J Anesth (1995) 9:11–14

Journal of
Anesthesia

Optimal administration time of intramuscular midazolam premedication

Tomoki Nishiyama[1], Masaki Nagase[1], Hisayoshi Tamai[1], Shinichi Watanabe[1], Tatsuo Iwasaki[3], and Akihito Hirasaki[3]

[1] Department of Anesthesiology, JR Tokyo General Hospital, 2-1-3 Yoyogi, Shibuya-ku, Tokyo, 151 Japan
[2] Department of Anesthesiology, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka, 565 Japan
[3] Department of Anesthesiology, Kagawa Prefectural Central Hospital, 5-4-16 Ban-cho, Takamatsu, Kagawa, 760 Japan

Abstract: The optimal administration time for intramuscular injection of midazolam as premedication was studied. Sixty patients ranging in age from 40 to 65 were included. A combination of atropine 0.3–0.5 mg and midazolam 0.08 mg·kg^{-1} was given to four groups of 15 subjects each in intramuscular injections 45, 30, 15 min, and immediately before entering the operating room. Blood pressure, heart rate, respiratory rate, depression of the root of the tongue, eyelash reflex, degree of sedation, and amnestic effect at the time of arriving the operating room were compared among the groups. There was no difference among the groups in blood pressure, heart rate, and respiratory rate. The depression of the root of the tongue, disappearance of verbal response, and eyelash reflex were found in the 30- and 45-min groups. The degree of sedation and amnestic effect were good except for the group who received midazolam immediately before entering the operating room. From the above results, intramuscular injection of midazolam 0.08 mg·kg^{-1} with atropine 0.3–0.5 mg is considered best when administered 15 min before entering the operating room.

Key words: Anesthesia, Premedication, Midazolam, Intramuscular, Optimal administration time

Introduction

Because midazolam is water soluble [1] and has low tissue irritability, intramuscular injection causes little pain [2]. In addition to the excellent quality of sedation, midazolam is short-acting and has an amnestic action [3]. It is frequently used as premedication [4–6]. However, its reported administration time varies from 30 min to 1 h before entering the operating room [4–8]. We studied the optimal time for intramuscular injection of midazolam as premedication.

Address correspondence to: T. Nishiyama
Received for publication on February 24, 1994; accepted on July 12, 1994
This paper was presented at the 40th meeting of the Japan Society of Anesthesiology held in Morioka in 1993

Patients and methods

Sixty patients for elective surgery ranging in age from 40 to 65 years who had no hepatic, renal, circulatory, or respiratory abnormalities were randomly divided into four groups according to the administration time of midazolam. The study protocol was approved by the Institutional Ethics Committee. Informed consent was obtained from each patient. As the premedication, atropine 0.3–0.5 mg and midazolam 0.08 mg·kg^{-1} were injected intramuscularly at the following times: group 0, immediately before entering the operating room; group 15, 15 min before entering the operating room; group 30, 30 min before entering the operating room, and group 45, 45 min before entering the operating room.

After arriving in the operating room all patients were inserted with an intravenous line. The patients receiving general anesthesia were given an oxygen mask and induced with thiamylal 5 mg·kg^{-1} and maintained with sevoflurane 1.0–2.0% and nitrous oxide 2 l·min^{-1} in oxygen 3 l·min^{-1}. In the patients receiving spinal anesthesia, lumbar puncture was performed at the L4-5 intervertebral space and no sedatives were given during anesthesia.

Blood pressure and heart rate were examined before administering the premedication and at the time of arriving in the operating room. Respiratory rate, depression of the root of the tongue, eyelash reflex, and the degree of sedation were studied on arrival in the operating room. Blood pressure and heart rate were measured with the patient in the supine position by pressure cuff and electrocardiogram, respectively. The depression of the root of the tongue was judged by

snoring. In addition, as a test of memory after administration of premedication (anterograde amnestic action), we asked the patients on the morning after surgery if they remembered being brought from the ward to the operating room, secured with intravenous line, given an oxygen mask, or given a spinal puncture. The degree of sedation was evaluated on the six-step scale which had been used previously [9] and indicated in scores as follows: 1, complete sleep (without response to verbal command); 2, sleep (with reaction to verbal command); 3, calm without any complaint or body motion; 4, calm with small complaint or body motion; 5, not calm with a lot of complaint or body motion; and 6, excited with many complaints or body motions.

All data are expressed as mean ± standard deviation (SD). For statistical analysis, the χ^2 test was used for age, body weight, sex, kinds of anesthesia, and the number of patients with memory disturbance. One-way analysis of variance followed by Student's *t*-test was used for other data. A P value less than 0.05 was considered statistically significant.

Results

No difference was found among the groups in terms of age, body weight, sex, anesthetic method (general or spinal), duration of surgery and anesthesia, and atropine dosage administered (Table 1).

No Significant difference was found among the four groups on blood pressure before premedication and at the time of arriving in the operating room (Table 2). No hypotension or hypertension that required treatment was found in any case.

Although no significant difference was found among the four groups on the heart rates before premedication, those of group 45 were significantly higher than those of group 0 on arrival in the operating room (Table 2). There was no arrhythmia, tachycardia, or bradycardia that required treatment in any case.

The respiratory rates on arrival in the operating room for group 30 were significantly lower than for the other three groups as indicated by the number of respirations per minute as follows: group 0, 16.9 ± 2.8; group 15, 18.1 ± 2.3; Group 30, 14.9 ± 3.3; and Group 45, 17.9 ± 2.4. Depression of the root of the tongue on arrival in the operating room was found only in three cases in Group 45. None of the patients needed respiratory support.

The number of cases who had no eyelash reflex was zero for groups 0 and 15, two for group 30, and six for group 45. The number of cases who had no reaction to verbal commands was zero for groups 0 and 15, one for group 30, and three for group 45. The degree of sedation was significantly higher (lower scores) for groups 15, 30, and 45 compared with group 0. In addition,

Table 1. Patient background

	Group 0	Group 15	Group 30	Group 45
Age (years)	52.4 ± 7.6	53.9 ± 6.9	50.5 ± 7.4	54.7 ± 5.8
Body weight (kg)	60.7 ± 5.7	61.7 ± 10.4	57.1 ± 5.6	58.1 ± 6.7
Sex (male/female)	8/7	9/6	5/10	10/5
Anesthesia (general/spinal)	8/7	9/6	11/4	12/3
Duration of surgery (min)	178.3 ± 104.6	142.7 ± 92.3	151.0 ± 88.1	177.3 ± 79.8
Duration of anesthesia (min)	241.7 ± 125.0	205.0 ± 101.1	222.0 ± 110.0	240.0 ± 98.6
Atropine dosage (mg)	0.45 ± 0.08	0.44 ± 0.08	0.41 ± 0.09	0.45 ± 0.08

All values are mean ± SD.

Table 2. Blood pressure and heart rate

	Group 0	Group 15	Group 30	Group 45
Blood pressure (mmHg)				
Systolic pressure				
Before premedication	117 ± 17.6	124 ± 16.5	115 ± 7.5	121 ± 17.7
On arrival in operating room	121 ± 15.0	114 ± 12.8	113 ± 14.6	121 ± 18.2
Diastolic pressure				
Before premedication	74 ± 9.4	77 ± 11.6	74 ± 9.7	79 ± 13.6
On arrival in operating room	69 ± 10.3	72 ± 10.9	71 ± 9.6	74 ± 13.2
Heart rate (beats·min^{-1})				
Before premedication	72 ± 6.7	74 ± 10.3	72 ± 10.4	75 ± 5.6
On arrival in operating room	77 ± 8.9	82 ± 11.4	87 ± 24.2	86 ± 12.7*

All values are mean ± SD.
* $P < 0.05$ compared with group 0.

Table 3. Degree of sedation and memory

	Group 0	Group 15	Group 30	Group 45
Score of sedation (mean ± SD)	3.0 ± 0.97	2.3 ± 0.47*	2.3 ± 0.60*	2.1 ± 0.72*
Number of cases who had no memory of:				
Moving from the ward to the operating room	2	8	12*	12*
Securing intravenous line	6	14*	12	13*
Having oxygen mask or spinal puncture	12	14	12	13

* $P < 0.05$ compared with group 0.

group 45 had significantly lower scores than group 15 (Table 3).

The number of patients who had no memory of arriving in the operating room was significantly higher in groups 30 and 45 than in group 0. The number of patients who had no memory of a secured intravenous line was significantly higher in groups 15 and 45 than in group 0. For the number of cases with no memory of having an oxygen mask or a spinal puncture, there was no difference among the four groups (Table 3).

Discussion

The objective of premedication is to decrease anxiety, and pain or secretion. To decrease anxiety and pain, sedatives are often used. Previously, hydroxyzine, which has a hypnotic action, has been used frequently. However, it has tissue irritability [2], it causes pain when intramuscularly injected, and flares are often found at the site of injection. On the contrary, midazolam, which has less tissue irritability, as now frequently used for premedication in addition to having an anterograde amnestic action [4–6].

Because midazolam has a strong sedative action, administration at the wrong dosage or time increases the risk of respiratory or circulatory suppression resulting from oversedation. Several reports were found on the optimal dose for intramuscular premedication of midazolam such as 0.05 mg·kg^{-1} [10], or 0.07–0.10 mg·kg^{-1} [2,3,8]. Most of those reports took a sufficient sedation for the index of effectiveness. We are now examining the optimal dose by taking safety into consideration. In the present study, we kept the dose constant to isolate the effects of administration time. In this study, we might have used a slightly greater dose (0.08 mg·kg^{-1}) because the patients we chose were of a relatively younger age, between 40 and 65, who had no complications.

Midazolam is usually injected intramuscularly 30 min to 1 h before surgery [4–8]. However, it is reported that midazolam is quickly absorbed when intramuscularly injected and reaches a peak blood concentration 20–45 min after injection [11]. The sedative effect is said to appear clinically 5–10 min after injection [12], reach a peak at 30–40 min, and to be maintained for about 60 min [3,6,13]. From these facts, if it is administered 60 min preoperatively, the peak effect is obtained before arriving in the operating room. In most hospitals in Japan, the premedication is administered in the ward, and patients are not under sufficient supervision after premedication. Thus, the risk of respiratory or circulatory suppression will be increased if the maximum effect is obtained in the ward. Therefore, we excluded the 60-min preoperative administration from this study.

Wong et al. [14] reported that they found a significant decrease in blood pressure after 2–3 mg of midazolam injection, but usually the circulatory change is small after intramuscular injection of midazolam [3,15]. From the present results, with relatively large amounts of midazolam administered, no change was observed in the circulatory system, although this may have been because we used subjects younger than those reported by Wong et al. and we combined midazolam with atropine [3].

With regard to respiration, we could not check oxygen saturation or arterial oxygen tension. Although group 30 showed significantly lower respiratory rates than the other three groups, this was not considered to be problematic because none of the patients needed respiratory support in this study. However, depression of the root of the tongue was found in three patients in group 45. In all of these three cases, there was no response to verbal commands nor was there an eyelash reflex. In addition, the arterial oxygen saturation might have decreased in all these cases, as in Akatsuka's report [16]. Therefore, administration of premedication 45 min before entering the operating room is potentially dangerous.

In group 30, there was one case who had no reaction to verbal command and two cases who had no eyelash reflex. There was no difference between groups 15 and 30 on the degree of sedation and the amnestic action after securing the intravenous line. The only time at which group 15 had better memory recall than group 30 was on arrival in the operating room. However, since patients were completely satisfied that they had no memory after the intravenous line was secured, it was

considered that there was no difference in effectiveness between groups 15 and 30. Therefore, when considering the safety and effect of premedication, administration at 15 min before entering the operating room is considered optimal.

In summary, we have studied the optimal administration time of intramuscular injection of midazolam as premedication. When administering midazolam 0.08 $mg \cdot kg^{-1}$ in combination with atropine 0.3–0.5 mg to patients 40–65 years of age who have no complications, it is considered optimal 15 min before entering the operating room.

References

1. Conner JT, Katz RL, Pagano RR, Graham CW (1978) R0 21-3981 for intravenous surgical premedication and induction of anesthesia. Anesth Analg 57:1–5
2. Fragen RJ, Fink DI, Avram MJ, Costello C, DeBruine K (1983) Midazolam versus hydroxyzine as intramuscular premedicants. Can Anaesth Soc J 30:136–141
3. McAteer EJ, Dixon J, Whitwam JG (1984) Intramuscular midazolam. A comparison of midazolam with papavertum and hyoscine for intramuscular premedication. Anaesthesia 39:1177–1182
4. Tabuchi Y (1992) Optimal dose of midazolam as premedicant for combined spinal and epidural anesthesia with midazolam sedation (in Japanese with English Abstract). Masui (Jpn J Anesthesiol) 41:544–560
5. Tabuchi Y (1992) The effect of age and gender on the effect of midazolam as intramuscular premedicant (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 41:938–944
6. Shafer A, White PF, Urquhart ML, Doze VA (1989) Outpatient premedication: Use of midazolam and opioid analgesics. Anesthesiology 71:495–501
7. Tabuchi Y, Ishida H, Nagai K (1991) Comparison of midazolam and hydroxyzine as premedicants for combination of spinal and epidural anesthesia with midazolam (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 40:184–189
8. Vinik HR, Reves JG, Wright D (1982) Premedication with intramuscular midazolam: A prospective randomized double-blind controlled study. Anesth Analg 61:933–937
9. Nishiyama T, Hirasaki A, Odaka Y, Konishi H, Tsubaki N, Seto K (1992) Epidural midazolam with bupivacaine—Optimal dose for postoperative pain relief—(in Japanese with English abtract). Masui (Jpn J Anesthesiol) 41:1113–1118
10. Behne M, Janshon G, Asskali F, Förster H (1989) Die Pharmakokinetik des Midazolam nach intramuscularer Gabe (in German with English abstract). Anesthesist 38:278–284
11. Holazo AA, Winkler MG, Patel IH (1988) Effects of age, gender and oral contraceptives on intramuscular midazolam pharmacokinetics. J Clin Pharmacol 28:1040–1045
12. Reinhart K, Dallinger-Stiller G, Dennhardt R, Heinemeyer G, Eyrich K (1985) Comparison of midazolam, diazepam and placebo i.m. as premedication for regional anaesthesia. A randomized double-blind study. Br J Anaesth 57:294–299
13. Van de Velde A, Camu F, Claeys MA (1986) Midazolam for intramuscular premedication: dose-effect relationships compared to diazepam, fentanyl and fentanyl-droperidol in a placebo controlled study. Acta Anaesth Belg 37:127–136
14. Wong HY, Fragen RJ, Dunn K (1991) Dose-finding study of intramuscular midazolam preanesthetic medication in the elderly. Anesthesiology 74:675–679
15. Artu AA, Dhamee MS, Seifen AB (1984) Premedication with intramuscular midazolam: Effect on induction time with intravenous midazolam compared to intravenous thiopentone or ketamine. Can Anaesth Soc J 31:359–363
16. Akatsuka M, Sasaki H, Kataoka H, Hyodo M, Ohno F, Umegaki H (1990) Usefulness of midazolam for premedication before local anesthesia (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 39:70–74