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The Effect of Midazolam Pre-medication on Rocuronium-induced Neuromuscular Blockade*

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We investigated the effect of midazolam pre-medication on rocuronium-induced neuromuscular blockade during sevoflurane anaesthesia. Twenty-two patients scheduled for elective surgery were randomly divided to receive either no pre-medication (control group) or pre-medication with 0.1 mg/kg midazolam intramuscularly (midazolam group). Anaesthesia was induced with fentanyl and propofol, and maintained with sevoflurane and nitrous oxide in oxygen. Neuromuscular responses were monitored using acceleromyography. The onset and clinical duration of action, time to recovery of first twitch of train-of-four (TOF) response to 75% of control, recovery index and time for TOF recovery to 25% and 50% were recorded. Patient-related data were similar in both groups. The parameters recorded were not significantly different between the groups. Midazolam pre-medication does not influence the time-course of action of rocuronium during sevoflurane anaesthesia.

KEY WORDS: MIDAZOLAM; ROCURONIUM; DRUG INTERACTIONS; NEUROMUSCULAR RESPONSES

Introduction

Midazolam, a water-soluble benzodiazepine, is the most widely used pre-operative anxiolytic drug in anaesthetic pre-medication.[1] The onset of sedation occurs about 15 min after administration of intramuscular midazolam, and reaches a peak at 30 – 60 min after administration.[2]

This prospective clinical study was designed to evaluate the effect of midazolam as a pre-medication agent on rocuronium-induced neuromuscular blockade during sevoflurane-based anaesthesia.

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Materials and methods

PATIENTS

After obtaining approval from the Dokuz Eylül University Hospital Ethics Committee, and written informed consent from each patient, 22 adult patients (American Society of Anesthesiologists [ASA] grades I and II; healthy or with mild systemic disease that did not limit activity), scheduled for elective surgeries with general anaesthesia, were recruited to this study. All patients were free from cardiac, pulmonary, hepatic or renal disease, and were taking no medication that might interfere with neuromuscular transmission. Elderly patients (> 65 years) were excluded.

STUDY DESIGN

The patients were randomly divided into two groups, the control group (n = 11, no pre-medication) and the midazolam group (n = 11, pre-medicated with 0.1 mg/kg midazolam intramuscularly approximately 30 min before the induction of anaesthesia). Anaesthesia was induced with 10 µg/kg atropine, 2 µg/kg fentanyl and 2 – 3 mg/kg propofol, and maintained with 1 – 2% inspired concentration of sevoflurane and 60% nitrous oxide in oxygen. As an anaesthetic supplement, 1 µg/kg fentanyl was administered.

MEASUREMENTS

In all patients, heart rate, non-invasive systemic blood pressure, arterial oxygen saturation (SpO_2), percentages of inspired concentrations of oxygen, nitrous oxide and sevoflurane, and end-tidal carbon dioxide (Viridia CMS, Hewlett Packard, USA) were monitored. Lungs were ventilated mechanically and adjusted to maintain an end-tidal carbon dioxide pressure between 30 mmHg and 35 mmHg.

Acceleromyographic responses of the adductor pollicis muscle to stimulation of the ulnar nerve (TOF-Guard®, OrganonTeknika/ Biometer, Denmark) were used to monitor neuromuscular function. After induction of anaesthesia, stimulating electrodes were placed over the ulnar nerve. The thenar eminence temperature was maintained above 32°C. The current necessary for supramaximal stimulation was determined and set automatically at the beginning of the monitoring period. After a stabilization period performed by train-of-four (TOF) stimuli (2 Hz) every 15 s for at least 10 min, and after obtaining the control twitch height, 0.6 mg/kg rocuronium was administered. The first twitch of TOF response (T_1) was considered as the twitch height. When T_1 disappeared, the trachea was intubated. Onset of action (time between the end of the rocuronium injection and maximal depression of T_1 from the control value); clinical duration of action (time for recovery of T_1 to 25% of control); time for T_1 recovery to 75% of control; recovery index (time for recovery of T_1 from 25% to 75% of control); time for TOF recovery to 25%; and time for TOF recovery to 50% were determined.

STATISTICAL ANALYSIS

The χ^2 test was used to analyse gender distribution. Other demographic variables and neuromuscular data between the two groups were analysed using the Mann–Whitney U-test. The results were expressed as means ± SDs, and $P < 0.05$ was considered to be statistically significant.

Results

The patient demographics show that there was no difference between the groups with regard to age, body weight or gender (Table 1).

The data from neuromuscular responses to rocuronium are given in Table 2. There were no significant differences between onset of action, clinical duration of action (T_1 recovery to 25% of control), T_1 recovery to 75% of control, and recovery index in the two groups. In addition, times for TOF recovery to 25% and 50% did not differ significantly between the groups.

Discussion

This prospective clinical study investigated, for the first time, the effect of midazolam as an intramuscular pre-medication agent on the time-course of action of an intubating dose of rocuronium during sevoflurane-based anaesthesia.

The possible interaction of midazolam with different non-depolarizing neuromuscular

TABLE 1:
Demographics of patients receiving no pre-medication (control group) or pre-medication with midazolam (midazolam group) prior to rocuronium-induced neuromuscular blockade

	Control (*n* = 11)	Midazolam (*n* = 11)
Age (years)	41.6 ± 11.2	37.2 ± 13.0
Weight (kg)	70.2 ± 10.9	67.8 ± 11.1
Gender (female/male)	5/6	7/4

Values are means ± SDs.
Differences between groups are not statistically significant.

TABLE 2:
Onset and recovery characteristics of 0.6 mg/kg rocuronium-induced neuromuscular blockade in patients receiving either no pre-medication (control group) or pre-medication with midazolam (midazolam group)

	Onset of action (s)	T_1 25% (min)	T_1 75% (min)	Recovery index (min)	TOF 25% (min)	TOF 50% (min)
Control (*n* = 11)	98.2 ± 35.7	36.2 ± 7.1	50.7 ± 9.0	14.5 ± 3.1	46.7 ± 9.8	58.3 ± 12.3
Midazolam (*n* = 11)	103.6 ± 37.6	36.5 ± 10.7	51.0 ± 16.6	14.5 ± 6.3	45.4 ± 11.5	54.5 ± 15.2

Values are means ± SDs.
Onset of action, time from the end of the rocuronium injection to maximal depression of twitch height; T_1 25%, time for recovery of T_1 to 25% of control; T_1 75%, time for recovery of T_1 to 75% of control; recovery index, time to recovery of T_1 from 25% to 75%; TOF 25%, time for train-of-four recovery to 25%; TOF 50%, time for train-of-four recovery to 50%.
Differences between groups are not statistically significant.

blocking drugs has been studied previously in animals.[3,4] Midazolam significantly enhanced a constant 50% neuromuscular block produced by infusion of vecuronium or pancuronium in cats.[3] By using an *in vivo* sciatic nerve–tibialis anterior muscle preparation of the rat, midazolam depressed the twitch height after a steady-state blockade produced by vecuronium or tubocurarine.[4]

In humans, the interaction between benzodiazepines (diazepam, lorazepam, lormetazepam and midazolam) and non-depolarizing neuromuscular blocking agents (vecuronium and atracurium) has been investigated with the administration of these drugs during the induction of anaesthesia.[5,6] Driessen *et al.*[5] reported that benzodiazepines did not cause significant potentiation of the neuromuscular blocking agents. In their subgroups, they found that durations to 25% and to 75% recovery of the twitch height after vecuronium were longer in patients receiving midazolam than in those receiving diazepam. Also, the duration to 25% recovery of the twitch height after atracurium was longer with midazolam than with diazepam.

Khuenl-Brady *et al.*[7] investigated the influence of intravenous anaesthetics on rocuronium-induced neuromuscular blockade in animals. They reported that neither the potency nor the duration of action of rocuronium in cats receiving anaesthetic

drugs differed from those in the control group. Olkkola and Tammisto[8] were the first to investigate the interaction of midazolam, administered intravenously to induce and maintain anaesthesia, with rocuronium in humans. They found no potentiation. The results of these two studies suggest that there is no pharmacological interaction between intramuscular midazolam and rocuronium.[7,8] The present study appears to confirm this assumption. Here, it is evident that midazolam used as an intramuscular anaesthetic pre-medication does not influence the time-course of action of rocuronium.

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