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Neuromuscular and Hemodynamic Effects of Mivacurium and Succinylcholine in Adult Patients During Nitrous Oxide-Propofol-Fentanyl Anesthesia

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The neuromuscular and hem+odynamic effects of mivacurium 0.15 mg/kg and succinylcholine 1 mg/kg were compared in 26 adult patients (ASA I and II) during nitrous oxide-oxygen-propofol-fentanyl anesthesia. Neuromuscular block was monitored by recording the compound electromyogram of the hypothenar muscle resulting from supramaximal train-of-four stimuli applied to the ulnar nerve. Time to onset of over 95% block and duration to 25% recovery of control twitch after injection of mivacurium were significantly longer than for succinylcholine (201±37.6 vs 54±5.2 sec and 13.0±2.2 vs 8.4±2.1 min; mean±SD). Onset of mivacurium with priming technique was shortened (125±20.7 sec), but was also slower than that of succinylcholine. Although the recovery index during spontaneous recovery was significantly longer for mivacurium than for succinylcholine (6.9± 1.3 vs 5.1±0.9 min), antagonism with neostigmine at 25% recovery of twitch height sufficiently facilitated the recovery index of mivacurium (4.5± 1.0 min) to a level similar to that of succinylcholine with no statistical difference. The hemodynamic effects of mivacurium were few as compared to those of succinylcholine. In conclusion, mivacurium is considered to have additional advantages for short procedures when succinylcholine is undesirable.

Key Words: *Neuromuscular Relaxants; mivacurium, succinylcholine, Henodynamic Effects.*

INTRODUCTION

With the introduction of nondepolarizing muscle relaxants and their widespread clinical use, it may be said that the preconditions set forth by Savarese and Kitz (1975) for ideal muscle relaxants have been satisfied to a certain extent by atracurium and vecuronium as intermediate-acting, and pipecuronium and doxacurium as long-acting muscle relaxants. However, the development of a short-acting muscle relaxant remains on-going as of yet.

Although succinylcholine is often used in cases where rapid onset and short duration of neuromuscular blockade are required, there are many clinical situations in which the various side-effects of succinylcholine make its use undesirable. Therefore, the need for the development of a more optimal short-acting nondepolarizing muscle relaxant is being ever more keenly felt.

Mivacurium, a new benzylisoquinolinium nondepolarizing muscle relaxant, is metabolized by pseudocholinesterase at a rate of 70-88% of that of

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succinylcholine, and is now being introduced as a short-acting muscle relaxant (Savarese et al., 1988a; Cook et al., 1989).

This study was accordingly conducted to evaluate the neuromuscular blocking action and hemodynamic effects of mivacurium and compare the results with cases of succinylcholine.

PATIENTS AND METHODS

26 adult patients, ASA physical status I and II without any factors to interact with muscle relaxants or abnormalities in their neuromuscular transmission, were selected randomly and their informed consent was obtained. The patients were premedicated with hydroxyzine 1.5 mg/kg and glycopyrrolate 0.2 mg intramuscularly (IM) 1 hour before anesthesia was induced. Anesthesia was induced with propofol 2mg/kg and fentanyl 2-5 mcg/kg intravenously (IV) with nitrous oxide (67%) and oxygen inhalation through the face mask, and maintained with intermittent fentanyl 2-3 mcg/kg IV as needed. End-tidal CO2 tension and body temperature were kept at normal ranges throughout the entire procedure. The trachea was intubated at least 5 minutes after injection of muscle relaxant to avert any effects from hemodynamic changes.

The ulnar nerve was stimulated supramaximally with repeated trains-of-four (TOF, 2 Hz at 20-second intervals) via surface electrodes at the wrist. The compound electromyograms of the hypothenar muscles were recorded using a Relaxograph (Datex Co, Filand). Neuromuscular blockade was quantified by the amplitude of first twitch (T1) of TOF response and represented as a percent of control T1 response.

After a stable control twitch response was obtained, patients were divided into three groups; 1) the SCC group (n=10) in whom succinylcholine 1 mg/kg was injected, 2) the M-1 group (n=8) in whom mivacurium 0.15 mg/kg (2×ED95) was injected as a bolus and allowed to recover spontaneously, and 3) the M-2 group (n=8) in whom mivacurium 0.135 mg/kg was injected after 5 minutes priming of 0.015 mg/kg and antagonized with neostigmine 0.04 mg/kg mixed with atropine 0.02 mg/kg at 25% recovery of T1. The rate of injection was 10-15 seconds for both succinylcholine and mivacurium. The following values were obtained from analysis of T1 recording: onset time (from the end of injection to over 95% depression of control twitch height); duration (from the end of injection to 25% recovery of control twitch height); and recovery index (time from 25% to 75% recovery of control twitch height).

Heart rate (HR) and mean arterial pressure (MAP) were measured every minute beginning at 1 minute before muscle relaxant injection (baseline) and continuing for 5 minutes following injection of the drug by using a non-invasive method (Datascope 2100).

All data were shown in mean±SD. Wilcoxon signed rank and Mann-Whitney U tests were used to analyze where appropriate, and differences were considered statistically significant at $P<0.05$.

Table 1. Demographic Data

Group	Age (years)	Sex (m;f, No)	Weight (kg)
SCC (n=10)	32 ± 3.8	5:5	59 ± 3.0
M-1 (n=8)	31 ± 5.8	5:3	57 ± 5.2
M-2 (n=8)	29 ± 3.7	4:4	58 ± 8.6

Values except Sex Column are means±SD.
The M-1 group: one in which mivacurium 0.15 mg/kg was injected as a bolus and allowed to recover spontaneously. The M-2 group: one in which mivacurium 0.135 mg/kg was injected after 5 minutes priming of 0.015 mg/kg and antagonized with neostigmine 0.04 mg/kg mixed with atropine 0.02 mg/kg at 25% recovery of T_1.
m: male, f: female.
There are no significant differences between the succinylcholine (SCC) and either mivacurium (M-1 and M-2) groups.

Table 2. Neuromuscular Effects of Succinylcholine (SCC) and Mivacurium (M) during Nitrous oxide-Fentanyl Anesthesia.

Group	Onset (Sec)	Duration (min)	Recovery Index (min)
SCC	54 ± 5.2	8.4 ± 2.14	5.1 ± 0.93
M-1	201 ± 37.6*	13.0 ± 2.20*	6.9 ± 1.31*
M-2	125 ± 20.7*,#	13.2 ± 1.47*	4.5 ± 1.00#

Values are means±SD.
The M-1 group: one in which M 0.15 mg/kg was injected as a bolus and allowed to recover spontaneously. The M-2 group: one in which M 0.135 mg/kg was injected after 5 minutes priming of 0.015 mg/kg and antagonized with neostigmine 0.04 mg/kg mixed with atropine 0.02 mg/kg at 25% recovery of T_1.
* : Significantly different from SCC group. $P<0.05$
# : Significantly different from M-1 group. $P<0.05$

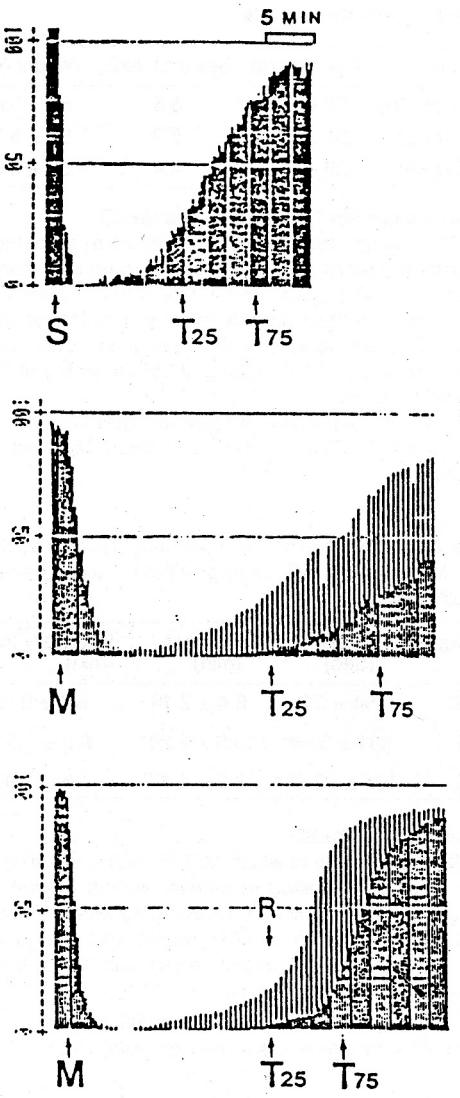

Fig. 1. Relaxograph traces of neuromuscular block following injection of succinylcholine (S) I mg/kg (top), mivacurium (M) 0.15 mg/kg as a bolus (middle), and mivacurium (M) 0.135 mg/kg after 5 min priming of 0. 015 mg/kg and antagonism (R) with neostigmine 0.04 mg/kg mixed with atropine 0.02 mg/kg at 25% recovery of control twitch height (bottom). T_{25} and T_{75} represent 25% and 75% recovery of T_1 respectively.

RESULTS

There were no significant differences among the groups in regard to age, body weight, and sex distribution (Table 1).

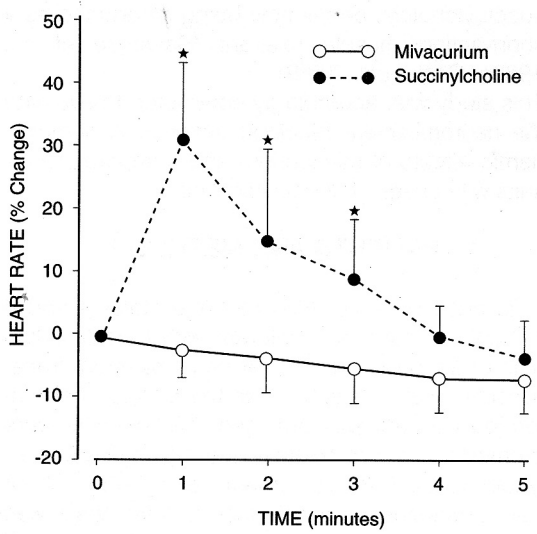

Fig. 2. The percent changes in heart rate after injection of a bolus dose of mivacurium 0.15 mg/kg and succinylcholine 1 mg/kg. Each symbol and bracket represents the mean±SD. Asterisk indicates a significant difference ($P<0.05$) from the baseline value.

The onset was significantly slower in the M-1 group (201±37.6 sec) than in the SCC group (54 ±5.2 sec). Although the onset in the M-2 group with priming technique of mivacurium (125±20.7 sec) was significantly faster than that in the M-1 group, it was slower than that in the SCC group. The duration was also significantly longer in either mivacurium group (13.0±2.2 min in M-1 group and 13.2±1.5 min in M-2 group) than that in the SCC group (8.4±2.1 min). The recovery index of mivacurium was also longer (6.9±1.3 min) than that of succinylcholine (5.1±0.9 min), but its antagonism with neostigmine distinctly and sufficiently facilitated the recovery index of mivacurium (4.5±1.0 min) to a level similar to that of succinylcholine with no statistical difference (Table 2, Fig. 1).

There were no clinically significant changes in HR and MAP for 5 min after administration of mivacurium 0.15 mg/kg, maintaining a range within -7% and -4% changes respectively as compared to baseline values. However, significant changes in HR and MAP were noted after administration of succinylcholine 1 mg/kg, +30% and ±15% changes respectively as compared to baseline (Fig. 2, 3). No other adverse side effects were observed in any patients.

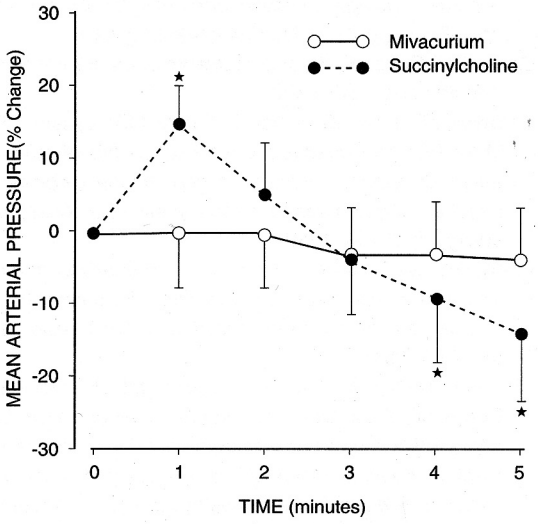

Fig. 3. The percent changes in mean arterial pressure after injection of a bolus dose of mivacurium 0.15 mg/kg and succinylcholine 1 mg/kg. Each symbol and bracket represents the mean±SD. Asterisk indicates a significant difference ($P<0.05$) from the baseline value.

DISCUSSION

The ED95 for mivacurium in adults under narcotic anesthesia is known to be 0.07-0.08 mg/kg (Ali et al., 1988; Choi et al., 1989; Caldwell et al., 1989), but the optimum recommended intubating dose is up to and including 2×ED95 (0.15 mg/kg) because of side effects resulting from histamine release in case of larger dose (Savarese et al., 1988b). Given that the ED95 for succinylcholine is about 0.2 mg/kg (Fauvel, 1993), the mivacurium 0.15 mg/kg and succinylcholine 1 mg/kg used in this study are not equipotent; but these doses were chosen for the purpose of comparing the neuromuscular blocking action and hemodynamic changes which occur with the clinical intubating doses.

It is said that the reason for the very rapid onset of the depolarizing muscle relaxant, succinylcholine, in contrast to nondepolarizing muscle relaxants lies in the short time required by the drug to be equilibrated between plasma and neuromuscular junction (biophase) due to its rapid metabolism or redistribution, and the consequent reduction in plasma concentration (Donati, 1993). Accordingly, it was expected that the onset of mivacurium, which is metabolized by pseudocholinesterase like succinylcholine, would also be quite short because of its metabolic rate reaching 70-88% of that of succinylcholine. But as shown by this and other studies (Ali et al., 1988; Weber et al., 1988; From et al., 1990), the onset of mivacurium is considerably slower than that of succinylcholine, with no difference to the case of a 2× ED95 dose of atracurium or vecuronium (Bevan et al., 1992). It was also discovered that while the onset could be somewhat shortened with the introduction of the priming technique, the onset of succinylcholine blockade is thus far unrivalled.

Feldman et al. (1990) had proposed the hypothesis using the concept of margin of safety that the onset of nondepolarizing muscle relaxants is slower than that of succinylcholine because the latter has an action similar to acetylcholine, which has to occupy only 20% of acetylcholine receptors in the neuromuscular junction in order to sufficiently depolarize the motor endplates, while nondepolarizing muscle relaxants have to occupy over 80% of the receptors to produce a neuromuscular block. We therefore agree that the difference in onset between depolarizing and nondepolarizing muscle relaxants is due to the discrepancy in the proportion of occupancy of receptors in the neuromuscular junction. But at the same time, we could not exclude the possibility that the larger dose of succinylcholine to mivacurium had an effect on the onset.

If the clinical duration of a muscle relaxant is the time from injection to return of twitch to 25% of control twitch height, then the 13 min for mivacurium in this study is consistent with the results of other studies (Savarese et al., 1988a; Weber et al., 1988; From et al., 1990). The figure is quite long in comparison to about 8 min for succinylcholine, but it is a mere 1/2 of that of atracurium 0.4 mg/kg or 1/3 of that of vecuronium 0.08 mg/kg. Thus it provides sufficient grounds to believe that mivacurium could be a useful alternative in management of short surgical cases requiring rapid recovery.

The duration of action of a muscle relaxant depends on its affinity with receptors, but more important is its ease of dissociation from receptors due to the concentration gradient between plasma and neuromuscular junction. Since the plasma concentration of a muscle relaxant may be an important factor in deciding the concentration gradient, the rapid hydrolysis of mivacurium by pseudocholinesterase may be deemed as the cause for the short duration of action.

Antagonism with neostigmine at 25% recovery

of twitch height sufficiently facilitated the recovery index of mivacurium to a level similar to that of succinylcholine. It would appear that this occurs because neostigmine is more potent in inhibiting true cholinesterase at the neuromuscular junction than pseudocholinesterase (Cook et al., 1992). Atack et al. (1989) also claimed in their experimental study that neostigmine is 6 to 50 times more potent against true cholinesterase than against pseudocholinesterase. On the other hand, there were also thoughts that, when twitch recovered to 25% of control twitch height, inhibition of pseudocholinesterase activity by neostigmine might have little effect on the metabolism of mivacurium as plasma concentration will already have dropped by then due to rapid metabolic rate.

Mivacurium is well known to cause elevation of plasma histamine level together with associated phenomena such as cutaneous flushing and hypotension (Savarese et al., 1988b; Cheng et al., 1988). Savarese et al. (1989) found that histamine-related events occur primarily at doses above the maximum recommended adult dose of 0.15 mg/kg and depend on the rate of injection. In the dose evaluated in this study, however, hemodynamic change was little and no other clinical signs of histamine release were observed after 10-15 sec injection rate of mivacurium. The tendency of slight decrease in HR (-7%) and MAP (-4%) after administration of mivacurium should be presumably due to fentanyl.

It is concluded that mivacurium is a short-acting nondepolarizing muscle relaxant causing few hemodynamic changes at the slow bolus dose of 0.15 mg/kg. Although onset and duration of neuromuscular block were longer for mivacurium than for succinylcholine, recovery from mivacurium-induced neuromuscular block could be expected to reach a level similar to that of succinylcholine by antagonizing with neostigmine. Therefore, mivacurium is considered to have additional advantages for short procedures when succinylcholine is undesirable.

REFERENCES

Ali HH, Savarese JJ, Embree PB, Basta SJ, Stout RG, Bottros LH, Weakly JN: *Clinical pharmacology of mivacurium chloride (BW B1090U) infusion; Comparison with vecuronium and atracurium. Br J Anaesth 61:541-546, 1988.*

Atack JR, Yu QS, Soncrant TT, Brossi A, Rapoport SI: *Comparative inhibitory effects of various physostigmine analogs against acetyl- and butyrylcholinesterases. J Pharmacol Exp Ther 249:149-202, 1989.*

Bevan DR, Donati F: *Muscle relaxants of the future. Sem Anesth 9:123-130, 1992.*

Caldwell JE, Kitts JB, Heier T, Fahey MR, Lynam DP, Miller RD: *The dose-response relationship of mivacurium chloride in humans during nitrous oxide-fentantyl or nitrous oxide-enflurane anesthesia. Anesthesiology 70:31-35, 1989.*

Cheng M, Lee C, Yang E, Cantley E: *Comparison of fast and slow bolus injections of mivacurium chloride under narcotic-nitrous oxide anesthesia. Anesthesiology 69:A877, 1988.*

Choi WW, Mehta MP, Murray DJ, Sokoll MD, Forbes RB, Gergis SD, Abou-Donia M, Kirchner J: *Neuromuscular and cardiovascular effects of mivacurium chloride in surgical patients receiving nitrous oxide-narcotic or nitrous oxide-isoflurane anaesthesia. Can J Anaesth 36:641-50, 1989.*

Cook DR, Stiller RL, Weakly JN, Chakravorti S, Brandom BW, Welch RM: *In vitro metabolism of mivacurium chloride (BW B1090U) and succinylcholine. Anesth Analg 68:452-456, 1989.*

Cook DR, Chakravorti S, Brandom BW, Stiller RL: *Effects of neostigmine and edrophonium on the in vitro metabolism of mivacurium; Clinical correlates. Poster Discussion 1-b at the 4th Int'l neuromuscular meeting, Montreal, 1992.*

Donati F: *Effect of dose and potency on onset. Anaesth Pharmacol Rev 1:34-43, 1993.*

Fauvel NJ: *Onset of neuromuscular block. Anaesth Pharmacol Rev 1:44-48, 1993.*

Feldman S, Fauvel NJ, Harrop-Griffiths AW: *Onset of neuromuscular block - an hypothesis. Br J Anaesth 65:585P, 1990.*

From RP, Pearson KS, Choi WW, Abou-Donia M, Sokoll MD: *Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide-fentanyl-thiopentone and nitrous oxide-halothane anaesthesia. Br J Anaesth 64:193-198, 1990.*

Savarese JJ, Kitz RJ: *Does clinical anesthesia need new neuromuscular blocking agents? Anesthesiology 42: 236-239, 1975.*

Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RPF, Sunder N, Weakly JN, Wastila WB, El-Sayad HA: *The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). Anesthesiology 68:723-732, 1988a.*

Savarese JJ, Roscow CE, Embree PB, Schwartz AF, Basta SJ: *A quantal analysis of the dose-response of mivacurium for plasma histamine increase, facial erythema and arterial pressure decrease. Anesthesiology 69:A527, 1988b.*

Savarese JJ, Ali HH, Basta SJ, Scott RPF, Embree PB, Wastila WB, Abou-Donia MM, Gelb C: *The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide-opiate-barbiturate anesthesia. Anesthesiology 70:386-394, 1989.*

Weber S, Brandom BW, Powers DM, Sarner JB, Woelfel SK, Cook RD, Foster VJ, McNulty BF, Weakly JN: *Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide-isoflurane and nitrous oxide-narcotic anesthesia in adult surgical patients. Anesth Analg 67:495-499, 1988.*