic degradation of muscle relaxants should increase the onset time of neuromuscular block.

Methods: Twenty pigs received either suxamethonium or mivacurium. Dose finding (70% block) was done for each pig. The enzymic degradation of the muscle relaxant was randomly inhibited by selective inhibition of plasma cholinesterase activity by tetraisopropyl pyrophosphoramidate (10 pigs) or was not inhibited (10 pigs). Plasma cholinesterase activities and the mechanomyographic muscle response after peroneal nerve stimulation (0.1 Hz) were measured.

Results: Inhibition of plasma cholinesterase activity (by 93% and 89%, respectively) increased the onset time of suxamethonium from a median of 40 s (range, 20–45 s) to 131 s (range, 114–166 s; $P = 0.009$) and of mivacurium from a median of 52 s (range, 40–59 s) to 105 s (range, 90–125 s; $P = 0.009$). Inhibition of degradation decreased the effective dose of suxamethonium that resulted in 70% depression of the initial twitch height from 900 $\mu\text{g/kg}$ (range, 400–1,000 $\mu\text{g/kg}$) to 150 $\mu\text{g/kg}$ (range, 135–150 $\mu\text{g/kg}$) and of mivacurium from 100 $\mu\text{g/kg}$ (range, 80–150 $\mu\text{g/kg}$) to 35 $\mu\text{g/kg}$ (range, 20–50 $\mu\text{g/kg}$).

Conclusions: Inhibition of the enzymic degradation of suxamethonium and mivacurium increases the onset time of submaximal neuromuscular block. Therefore, pharmacokinetics influence the onset time of submaximal neuromuscular block. These results imply that to obtain an ultrashort onset time, muscle relaxants should be developed that not only have a low affinity for the receptor but also rapidly disappear from plasma. (Key words: Neuromuscular blocking agents; onset of action; plasma clearance; time course of action.)

This article is featured in "This Month in Anesthesiology."
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Received from the Research Group for Experimental Anesthesiology and Clinical Pharmacology, University of Groningen, Groningen, The Netherlands. Submitted for publication October 16, 1997. Accepted for publication May 21, 1998. Supported by the Foundation for Experimental and Clinical Anesthesiology, Groningen, The Netherlands. Presented in part at the Anaesthetic Research Society Meeting, November 23, 1995, Manchester, United Kingdom.

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IN the search for a nondepolarizing muscle relaxant to replace suxamethonium, it is essential to know which factors influence the onset time of a submaximal (<100%) neuromuscular block. Thus far, these factors are not fully known. Onset time is defined as the time elapsed between the end of administration of the muscle relaxant and the time of the peak effect. When doses are given that completely ablate twitch, it is impossible to determine the time to peak effect. Instead, the time to complete ablation of twitch, which is a function of the magnitude of the overdose of muscle relaxant, can be determined. However, to learn the time to peak effect (which is the same as the time to the maximal concentration in the biophase), doses producing less than complete paralysis must be administered. At peak effect the concentrations of muscle relaxant in plasma and biophase are similar.¹

Several factors have been suggested to determine the onset time. Based on *in vitro* studies, differences in receptor affinity were suggested to account for the differences in onset time between muscle relaxants.^{2,3} Al-

though factors such as circulation time,⁴ cardiac output,^{4,5} and muscle blood flow⁶ were also shown to contribute to the onset time, these factors cannot explain the differences in onset time between muscle relaxants.

Theoretically, a rapid decrease in the concentration of a muscle relaxant in plasma, due to a high rate in the early distribution or elimination of muscle relaxant from plasma, results in a rapid equilibration of the muscle relaxant between plasma and biophase, and thus in a short onset time (fig. 1). Therefore we hypothesized that the rate of decrease in the concentration of a muscle relaxant in plasma influences the onset time of neuromuscular block. To test our hypothesis, we inhibited the enzymic degradation of suxamethonium and of mivacurium using a selective plasma cholinesterase-inhibitor, thus decreasing the rate of disappearance of the muscle relaxant from plasma. If our hypothesis is valid, inhibition of the enzymic degradation of a muscle relaxant should increase the onset time. Because the enzymic degradation of suxamethonium and of mivacurium in plasma can be inhibited easily, these two muscle relaxants were studied.

Materials and Methods

Preliminary Preparation

With approval of the Ethical Committee on Animal Experiments of the Faculty of Medicine, Groningen, The Netherlands, 20 male pigs (Yorkshire F₁ hybrid; 20–27 kg body weight) were studied. After a fasting period of 16 h with free access to water, the pigs were anesthetized with 15 mg midazolam and 500 mg ketamine given intramuscularly. After weighing, an ear vein was cannulated and infusions of 5 mg · kg⁻¹ · h⁻¹ pentobarbital, 2–4 µg · kg⁻¹ · h⁻¹ fentanyl, and 2 ml · kg⁻¹ · h⁻¹ isotonic glucose in saline were started. If necessary, the rate of infusion of pentobarbital was adjusted to maintain an adequate depth of anesthesia, which was defined by the lack of cardiovascular responses to surgical preparation or nerve stimulation. The trachea was intubated and the lungs were artificially ventilated with air using a Camco UV 705 respirator (frequency, 24/min; pressure, 20 cm H₂O, Camco, Sweden). The end-tidal carbon dioxide level was maintained between 30 and 38 mmHg (4 or 5 kPa; Godart Capnograph Mark 11; E. Jaeger, Wuerzburg, Germany). If necessary, ventilation was adjusted according to the results obtained from blood gas analysis. The right femoral artery was cannulated to

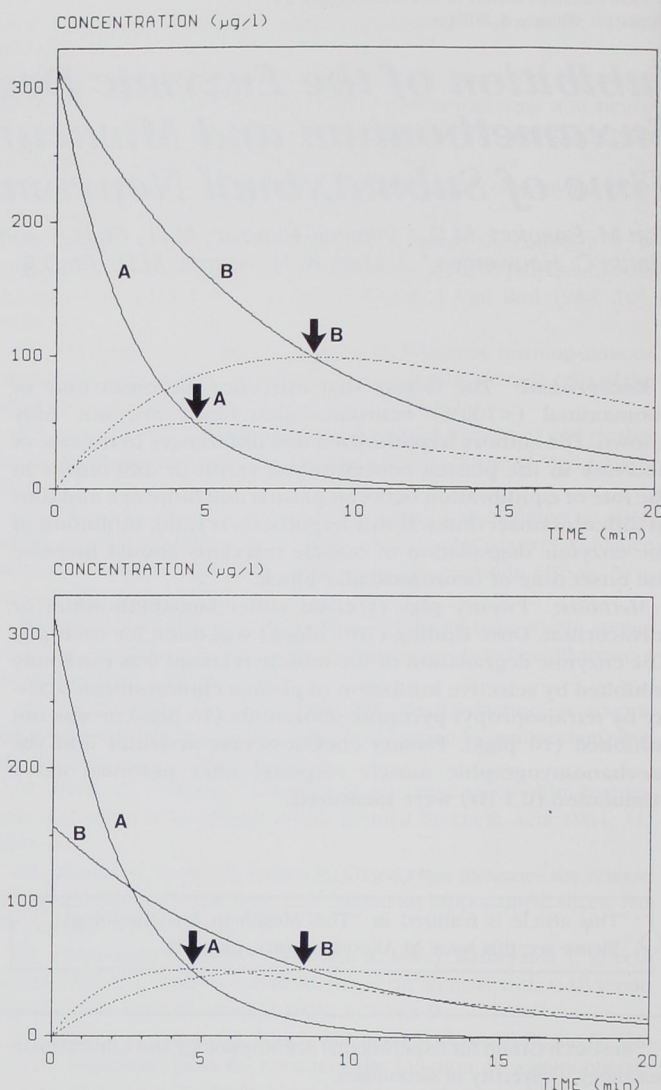
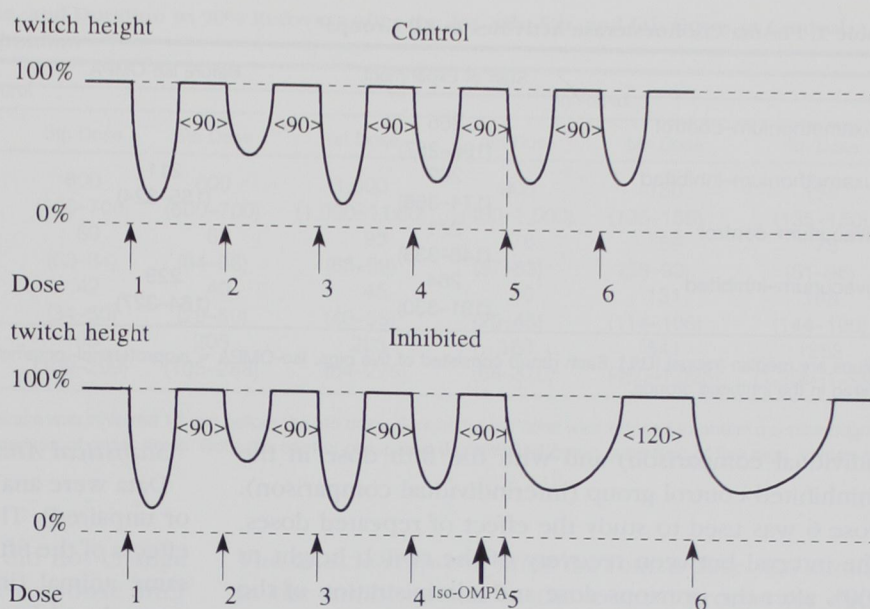


Fig. 1. Theoretical changes, after a bolus dose, in the concentration of a muscle relaxant in plasma (solid lines) and in the biophase (broken lines) in time. (A) The concentration of a drug in plasma decreases as a result of clearance of the drug from plasma (curve A). The concentration in the biophase increases because of transfer of the drug from plasma to the biophase. When the concentrations in plasma and biophase are similar (arrow A), the maximum concentration in the biophase is reached and the peak effect is obtained. Thus the moment of equilibration between plasma and biophase determines the onset time. If the same drug is administered in the same dose but with a reduced clearance (curve B), the moment of equilibration would be later (arrow B) and at a higher maximum concentration in the biophase. Consequently, the onset time would increase and the peak effect would be larger. (B) In the case of a reduced plasma clearance (curve B), the dose must be reduced to obtain a peak effect similar to that induced by the drug with a normal plasma clearance (curve A). The time to maximum concentration in the biophase is not affected by the dose.

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Fig. 2. The study design used for the current investigation. Changes in twitch height after six doses of muscle relaxant are shown. The first dose of the muscle relaxant was similar in the control and in the inhibited group. The second and third doses were used to estimate the dose resulting in 70% depression of the initial twitch height, which was administered in the fourth, fifth, and sixth doses. The numbers between brackets depict the time (in minutes) between complete recovery of the twitch height after the previous dose and administration of the next dose. (Upper) Control experiment. (Lower) Inhibited experiment (tetraiso-propyl pyrophosphoramidate is the inhibitor of plasma cholinesterase).



measure blood pressure (Statham P23Db, Gould; KWS 3005 HSE Electro-Manometer) and to collect blood samples. The right femoral vein was cannulated to administer muscle relaxants. Both heart rate (B-1200 Biotachometer, MS 35, Electrodyne Co., Inc., USA) and rectal temperature were measured continuously. A heating blanket maintained the animal's temperature at 38°C.

The left common peroneal nerve was exposed and two silver stimulation electrodes were attached to it. The nerve was ligated proximal to the electrodes. After closure of overlying skin, the nerve was stimulated supramaximally with square-wave stimuli lasting 0.2 ms at a frequency of 0.1 Hz (model S 88; Grass Instruments, Quincy, MA). The response of the tibialis anterior muscle was registered mechanomyographically using a force transducer (model LB 8000 25N; Maryland Instruments Ltd., Maywood, USA) connected to a muscle relaxation monitor MK 11 and to a recorder (Astro-Med MT 9500, Rhode Island). Preload was measured continuously and kept constant at approximately 400g. At the end of the experiments, the pigs received an overdose of pentobarbital until circulatory arrest ensued.

Study Design

After the preliminary preparation, the muscle response was allowed to stabilize for at least 30 min. The study was designed such that the only difference between pigs was the choice of muscle relaxant (an identical design was used for both muscle relaxants) and whether pigs received the cholinesterase inhibitor. Of the 20 pigs, 10

received suxamethonium and 10 received mivacurium. In half of the pigs in both groups, plasma cholinesterase was inhibited (inhibited group) by tetraiso-propyl pyrophosphoramidate (iso-OMPA; Merck, Amsterdam, The Netherlands), whereas the other half served as controls and were not inhibited (control group). Pigs were randomly assigned to either the inhibited or the control groups. Each pig received only one muscle relaxant. For each muscle response, the lag time (the time from end of injection until the first reduction in twitch height), the onset time, the onset time to 50% twitch depression (onset time 50%), the peak effect, and the duration until 90% recovery of the twitch height (duration 90%) were determined.

According to the study design, each pig received six sequential doses of one muscle relaxant (fig. 2). Dose 1 was similar in the control and in the inhibited groups and consisted of the dose resulting in 90% depression of the initial twitch height (ED_{90}), which was determined in pilot experiments. For dose 2, we aimed at a peak effect between 50% and 90% depression of the initial twitch height. Depending on the peak effect obtained in dose 2, dose 3 was chosen such that the ED_{70} could be determined from the log dose-logit effect relation obtained from doses 2 and 3 by means of interpolation. The estimated ED_{70} dose was administered in doses 4, 5, and 6. Because the inhibitor of plasma cholinesterase was, in the inhibited group, administered between the fourth and the fifth dose, the fifth dose was used for comparison both with the fourth dose in the same animal (intra-

Table 1. Plasma Cholinesterase Activities in All Groups*

	Start of Experiment	Before Iso-OMPA	After Iso-OMPA	End of Experiment
Suxamethonium-control	255 (198-287)			252 (197-301)
Suxamethonium-inhibited	269 (174-366)	211 (155-324)	16 (8-37)	24 (7-40)
Mivacurium-control	271 (146-336)			242 (172-274)
Mivacurium-inhibited	264 (191-330)	229 (164-327)	32 (14-39)	31 (13-34)

Values are median (range) (U/L). Each group consisted of five pigs. Iso-OMPA = isoproterenol-octamethylpyrophosphoramidate. * Iso-OMPA was only administered in the inhibited groups.

individual comparison) and with the fifth dose in the uninhibited control group (interindividual comparison). Dose 6 was used to study the effect of repeated doses. The interval between recovery of the twitch height to 100% after the previous dose and administration of the next dose was 90 min, which was sufficient to prevent accumulation.

The study design in the inhibited group was identical to that in the control group apart from the administration of the plasma cholinesterase inhibitor (iso-OMPA). Iso-OMPA (7.5 μ mol/kg) was administered intravenously 15 min before administration of the fifth dose of suxamethonium or mivacurium. Iso-OMPA was chosen because it is widely accepted as a selective inhibitor of plasma cholinesterase that does not influence junctional acetylcholinesterase.⁷⁻⁹ To obtain a similar degree of neuromuscular block before and after inhibition, the fifth dose of the muscle relaxant was reduced according to the results obtained from previous dose-finding experiments (also see the Discussion). The interval between the fifth and sixth doses in the inhibited group was longer than the other intervals (*i.e.*, 120 min) to compensate for the reduced clearance and to prevent accumulation of the muscle relaxant in the presence of iso-OMPA.

Measurement of Plasma Cholinesterase Activity

In all pigs, plasma cholinesterase activity was determined according to the method of Knedel and Böttger¹⁰ using ultraviolet spectrophotometry at 405 nm with butyrylthiocholine as the substrate. In the control groups, the activity was measured in blood sampled before the start of the experiment and at the end of the experiment. In the inhibited groups, plasma cholinesterase activity was also determined immediately before the administration of iso-OMPA and 15 min thereafter.

Statistical Analysis

Data were analyzed using a Mann-Whitney test (paired or unpaired). The paired test was used to compare the effects of the fifth dose to those of the fourth dose in the same animal (intraindividual comparison) in both the control and in the inhibited groups. The unpaired test was used to compare the effects of the fifth dose in the inhibited group with those of the fifth dose in the control group (interindividual comparison). Values are expressed as medians \pm range, unless stated otherwise. A value of $P < 0.05$ was considered significant. Randomization was performed with a dice (even value = no inhibition, uneven value = inhibition).

Results

Total body weight of the animals was 22.5 ± 2 kg (mean \pm SD), and no differences in body weight were found between the four groups. Plasma cholinesterase activity at the start of the experiments was similar in the suxamethonium and mivacurium groups, in the control and inhibited groups of each muscle relaxant, and between the start and end of the experiment in each control group (table 1). Plasma cholinesterase activity was reduced after administration of iso-OMPA ($P = 0.009$ [suxamethonium], $P = 0.009$ [mivacurium]; table 1). The reduction in plasma cholinesterase activity was 93% (range, 86-97%) in the suxamethonium group and 89% (range, 88-93%) in the mivacurium group, a degree of reduction that was not significantly different between the groups ($P = 0.18$). The size of the dose and the response of the tibialis anterior muscle to the first, fourth, fifth, and sixth dose of suxamethonium are presented in table 2, and those of mivacurium are shown in table 3. For the sake of clarity, only the peak effect, the onset time, and the

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Table 2. Size of Dose, Peak Effect, Onset Time, and Duration to 90% Recovery after the 1st, 4th, 5th, and 6th Doses in Control and in Inhibited Experiments with Suxamethonium

	Control				Inhibited			
	1st Dose	4th Dose	5th Dose	6th Dose	1st Dose	4th Dose	5th Dose	6th Dose
Dose Size ($\mu\text{g} \cdot \text{kg}^{-1}$)	1,000 (1,000–1,000)	600 (500–700)	600 (500–700)	600 (500–700)	1,000 (1,000–1,000)	900 (400–1,000)	150 (135–150)	150 (135–150)
Peak effect (%)	99 (98–100)	70 (65–86)	69 (62–84)	68 (64–88)	95 (88–99)	78 (57–83)	89 (56–93)	76 (61–96)
Onset time (s)	45 (38–60)	40 (40–50)	42 (34–50)	40 (28–50)	45 (40–55)	40 (20–45)	131 (114–166)	168 (144–190)
Duration 90% (s)	241 (170–309)	205 (100–280)	195 (109–299)	205 (105–288)	203 (84–275)	188 (68–310)	541 (460–1,025)	1282 (1,230–1,334)

Note that in the inhibited experiments plasma cholinesterase was inhibited 15 min before the 5th dose. Size of the 5th dose was reduced to obtain a similar degree of peak effect before and after inhibition to allow comparison of onset times. Both the control group and the inhibited group consisted of five pigs. Values are median (range).

duration 90% are presented. Lag time did not change in any of the experiments. The muscle response after the first dose of each muscle relaxant was similar in the inhibited and in the control groups (table 2). The size of the second and third doses of suxamethonium in the control group were 500 $\mu\text{g}/\text{kg}$ (range, 500–500 $\mu\text{g}/\text{kg}$) and 500 $\mu\text{g}/\text{kg}$ (range, 300–700 $\mu\text{g}/\text{kg}$), respectively, and in the inhibited group it was 500 $\mu\text{g}/\text{kg}$ (range, 400–500 $\mu\text{g}/\text{kg}$) and 700 $\mu\text{g}/\text{kg}$ (range, 250–800 $\mu\text{g}/\text{kg}$), respectively. For mivacurium, these values in the control group were 125 $\mu\text{g}/\text{kg}$ (range, 125–150 $\mu\text{g}/\text{kg}$) and 150 $\mu\text{g}/\text{kg}$ (range, 125–225 $\mu\text{g}/\text{kg}$), respectively, and in the inhibited group they were 125 $\mu\text{g}/\text{kg}$ (range, 100–125 $\mu\text{g}/\text{kg}$) and 100 $\mu\text{g}/\text{kg}$ (range, 75–150 $\mu\text{g}/\text{kg}$), respectively. The ED_{70} estimated from doses 2 and 3 resulted in an approximately 70% block after the fourth dose in all groups.

The muscle response after the fourth dose was similar in the inhibited and in the control groups for each muscle relaxant.

Intraindividual Comparisons (between the Fourth and the Fifth Dose in the Inhibited Group)

In the control groups, no differences in muscle response were found between the fourth and fifth doses of either suxamethonium or mivacurium. In the inhibited groups, however, significant differences were found between these doses. At a similar degree of suxamethonium-induced block, inhibition of plasma cholinesterase increased the onset time (table 2; $P = 0.009$), the onset 50% (from 23 s [range, 18–30 s] to 46 s [range, 27–95 s]; $P = 0.02$) and the duration 90% (table 2; $P = 0.009$). At a similar degree of mivacurium-induced block, inhibition of plasma cholinesterase increased the onset time (table

Table 3. Size of Dose, Peak Effect, Onset Time, and Duration to 90% Recovery after the 1st, 4th, 5th, and 6th Doses in Control and in Inhibited Experiments with Mivacurium

	Control				Inhibited			
	1st Dose	4th Dose	5th Dose	6th Dose	1st Dose	4th Dose	5th Dose	6th Dose
Dose Size ($\mu\text{g} \cdot \text{kg}^{-1}$)	225 (200–225)	150 (125–175)	150 (125–165)	150 (125–165)	225 (225–225)	100 (80–150)	35 (20–50)	35 (25–50)
Peak effect (%)	94 (80–98)	76 (65–83)	78 (68–81)	70 (59–80)	98 (94–99)	69 (68–80)	73 (45–86)	78 (53–93)
Onset time (s)	53 (51–59)	59 (51–62)	55 (50–68)	55 (50–64)	50 (41–60)	52 (40–59)	105 (90–125)	115 (108–142)
Duration 90% (s)	471 (421–723)	391 (269–411)	412 (275–420)	390 (275–433)	454 (301–830)	270 (238–488)	1,150 (660–1,385)	—

Note that in the inhibited experiments plasma cholinesterase was inhibited 15 min before the 5th dose. Size of the 5th dose was reduced to obtain a similar degree of peak effect before and after inhibition to allow comparison of onset times. Both the control group and the inhibited group consisted of five pigs. Values are median (range). — = no duration 90% available due to very prolonged recovery.

3; $P = 0.009$), the onset 50% (from 29 s [range, 28–39 s] to 48 s [range, 44–70 s]; $P = 0.01$) and the duration 90% (table 3; $P = 0.009$).

Interindividual Comparisons (between the Fifth Dose of the Control Group and the Fifth Dose of the Inhibited Group)

When the muscle response after the fifth dose of suxamethonium in the inhibited group was compared with that in the control group, the onset time (table 2; $P = 0.009$), the onset 50% (from 29 s [range, 19–30 s] to 46 s [range, 27–95 s]; $P = 0.047$) and the duration 90% (table 2; $P = 0.009$) were prolonged at a similar degree of block. Similarly for mivacurium, the onset time (table 3; $P = 0.009$), the onset 50% (from 30 s [range, 27–37 s] to 48 s [range, 44–70 s]; $P = 0.014$) and the duration 90% (table 3; $P = 0.009$) were prolonged at a similar degree of block.

The increase in onset time after inhibition of plasma cholinesterase was larger for suxamethonium than for mivacurium. For suxamethonium, the absolute increase in onset time between the fourth and fifth dose was 0 s (range, –6 to +2 s) in the control group compared with 102 s (range, 90–121 s; $P = 0.009$) in the inhibited group. For mivacurium, these values were –1 s (range, –4 to +6 s) and 53 s (range, 37–66 s; $P = 0.009$), respectively. In addition, the relative increase in onset time was greater for suxamethonium than for mivacurium (3.7 and 2.1 times the preinhibition values, respectively). In both control groups, the muscle response after the sixth dose was similar to that after the fifth dose, excluding an influence of accumulation.

Discussion

Our study shows that inhibition of the enzymic degradation of suxamethonium and mivacurium increases the onset time of submaximal neuromuscular block and decreases the ED_{70} . Although differences in plasma clearance have been suggested as a determining factor of onset time,^{11–16} the influence of plasma clearance on the onset time has never been studied as such. Theoretically, a rapid decrease in the concentration of a muscle relaxant in plasma results in a rapid equilibration of the muscle relaxant between plasma and biophase, and thus in a short onset time. The concentration of a drug in plasma decreases as a result of clearance of the drug from plasma (fig. 1A). The concentration in the biophase increases as a result of transfer of the drug from plasma

to the biophase. When the concentrations in plasma and biophase are similar (arrow A), the maximum concentration in the biophase is reached and the peak effect is obtained. Thus the onset time is determined by the moment of equilibration between plasma and biophase. If the same drug would be administered in the same dose but with a reduced clearance (e.g., by inhibition of plasma cholinesterase; curve B), the moment of equilibration would be later (arrow B) and at a higher maximum concentration in the biophase. Consequently, the onset time would be longer and the peak effect larger. However, the onset time can be determined reliably only when the peak effect is between 50% and 90%. Because the reduction in the dose of muscle relaxant after inhibition necessary to obtain a peak effect of 70% was in our study 83% and 65% for suxamethonium and mivacurium, respectively, the dose of muscle relaxant after inhibition must be reduced (fig. 1B, curve B). The size of this reduction corresponds with the fivefold increase in potency of suxamethonium in patients who are homozygous for atypical plasma cholinesterase.^{17–19} The time to maximum concentration in the biophase is not affected by the dose given. The increase in onset time found in our study correlates with observations made by several investigators in animals and in humans.^{20–23} Unfortunately, in these investigations either a 100% block was obtained or only the plasma clearance of the muscle relaxant after iso-OMPA was determined without measurement of neuromuscular block. The onset time of a submaximal block induced by suxamethonium was prolonged in three patients with atypical plasma cholinesterase. Cass *et al.*¹⁷ found in such a patient onset times for suxamethonium (0.05–0.1 mg/kg) on four separate occasions ranging from 7 to 9 min (80–99% block). Hickey *et al.*¹⁸ found in such a patient an onset time for suxamethonium (0.04 mg/kg) of 6 min (92% block). In the same patient they also found an onset time for atracurium (0.23 mg/kg) of 6 min (87% block). Smith *et al.*¹⁹ found in such a patient an onset time for suxamethonium of 1.3 min (only 16% block). The onset time of suxamethonium in patients with atypical plasma cholinesterase^{17,18} is similar to that of nondepolarizing muscle relaxants in the general population, suggesting that the short onset time of suxamethonium is not a result of its depolarizing mode of action but of its rapid degradation in plasma.

Proost *et al.*¹⁶ used pharmacokinetic–dynamic modeling to show that the inverse relation between the onset time and ED_{50} , as observed for a series of muscle relaxants in cats^{24,25} and in humans,²⁶ respectively, may be

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the result of differences in receptor affinity and in plasma clearance. Iontophoretic studies have suggested that receptor affinity influences the onset time of muscle relaxants.^{2,3} *In vivo*, however, this relation has not been shown convincingly. In this study, we found that decreased clearance is associated with an increase in onset time and a decrease in ED₇₀.

The relative contribution of receptor affinity and clearance to the onset time, to the potency (ED₉₀), and to the potency (ED₉₀)-onset time relation is unknown and may be different for each muscle relaxant.¹⁶ A high initial plasma clearance alone is not enough to obtain a fast onset of block. For example, mivacurium has a high rate of metabolism²⁷ but not a short onset time,²⁸ probably as a result of its high potency.^{27,29,30} Compared with vecuronium, Org 9487 has a much lower receptor affinity (data on file) and a relatively high clearance.³¹ So the short onset time of Org 9487 has two explanations. Org 9488, the 3-OH metabolite of Org 9487, has a receptor affinity that is 2 to 2.5 times as high as that of Org 9487, and it has a much lower clearance.³² The higher affinity and lower clearance result in a much longer onset time of Org 9488 compared with Org 9487.

Initially, it was thought that the short onset time of suxamethonium could be explained by the smaller amount of nicotinic acetylcholine receptors that must be blocked by a depolarizing muscle relaxant (15-25%) compared with a nondepolarizing muscle relaxant ($\geq 70\%$).^{13,33-36} A decisive role for the number of receptors to be blocked does not correspond with the results obtained by Katz and Eakins,³⁷ who showed that decamethonium, although a depolarizing muscle relaxant in the cat, has a long onset time (6 min *vs.* 1.3 min for suxamethonium). In addition, Org 7617 and Org 9487, nondepolarizing muscle relaxants with onset times in humans that are similar (Org 7617) or nearly similar (Org 9487) to that of suxamethonium, disprove this explanation.^{14,38,39}

The finding that the increase in onset time was greater for suxamethonium than for mivacurium corresponds with the observation that a smaller fraction of a dose of mivacurium is hydrolyzed by plasma cholinesterase than of a dose of suxamethonium.²⁷ Inhibition of hydrolysis thus will affect mivacurium less than suxamethonium. This is also reflected in the smaller reduction in the dose required to obtain a similar degree of block before and after inhibition (65% and 83% for mivacurium and suxamethonium, respectively).

For several reasons, the study design had to be rather elaborate. First, as discussed previously, the onset time

can be determined reliably only with a peak effect between 50% and 90%. Therefore, dose finding had to be done in each pig, and dose adjustment after inhibition was needed to obtain a 70% block in the doses used for comparison of onset times (the fourth and fifth doses, respectively). Second, to obtain an identical starting point for dose finding, the initial dose was identical for all pigs receiving that muscle relaxant. Third, dose finding was necessary to investigate the influence of inhibition on the onset time both intraindividually and interindividually. Therefore, one dose before and one after inhibition had to be given and a control group had to be included. Fourth, dose finding was required to study the effect of repeated doses because sequential doses were given. Therefore, a sixth dose was given in the control group. Characteristics of this dose could be compared with those of previous doses. Because administration of an irreversible inhibitor of plasma cholinesterase in humans is unethical, this study had to be performed in animals, which restricts our ability to extrapolate our conclusions to humans. However, it has been shown that both the onset time and the duration of action were prolonged in all three documented cases in humans of a submaximal suxamethonium-induced neuromuscular block in the presence of atypical plasma cholinesterase.¹⁷⁻¹⁹ On theoretical grounds and on the basis of our results, we suggest that the phenomenon of a rapid decrease in plasma concentration and a short onset time may be a general phenomenon.

In conclusion, inhibition of the enzymic degradation of suxamethonium and mivacurium increases the onset time of submaximal neuromuscular block. Therefore, pharmacokinetics influence the onset time of submaximal neuromuscular block. Our results imply that to obtain an ultrashort onset time (*i.e.*, ≤ 1 min), muscle relaxants should be developed that not only have a low affinity for the receptor but also rapidly disappear from plasma.

The authors thank Dr. J. C. J. M. Swaanenburg and Ms. A. Ploegman, Central Clinical Chemical Laboratory of the University Hospital, Groningen, The Netherlands, for the many determinations of plasma cholinesterase activity.

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