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The Dose–Response Relationship of Mivacurium Chloride in Humans during Nitrous Oxide–Fentanyl or Nitrous Oxide–Enflurane Anesthesia

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The dose–response relationships of mivacurium chloride during N_2O/fentanyl or N_2O/enflurane anesthesia were compared in 70 patients intraoperatively. Responses were defined in terms of percentage changes in the evoked twitch tension of the adductor pollicis muscle, and dose–response curves were constructed following probit transformation of the responses. End-tidal concentrations of enflurane during the were study were 0.9–1.2%. When compared with the dose–response curve determined during N_2O/fentanyl anesthesia the curve determined during N_2O/enflurane anesthesia was displaced significantly to the left ($P < 0.05$). As a result, the doses of mivacurium that depressed twitch tension by 50% (ED_{50}) and 95% (ED_{95}) were 39 and 67 μg/kg, respectively, during N_2O/fentanyl anesthesia, and 27 and 52 μg/kg during N_2O/enflurane anesthesia. Regression lines describing the relationship between the maximum depression of twitch tension (response) and the time interval between the injection of mivacurium and the return of twitch tension to 90% of the control value (duration) were constructed. The response–duration line for N_2O/enflurane anesthesia was displaced significantly to the left of the line for N_2O/fentanyl ($P < 0.05$), indicating that enflurane anesthesia was associated with a prolongation of mivacurium-induced neuromuscular blockade. The neuromuscular blocking effect of mivacurium is both enhanced by and prolonged during N_2O/enflurane compared with that during N_2O/fentanyl anesthesia. (Key words: Anesthetics, intravenous: fentanyl. Anesthetics, volatile: enflurane. Neuromuscular relaxants: mivacurium (BW B1090U). Pharmacology: dose–response curves.)

MIVACURIUM CHLORIDE® is a potentially useful new nondepolarizing neuromuscular blocking drug because it has a shorter duration of action than any other currently used nondepolarizing agent.[1] The aim of this study was to define the dose–response relationships of mivacurium during two different general anesthetic techniques. Because the action of the other neuromuscular blocking drugs is enhanced by the volatile anesthetics, we predicted that the same would be true for mivacurium. To test this prediction the dose–response relationships of mivacurium were compared in patients receiving N_2O/fentanyl or N_2O/enflurane anesthesia.

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Materials and Methods

With approval from our Committee for Human Research and written informed consent, we studied 70 patients (ASA physical status 1 or 2) undergoing various surgical procedures. No patient was taking drugs or had any disease known to affect neuromuscular function. The features common to both anesthetic techniques were: premedication with midazolam, 0.02–0.05 mg/kg iv, inhalation of nitrous oxide, 60–70% (end-tidal concentration), maintenance of esophageal temperature between 35 and 37° C, and end-tidal P_{CO_2} between 30 and 40 mmHg (measured by mass spectrometry). Mivacurium is metabolized by pseudocholinesterase[1,2]; therefore, a venous blood sample was drawn from each patient before mivacurium administration to measure plasma cholinesterase activity and dibucaine number (SmithKline Bio-Science Laboratories, Van Nuys, California). The normal ranges for pseudocholinesterase activity were 2.4–6.2 U/ml for males and 1.7–7.4 U/ml for females. The genotypes, defined by the dibucaine number, were homozygous for normal enzyme (73–90), heterozygous for an abnormal enzyme (54–70), and homozygous for atypical enzyme (16–28). Results from patients found to have abnormalities of pseudocholinesterase would be excluded.

In patients in the N_2O/fentanyl group (n = 36), anesthesia was induced with fentanyl, 5–10 μg/kg, followed by thiopental, 2–6 mg/kg iv. Tracheal intubation was performed 30–60 s after injection of the thiopental without the use of neuromuscular blocking drugs. Anesthesia was maintained with an iv infusion of fentanyl (2–6 $\mu g \cdot kg \cdot^{-1} \cdot h^{-1}$), supplemented by boluses of fentanyl or thiopental, if necessary, to maintain adequate anesthesia. In patients in the N_2O/enflurane group (n = 34), anesthesia was induced with thiopental, 2–6 mg/kg iv, and enflurane (4–7% inspired concentration). Tracheal intubation was performed during deep enflurane anesthesia without the use of neuromuscular blocking drugs. Anesthesia was then maintained using enflurane, 0.9–1.2% (end-tidal concentration), supplemented by boluses of fentanyl or thiopental, if necessary, to maintain adequate anesthesia. Respired gases and vapors were monitored by on-line mass spectrometry.

To monitor neuromuscular transmission, sc needle electrodes were inserted adjacent to the ulnar nerve at

TABLE 1. Neuromuscular Responses Following Mivacurium in the Patients Discovered to Have Abnormalities of Pseudocholinesterase

	N_2O/Fentanyl			N_2O/Enflurane	
Patient no.	1 (F)	2 (F)	3 (M)	4 (F)	5 (M)
Activity	2.6	7.7	7.6	2.4	2.2
Dibucaine no.	61	86	86	84	66
Genotype	Hetero	Homo	Homo	Hetero	Hetero
Dose (μg/kg)	40	50	70	15	20
Response (%)	88	69	73*	35†	67
Onset (min)	6.25	4.25	3.5*	7.25	8.0
Duration (min)	27.5	12.25	11.25*	23.75†	28.5

The normal range of activity of the enzyme in U/ml is 2.4–6.2 for males (M) and 1.7–7.4 for females (F). Genotype is either homozygous for the normal gene (Homo) or heterozygous for one normal and one abnormal gene (Hetero). Response (maximum depression of T1 twitch tension), onset (time from injecton of mivacurium to maximum T1 depression), and duration (time from injection until T1 twitch recovery to 90% of control) are given for each dose of mivacurium during N_2O/fentanyl and N_2O/enflurane anesthesia.

* Value less than any observed for other subjects in the same dosage group.

† Value greater than any observed for other subjects in the same dosage group.

the wrist. A Grass® S88 nerve stimulator delivered supramaximal impulses in a train-of-four (TOF) pattern (2 Hz) at intervals of 15 s. The evoked twitch tension of the adductor pollicis muscle was measured by a Gould Statham® UTC3 force transducer attached to the thumb. Twitch responses were recorded on a polygraph and, following analog-to-digital conversion, on microcomputer floppy disc.§ The amplitude of the first twitch response of each train (T1) was allowed to reach a plateau and stabilize. The T1 response immediately preceding the administration of mivacurium became the control to which all subsequent T1 responses were compared.

Each anesthesia group was divided into four dosage groups in which each patient received a single, rapidly administered iv bolus of mivacurium. Based on results published by Basta *et al.*,[3] an initial dose of 30 μg/kg was given to patients receiving N_2O/fentanyl anesthesia. Because of the known effect of enflurane on the potency of neuromuscular blocking drugs, we assumed that during N_2O/enflurane anesthesia the dose of mivacurium required to produce a similar T1 response would be approximately 30% less than during N_2O/fentanyl anesthesia. The initial dose in the N_2O/enflurane group was, therefore, 20 μg/kg. Dose–response curves were constructed by using information from completed groups to help determine the dose of mivacurium that should be administered to each subsequent group. As a result, the doses in the N_2O/fentanyl group were 30, 40, 50, and 70 μg/kg, and in the N_2O/enflurane group they were 15, 20, 30, and 40 μg/kg. The neuromuscular response to mivacurium was recorded as the maximum depression of T1 twitch, expressed as a percentage of the control T1. Onset was the time from injection of mivacurium until maximum T1 depression was achieved and duration of action was the time from injection until T1 recovered to 90% of control.

The percentage values for T1 depression were transformed to probits and plotted against the logarithm of the dose of mivacurium. Responses of 0% and 100% T1 depression were assigned values of 1% and 99%, respectively. Lines of best fit through these data points were computed by least-squares linear regression. To compare the duration of action of mivacurium during the two techniques of anesthesia, the duration of action was plotted against the maximum T1 depression for each anesthetic group, and linear regression performed. Regression lines were compared by analysis of covariance, and if found to be different they were compared for slope and position by *t* test. The ED_{50} and ED_{95} values (doses causing 50% and 95% depression of twitch tension, respectively) were calculated from the log-probit regression lines for each anesthetic group.

The dosage groups were compared for patient age, weight, gender, exposure time to anesthetic before administration of mivacurium, and pseudocholinesterase activity by Kruskal-Wallis one-way ANOVA. Within each dosage group linear regression was used to correlate T1 depression with the exposure time to anesthetic before administration of mivacurium and pseudocholinesterase activity.

Differences were considered significant at $P < 0.05$.

Results

Results from five patients who were discovered to have abnormalities of pseudocholinesterase, detailed in table 1, were not included in the analysis.

No differences were found between the dosage or anesthesia groups with respect to age, body weight, or gender. The length of exposure to enflurane prior to injection of mivacurium, and the pseudocholinesterase activity were similar in all groups. The overall mean time of exposure to enflurane before injection of mivacurium was 54 min (SD 19 min). There was no correlation between length of exposure to enflurane or pseudocholinesterase activity and T1 depression.

Analysis of covariance determined that the dose–response regression lines for the two anesthetic groups were significantly different. By *t* test the slopes of these lines were not different. The line for the N_2O/enflurane group was shifted significantly to the left of that for the N_2O/fentanyl group, indicating that enflurane enhances the neuromuscular blocking action of mivacurium (fig. 1). For

§ Thut PD, Pruzansky E, Rudo FG: Microcomputer use in measuring onset, duration, and recovery from nondepolarizing skeletal muscle relaxants in rabbits. Drug Development Research 5:281–290, 1985.

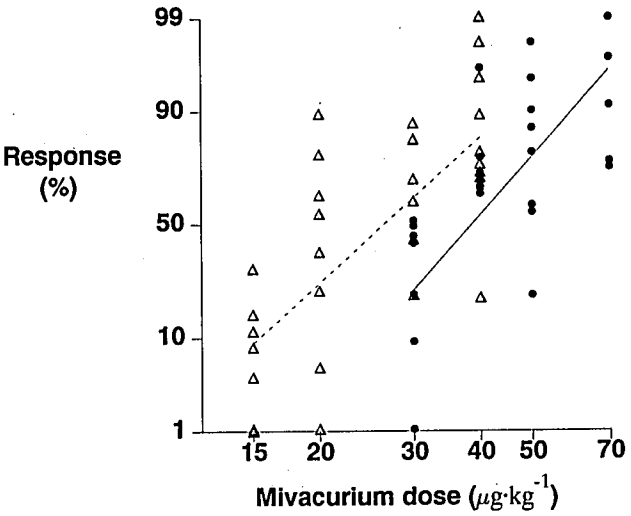

FIG. 1. Dose–response relationships for mivacurium chloride during N_2O/fentanyl (● ——) and N_2O/enflurane (Δ - - - -) anesthesia. The x-axis is a logarithmic plot of the dose of mivacurium administered and the y-axis is a probit plot of the maximum depression of the T1 twitch tension (response). Where two or more subjects had the same response the symbols overlap.

the purposes of this study the term "enhance" is used to describe the greater observed depression of the twitch response in the patients who received N_2O/enflurane anesthesia. No inference is intended as to whether the observed differences have a pharmacokinetic or pharmacodynamic basis. The ED_{50} and ED_{95} doses of mivacurium were 39 and 67 μg/kg, respectively, during N_2O/fentanyl anesthesia, and 27 and 52 μg/kg, respectively, during N_2O/enflurane anesthesia.

Onset and duration of action of mivacurium for each dosage group are detailed in table 2. There was a significant linear relationship between the time for T1 recovery to 90% and the maximum depression of T1 in both anesthesia groups. By analysis of covariance the response–duration lines were significantly different. By *t* test their slopes were not different, and the line for the N_2O/enflurane group was shifted significantly to the left of the line for the N_2O/fentanyl group (fig. 2). Therefore, mivacurium-induced neuromuscular blockade is prolonged during N_2O/enflurane anesthesia compared with that during N_2O/fentanyl anesthesia.

Discussion

It has been established that for neuromuscular blocking drugs with an intermediate duration of action the cumulative method of determining dose–response curves will underestimate the potency of the drug studied.[4,5] In this study, therefore, we used the single dose in preference to the cumulative technique to estimate the dose–response relationship of mivacurium.

TABLE 2. Neuromuscular Responses Following Mivacurium during N_2O/Fentanyl and N_2O/Enflurane Anesthesia

	N	Dose (μg/kg)	Response (%)	Onset (min)	Duration (min)
N_2O/fentanyl	9	30	24 ± 22	5.8 ± 1.5	12.6 ± 1.5
	8	40	71 ± 11	5.5 ± 1.7	15.9 ± 6.2
	8	50	73 ± 26	5.4 ± 0.9	18.6 ± 6.8
	8	70	91 ± 10	5.2 ± 1.3	22.1 ± 4.0
N_2O/enflurane	8	15	9 ± 10	5.9 ± 1.6	11.3 ± 5.7
	8	20	43 ± 33	7.6 ± 1.7	41.5 ± 19.8
	7	30	55 ± 27	6.1 ± 1.0	18.4 ± 7.9
	9	40	77 ± 24	5.9 ± 1.2	22.2 ± 3.1

Response (maximum depression of T1 twitch tension), onset (time from injection of mivacurium to maximum T1 depression), and duration (time from injection until T1 twitch recovery to 90% of control) are given for each dose of mivacurium. All values are mean ± SD.

The concentration of enflurane in our study ranged from 0.9% to 1.2%. It is known that the enhancement of neuromuscular blockade by enflurane is concentration-dependent.[6,7] However, because Fogdall *et al.*[6] found that enflurane in a concentration of 1.2% reduced twitch response by only 7% when compared with no enflurane, we consider that the small variation in the concentration of enflurane in our study had little influence on our results. Stanski *et al.*[8] demonstrated that there was a time-dependent increase in sensitivity to *d*-tubocurarine during enflurane anesthesia. The magnitude of this effect was a 9% decrease in twitch response per hour. We took as control the twitch response immediately preceding the administration of mivacurium; therefore, the time-related effect of enflurane during the time of onset of the neuromuscular response (5–8 min) would be negligible. In addition, we found no relationship between the length of exposure

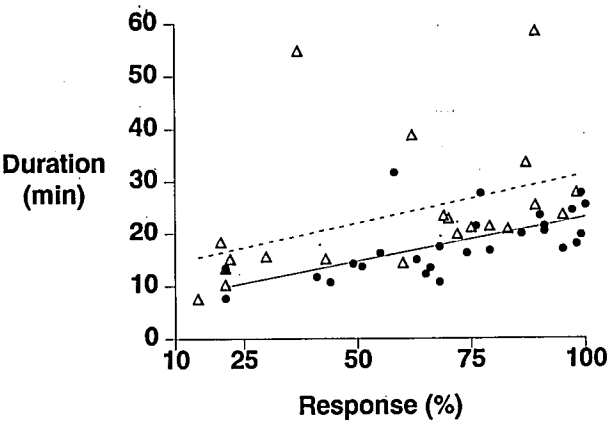

FIG. 2. Relationship between the maximum depression of T1 twitch tension (response) following mivacurium and the time from injection until recovery of T1 twitch tension to 90% of control (duration) during N_2O/fentanyl (● ——) and N_2O/enflurane (Δ - - - -) anesthesia. Only cases in which response >15% are included.

to enflurane, before administration of mivacurium, and the subsequent neuromuscular response. We consider that the differences in the concentrations of and times of exposure to enflurane for the patients in our study had no significant effect on our results.

We determined an ED_{50} for mivacurium during N_2O/fentanyl anesthesia of 39 μg/kg. Similar values were reported by Weber *et al.*,[9] 41 μg/kg, who used a single twitch mode of nerve stimulation and by Choi *et al.*,[10] 39 μg/kg, who used electromyography to measure neuromuscular response. These authors also used the single dose technique in their studies. The ED_{50} value, therefore, seems to give a reproducible estimate of the potency of mivacurium.

The range of values reported for the ED_{95} (58–80 μg/kg) has been wider than for the ED_{50}.[1,9,10] This variability is not surprising given the difficulty of accurately defining the extreme ranges of the dose–response curve. Choi *et al.*[10] reported a value of 0.75 mg/kg, which is presumably a typographical error, and the correct value should be 0.075 mg/kg. Weber *et al.*[9] reported an ED_{95} of 58 μg/kg using the evoked compound electromyogram. However, when they administered this dose to patients, the resulting mean twitch depression was only 68%, which suggests that this value is an underestimate of the ED_{95}. Using the results from these studies we can relate the potency of mivacurium to that of drugs in current use: it is approximately three times as potent as atracurium[11,12] and 70% as potent as vecuronium.[5]

We found that the ED_{50} of mivacurium was approximately 30% less during N_2O/enflurane (27 μg/kg) than that during N_2O/fentanyl anesthesia (39 μg/kg). Weber *et al.*[9] found that the ED_{50} of mivacurium was 41 μg/kg during N_2O/fentanyl anesthesia, and was reduced by approximately 30% to 29 μg/kg during N_2O/isoflurane anesthesia. The concentration of enflurane in our study, and isoflurane in Weber's study, are equivalent in terms of their respective MAC values. Therefore, enflurane and isoflurane appear to have a similar effect on the dose–response relationship of mivacurium. This is also consistent with the known effect of these volatile anesthetics on other neuromuscular blocking drugs.[13]

Because of the differences in the dose–response relationship, the duration of neuromuscular blockade following a given dose of mivacurium would be expected to be longer during N_2O/enflurane than during N_2O/fentanyl anesthesia. To determine if the duration of action of mivacurium was prolonged in the N_2O/enflurane group, independent of the greater twitch depression in this group we plotted the time of T1 recovery to 90% *versus* maximum depression of T1 (fig. 2).[7] By using this approach, we were able to demonstrate that enflurane prolongs the duration of action of mivacurium, independent of enhancement of neuromuscular blockade. Isoflurane also prolongs the recovery from mivacurium-induced blockade. Weber *et al.* reported that the recovery index (time for T1 to recover from 25% to 75% of control) was significantly longer during isoflurane than during N_2O-narcotic anesthesia.[9] In clinical practice, therefore, when volatile anesthetic agents are used, the dose of mivacurium required to produce a given duration of neuromuscular blockade may be significantly reduced.

The time for T1 to recover to 90% of control was longer in the group of patients who received 20 μg/kg of mivacurium during N_2O/enflurane anesthesia than in the other three N_2O/enflurane dosage groups (table 2). This difference just failed to achieve statistical significance but was clinically obvious. Slow recovery of TOF fade was also observed in this group. As already discussed, there is a time-dependent increase in sensitivity to tubocurarine during enflurane anesthesia, and we thought a similar effect might account for the prolonged recovery in this group.[11] There was, however, no difference in the mean time of exposure to enflurane before the injection of mivacurium in this group compared to the other groups, and no individual was subjected to prolonged exposure. We excluded the possibility that these patients received either an incorrect dose of mivacurium or a dose of another neuromuscular blocking agent. There were no characteristics in any of the patients that could account for the prolonged blockade. Having examined these factors that could have explained this effect, we have found nothing to account for it. This effect was not observed in our study during N_2O/fentanyl anesthesia nor has it been reported by other investigators[1,9,10,14]; however, no other study has involved the use of enflurane. We can only postulate that it may be a manifestation of an interaction at the neuromuscular junction between this small dose of mivacurium and the effects of enflurane. The observation has little clinical relevance because it was not seen with larger doses.

The mean onset times (5.2–7.6 min) of these subparalyzing doses of mivacurium are similar to those reported for equivalent doses of other nondepolarizing neuromuscular blocking drugs.[11,12,15] Mivacurium, therefore, does not appear to have a faster onset of action than currently available drugs. To decrease the onset time of mivacurium and thereby facilitate rapid endotracheal intubation, priming doses of 30 μg/kg have been used.[16–18] In our N_2O/fentanyl group twitch depression following this dose varied from 0% to 51% and was greater than 40% in four of the nine patients. In the normal clinical situation the priming dose is be given to an awake patient and the intubating dose administered before the peak effect of the priming dose has occurred, which greatly reduces the possibility of the priming dose inducing excessive blockade. However, if there is a delay between administering the priming and intubating doses, or if a patient is abnormally sensitive to mivacurium, perhaps due to pseudocholinesterase deficiency, then the possibility exists that this priming dose may produce significant impairment of neuromuscular function.

Mivacurium, like succinylcholine, is metabolized by pseudocholinesterase.[1,2] The duration of action of succinylcholine is affected by the activity and genotype of pseudocholinesterase,[19,20] and for this reason we excluded from analysis the five patients who had abnormalities of cholinesterase. The neuromuscular responses following mivacurium of these five patients showed no clear pattern (table 1). Patient 5 was heterozygous for the abnormal enzyme and had low enzyme activity but exhibited a degree and duration of blockade similar to the other patients in his group. In contrast, the duration of action of succinylcholine in this patient would likely be prolonged.[19,20] Patients 1 and 4 were heterozygous for the abnormal enzyme but had a normal level of enzyme activity. Patient 4 developed a greater degree of blockade and had a slower recovery than other patients in her group, which is the same pattern of response that would be expected if succinylcholine were administered to this patient.[20] In contrast, patient 1 appeared to have a normal response. Patients 2 and 3 had high levels of enzyme activity but differing responses. Patient 2 had a normal response, whereas patient 3 showed less neuromuscular blockade and a had a more rapid recovery than any other patient in his dosage group. In patients with normal pseudocholinesterase the duration of action of succinylcholine is inversely related to the enzyme activity, although within the normal range the effect is small.[19] For the patients in our study who had normal enzyme we found no correlation between pseudocholinesterase activity and the duration of action of mivacurium. It is difficult to draw firm conclusions from our data, however, because we used several different doses of mivacurium, which may have obscured any relationship between enzyme activity and duration of action. In addition, other metabolic pathways or routes of elimination make a significant contribution to the biodisposition of mivacurium.[2] We can conclude only that there is a possibility that the neuromuscular responses to mivacurium may be affected by abnormalities of pseudocholinesterase because two of five patients with such abnormalities had apparently altered neuromuscular responses.

In conclusion, we have demonstrated that the neuromuscular blocking action of mivacurium is both enhanced and prolonged by N_2O/enflurane anesthesia when compared with N_2O/fentanyl anesthesia.

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