

The effect of desflurane on rocuronium onset, clinical duration and maintenance requirements

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Abstract : Volatile anesthetics potentiate the effects of non-depolarizing agents. This study investigated the interaction between the inhalational anesthetic desflurane and rocuronium. Forty ASA I and II patients randomly received desflurane/N₂O/fentanyl, or propofol/N₂O/fentanyl anesthesia, and rocuronium 0.6 mg/kg. Neuromuscular block was assessed at the adductor pollicis muscle. Block onset and clinical duration times were measured ; a rocuronium infusion was started when the first twitch on train-of-four returned to 10% of control (T_{10%}). Maintenance infusion requirements and recovery profiles (spontaneous and after reversal) were recorded until recovery of twitch to 90% of control (T_{90%}). Rocuronium onset was prolonged by 67% (p = 0.034), clinical duration by 30% (p = NS), and infusion requirements were lower in the desflurane group (4.5 vs. 7.1 mg/kg/min, p = 0.003). Recovery times were not statistically different. Desflurane significantly delays the onset of neuromuscular block, potentiates rocuronium during maintenance infusion, but does not affect clinical duration or recovery.

Key words : Inhalational anesthetics, desflurane ; muscle relaxants, rocuronium ; neuromuscular block, monitoring.

INTRODUCTION

All volatile anesthetic agents are known to alter the pharmacodynamics of nondepolarizing neuromuscular blocking drugs. This study was undertaken to compare the effects of desflurane to those of propofol on rocuronium pharmacodynamics. Anesthesiologists seeking a relatively rapid onset of neuromuscular block, facile maintenance of neuromuscular relaxation, and fast emergence from general anesthesia and reversal of neuromuscular block use the desflurane/rocuronium drug combination frequently. It is important, therefore, to determine the extent to which desflurane affects rocuronium's onset, duration, maintenance and recovery profiles.

METHODS

This open-label, parallel group, randomized, two-center study was approved by the hospital Human Investigation Committees at both institutions. After giving informed, written consent, forty patients completed the study. All patients were between the ages of 21 and 69 years, classified as ASA physical status I or II, and scheduled to have elective procedures lasting more than two hours. Patients were excluded if they were not within 25% of their ideal body weight, had any renal, hepatic, or neuromuscular impairment or were taking any medications known to alter muscle relaxant pharmacodynamics. Patients with suspected difficult airways or requiring rapid sequence intubations also were excluded.

All patients were premedicated with intravenous (*iv*) midazolam (1-3 mg) after routine ASA monitors were applied. Following 2-4 minutes of preoxygenation, general anesthesia was induced using *iv* propofol (1-2 mg/kg). After confirming adequacy of the airway to mask ventilation, patients were randomized (according to a computer-generated list) to receive maintenance anesthesia consisting of either a propofol infusion (100-150 µg/kg/min *iv*) or desflurane (3-8% end-tidal concentration). Both groups received 50% N₂O in O₂ and were

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given intermittent *iv* boluses of fentanyl at the discretion of the anesthesiologist to maintain hemodynamic stability. End-tidal CO₂ was maintained between 30 and 40 mmHg and core body temperature was kept above 35° C by active warming. Neuromuscular function was monitored with a Datex 221 NMT device (Datex, Shrewsbury, MA) that measured the evoked electromyographic (EMG) response to serial train-of-four (TOF) stimulation of the adductor pollicis muscle. Superficial stimulation of the ulnar nerve was achieved *via* skin electrodes placed on the volar surface of the wrist. Neuromuscular monitoring was then allowed to stabilize for approximately 3 minutes, while serial single-twitch monitoring at 1 Hz was delivered. Following baseline stabilization, neuromuscular stimulation was continued with four supramaximal square-wave, 2-Hz pulses (TOF) at 20-second intervals while anesthesia was maintained with either propofol infusion or desflurane, and rocuronium (0.6 mg/kg) was then administered by rapid *iv* bolus into a port close to the *iv* insertion site. Mask ventilation was continued until the first twitch of the TOF (T₁) declined to 10% of the pre-relaxant baseline (T_c). At this point (defined as onset), the patient's trachea was intubated, and ease of intubation was assessed by a blinded investigator. Intubation scores were recorded as excellent (easy, vocal cords open, no patient movement), good (easy, cords open, coughing or bucking), fair (not easy and/or cord closed and/or excessive patient movement), or poor (unable to intubate). Neuromuscular monitoring and maintenance anesthesia were continued in the same fashion throughout the anesthetic. The neuromuscular block was allowed to recover until T₁ reached 10% of T_c (defined as time until recovery), at which point an *iv* infusion of rocuronium, 10-12 µg/kg/min was begun. The rocuronium infusion rate was titrated to keep T₁ at 10% (± 5%) of T_c. Infusion rates were recorded every 5 minutes, and whenever the rate was changed. Approximately 30 minutes prior to the end of surgery the infusion was discontinued and

spontaneous neuromuscular recovery was recorded as long as possible. When clinically indicated (e.g., once surgery was complete and T₄/T₁ ratio was still less than 0.75), the patient received pharmacologic-induced reversal with *iv* neostigmine (2-3 mg) and glycopyrrolate (0.5 mg) and EMG neuromuscular recovery was recorded for the next 10 minutes. Desflurane and propofol were discontinued after T₁ recovered to 90% of baseline.

Data comparisons between rocuronium with and without desflurane included onset, clinical duration times, and recovery times, as well as infusion dosing requirements. Data are expressed as mean ± SD (range). Groups were compared using ANOVA, and *p* < 0.05 was considered statistically significant.

RESULTS

Forty patients completed the protocol. Nineteen received propofol, and twenty-one received desflurane. There were no differences between groups with respect to patient demographics (Table 1). All patients demonstrated complete neuromuscular block (T₁ = 0) and "good" or "excellent" intubating conditions in response to 0.6 mg/kg of rocuronium (Table 2).

In the desflurane group, the onset of relaxation was significantly prolonged as compared with the propofol group: 198 ± 147 (21-614) and 118 ± 78 (24-333) seconds, in the desflurane and propofol groups, respectively (*p* = 0.034). The clinical duration of rocuronium tended to be prolonged in the desflurane group as compared with the propofol group: 39.0 ± 25 (7.2-134) and 29.3 ± 13 (10.7-61.8) minutes, respectively; *p* = NS (Table 3). Rocuronium infusions were started at the same T₁ percent recovery in each group, but the infusion requirements were significantly lower in the desflurane group (Table 4). All measured spontaneous recovery indexes (T_{10%}, T_{25%}, T_{50%} and T_{75%}) were prolonged in the desflurane group, but failed to achieve

Table 1

Patient Demographics

	Desflurane Group	Propofol Group	<i>p</i> Value
Age (years, mean ± SD)	40.8 ± 12.9	43.8 ± 12.2	0.442
Height (cm, mean ± SD)	165 ± 9	195 ± 9	0.920
Weight (kg, mean ± SD)	71 ± 11	73 ± 14	0.581
Gender (M/F)	5 / 16	5 / 14	0.855
Race (Caucasian/other)	17 / 4	18 / 1	0.188
ASA PS Class (I/II)	6 / 15	10 / 9	0.121

Table 2
Ease of Intubation Rating

Score	Desflurane Group		Propofol Group		p Value
	N	%	N	%	
Excellent	14	70	12	63	0.651
Good	6	30	7	37	
Total	20*		19		

* Data not recorded for one subject.

statistical significance (Table 5). Patients who received pharmacologic reversal with neostigmine after discontinuation of relaxant infusion (the majority of the study subjects), exhibited a slower rate of recovery in the desflurane group, but these differences also did not reach statistical significance. Percent recovery at the time of reversal was similar in both groups.

DISCUSSION

It is well known that volatile anesthetic agents tend to potentiate the effects of all commercially available non-depolarizing neuromuscular blocking agents, including rocuronium (1, 2, 4-8, 10-13, 15).

This study was designed to specifically investigate the extent to which desflurane (compared with an equipotent non-volatile anesthetic) affected rocuronium onset, maintenance, and recovery pharmacodynamics. We hypothesized that we could minimize the accumulation typically observed with steroidal relaxants by administering it in patients anesthetized with desflurane, thereby decreasing dosing requirements necessary to maintain intraoperative surgical relaxation. Further, since desflurane is relatively insoluble, its potentiating effect should be extremely short-lived and have minimal influence on neuromuscular recovery (either spontaneous or pharmacologic), soon after it is discontinued.

In this study, $2 \times ED_{95}$ of rocuronium administered by rapid *iv* bolus resulted in complete block in all patients in both groups. Intubating conditions for all patients were either excellent or good, with no significant differences observed between groups.

Onset times were significantly different between groups. We initially postulated that the onset time in the desflurane group would be significantly shorter than that in the propofol group because of desflurane's ability to potentiate neuromuscular block. Interestingly, we found that onset

Table 3
Relaxant Onset and Clinical Duration

	Desflurane Group	Propofol Group	p Value
Onset (seconds, mean \pm SD)	198 \pm 147	118 \pm 78	0.034
Onset range (seconds)	21 – 614	24 – 333	
Clinical duration (minutes, mean \pm SD)	39.0 \pm 25	29.3 \pm 13	0.122
Duration range (minutes)	7.2 – 134.0	10.7 – 61.8	

Table 4
Relaxant Infusion Durations and Rates

	Desflurane Group	Propofol Group	p Value
Infusion duration (minutes, mean \pm SD)	138.5 \pm 78	119.7 \pm 79	0.409
Duration range (min)	35.6 – 270.8	21.0 – 287.2	–
Infusion rate (mean \pm SD, μ g/kg/min)	4.5 \pm 2.3	7.1 \pm 2.7	0.003
Rate range (μ g/kg/min)	1.0 – 10.1	2.9 – 11.6	–

Table 5
Spontaneous Recovery Profiles

T ₁ /T _c Ratio (%)	Desflurane Group		Propofol Group		p Value
	N	Time (min) \pm SD	N	Time (min) \pm SD	
25	17	19 \pm 14	15	16 \pm 17	0.549
50	15	27 \pm 8	11	21 \pm 7	0.052
75	2	44 \pm 11	5	28 \pm 10	0.143
90	1	68	3	46 \pm 6	–

time in the desflurane group was, in fact, an average of 67% longer (80 seconds, $p = 0.034$) than in the propofol group. The range of onset times in the desflurane group also was much greater than in the propofol group (21-614 seconds *vs.* 24-333 seconds). The variable onset of rocuronium-induced neuromuscular block was magnified (nearly doubled) in the group receiving desflurane, making this regimen appear less reliable in situations where rapid and/or predictable block onset is desirable. For rapid sequence intubation situations, however, desflurane's effect on onset is immaterial, since patients would not be exposed to an inhalation anesthetic prior to intubation. The prolonged onset time in the desflurane group might be explained by the increase in sympathetic tone known to occur in patients after exposure to the inhalational agent, especially if the inhaled concentration is increased rapidly (3, 9). This increased tone would cause superficial vasoconstriction and delay delivery of rocuronium to the stimulated muscle group (in this case, the adductor pollicis muscle), especially as the vasodilating effect of propofol used for induction is antagonized. Whether this same postulated mechanism of vasoconstriction also affects the axial (diaphragmatic, laryngeal) musculature is yet unknown.

Clinical duration was prolonged by about 30% in the desflurane group, but the difference did not reach statistical significance. Again, the ranges of clinical duration were much greater in patients receiving desflurane. Relaxant infusion rates titrated to maintain a T_1/T_c ratio of 10% were 67% less in the desflurane group ($p = 0.003$), while there was no statistical difference in infusion duration between groups. After the first 30 minutes of administration, infusion rates in both groups remained relatively consistent until 120 minutes. These findings of a prolonged duration of action of rocuronium during desflurane anesthesia compared with propofol are consistent with previous reports (8).

Both spontaneous and pharmacologic neuromuscular recoveries were prolonged in the desflurane group, but the differences were not statistically significant. Similar findings have been reported previously (14). Spontaneous recovery to 25% (T_1/T_c ratio) from the time of infusion discontinuation was similar. By 50% recovery, the difference approached statistical significance (27 minutes in the desflurane group, 21 minutes in the propofol group, $p = 0.052$). By 75% and 90% recovery, the number of patients in each group was too small for statistical comparisons. Neuromuscular recovery

after reversal was also similar between groups during the first 10 minutes after reversal.

In summary, our data indicate that desflurane significantly potentiates rocuronium-induced neuromuscular block as compared with *iv* propofol, and significantly delays the onset of neuromuscular block at the adductor pollicis muscle.

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