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Sedative and respiratory effects of intramuscular midazolam as a premedicant: Influence of gender

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Abstract: We compared the sedative and respiratory effects of intramuscular midazolam in men and women in a randomized, single-blind trial. The patients (203 men and 195 women) received a single dose of midazolam (0.05, 0.075, 0.1, or 0.15 mg·kg^{-1}) intramuscularly 45 min before arriving at the operating room. Assessments in the operating room included sedation level and respiratory status rated on an objective four-point scale. Men given 0.075, 0.1, or 0.15 mg·kg^{-1} of midazolam exhibited greater sedation than did women given comparable doses. Midazolam 0.15 mg·kg^{-1} depressed respiration more frequently in men than in women. Plasma concentrations of midazolam were determined in 10 men and 10 women randomly selected from the patients who received 0.15 mg·kg^{-1} of midazolam. A higher plasma concentration of midazolam, associated with a higher degree of sedation and respiratory depression, was attained in men than in women. These findings suggest that the optimal dose per unit body weight of intramuscular midazolam as premedication should be lower in men than in women to prevent over-sedation and respiratory depression.

Key words: Benzodiazepines—Plasma concentrations—Sedation—Ventilation

Introduction

Midazolam, the first water-soluble benzodiazepine derivative, has been used intravenously for general anesthesia and sedation during local anesthesia, or intramuscularly as a preanesthetic medication [1]. The difference in neurological effects and pharmacokinetics of intravenous (IV) midazolam between men and women has been suggested [2,3]. However, in clinical practice, most investigators have paid no special attention to the patient's sex as a factor influencing the effects of intramuscular (IM) midazolam. It was reported in one study that a sex difference was not observed in the effects of IM midazolam, such as drowsiness, anxiolysis, and antegrade amnesia [4]. Thus, very little is known about this sex difference.

In the present study, we compared the responses in men and women to IM midazolam, particularly focusing on sedation and respiratory depression. We also measured plasma concentrations of midazolam as an index of the pharmacodynamic effect of midazolam in both sexes.

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Patients and methods

The protocol of this study was approved by the Committee on Ethics in Human Research of Saiseikai Kumamoto Hospital, and informed consent was obtained from 203 men and 195 women patients undergoing elective surgical and orthopedic procedures under either general or local anesthesia. The patients were 13–69 years of age, weighing within 20% of ideal body weight and were all ASA physical status I or II. The patients were randomly allocated to one of four dosing groups of midazolam (0.05, 0.075, 0.1 or 0.15 mg·kg^{-1}).

Midazolam was administered 45 min before the assessment in the operating room. The patients scheduled for general anesthesia received 0.5 mg of atropine at the same time. These medications were given in the deltoid muscle. All patients were monitored carefully throughout this study.

Sedation level and respiratory status were objectively determined by a trained anesthesiologist using the following scoring system.

Sedation scoring: awake and alert = 0; awake but drowsy = 1; asleep but responsive to verbal commands = 2; asleep and nonresponsive to verbal commands = 3.

Table 1. Patient characteristics and dosage of IM midazolam

	0.05 mg·kg^{-1}		0.075 mg·kg^{-1}		0.1 mg·kg^{-1}		0.15 mg·kg^{-1}	
Dose	Men	Women	Men	Women	Men	Women	Men	Women
Number	49	47	49	49	52	48	53	51
Age (years)	49.4 (16.8)	48.2 (17.1)	47.7 (16.7)	50.9 (13.3)	46.4 (18.5)	52.0 (13.3)	46.2 (17.1)	47.8 (16.6)
Weight (kg)	57.6 (7.2)*	50.4 (5.1)	60.3 (6.1)*	50.0 (5.6)	56.7 (6.6)*	50.0 (6.3)	57.1 (6.9)*	49.6 (5.5)
Height (cm)	164.3 (7.0)*	153.5 (4.7)	165.1 (5.5)*	152.0 (4.9)	162.9 (6.4)*	152.7 (6.7)	164.0 (6.5)*	153.4 (5.8)

Values of age, weight, and height are expressed as mean (SD).
* $P < 0.01$ *vs.* women.

Respiratory scoring: normal breathing = 0; snoring but airway support was unnecessary = 1; normal breathing but airway support was required = 2; breathing but at a slow respiration rate (less than 10 per min) even under airway support = 3.

Plasma concentrations of midazolam and albumin were determined in the 10 men and 10 women randomly selected from the 0.15 mg·kg^{-1} group. A venous blood sample was drawn immediately after the estimation of sedation and respiratory scores. It was centrifuged immediately and the plasma was divided into two aliquots, one of which was used for albumin analysis and the other was stored at −20°C for subsequent midazolam analysis at Teijin Bio Laboratories, Tokyo, by electron-capture gas-liquid chromatography as described by Puglisi et al. [5].

All data are expressed as mean ± SD. Patient characteristics were analyzed statistically using Student's *t*-test and one-way analysis of variance. Plasma concentrations of albumin and midazolam were compared between men and women using Student's *t*-test. The Mann-Whitney u-test was used to compare the scores between men and women. A *P* value of less than 0.05 was considered statistically significant.

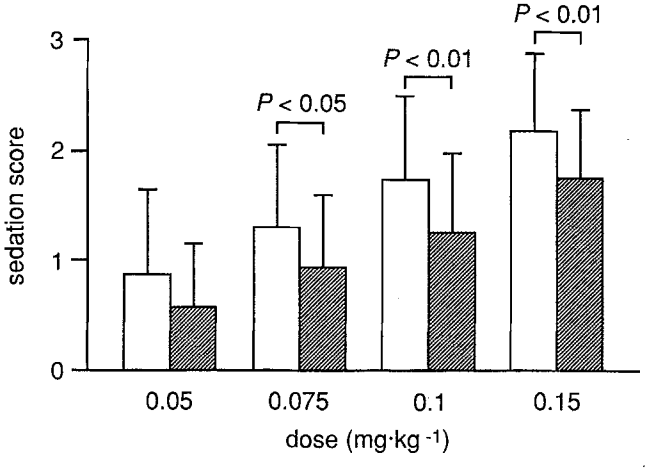

Fig. 1. Comparison of sedation score in men and women under different doses of IM midazolam. Mean ± SD values for score level are shown. *Open* and *hatched bars* represent men and women, respectively

Results

Randomization resulted in the dosage groups being well matched for age, weight, height, and sex. Men were heavier and taller than women in all groups (Table 1).

Sedation scores increased in a dose-dependent manner in both sexes, although the degree of sedation was greater in men than in women in all dosage groups except for the 0.05 mg·kg^{-1} group (Fig. 1).

Respiratory scores were higher among men in the 0.15 mg·kg^{-1} group (Table 2). A 65-year-old man developed apnea 15 min after the 0.15 mg·kg^{-1} dose of midazolam and required artificial ventilation for a while. However, no patient had slow respiration rate (respiratory score 3) at the assessment in the operating room.

Table 3 shows the plasma concentrations of midazolam and albumin in the 20 patients in the 0.15 mg·kg^{-1} group. Although the plasma concentration of albumin was similar in men and women, the plasma concentration of midazolam in men was significantly higher than in women.

Figure 2 illustrates the relations of sedation score and respiratory score to plasma concentration of midazolam of either sex shown in Table 3. Upon administration of the 0.15 mg·kg^{-1} IM midazolam, a higher plasma concentration of midazolam, resulting higher degree of

Table 2. Comparison of respiratory score in men and women under different doses of IM midazolam

		Respiratory score				
Dose		0	1	2	3	*P*
0.05 mg·kg^{-1}	men (n = 49)	47	1	1	0	NS
	women (n = 47)	47	0	0	0	
0.075 mg·kg^{-1}	men (n = 49)	47	2	0	0	NS
	women (n = 49)	49	0	0	0	
0.1 mg·kg^{-1}	men (n = 52)	48	4	0	0	NS
	women (n = 48)	48	0	0	0	
0.15 mg·kg^{-1}	men (n = 53)	31	11	11	0	<0.01
	women (n = 51)	46	4	1	0	

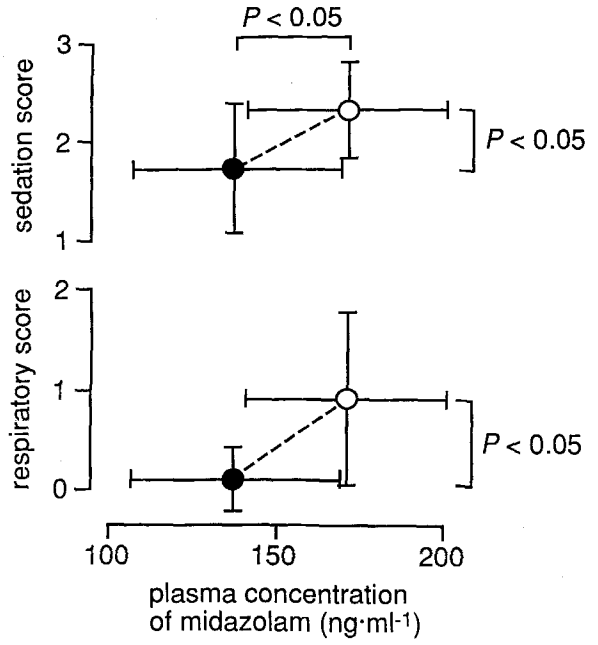

Fig. 2. Relations of sedation score and respiratory score to plasma concentration of midazolam in 20 patients who received 0.15 mg·kg^{-1} of midazolam. Mean ± SD values for each score level are shown. *Open* and *closed circles* represent men and women, respectively

Table 3. Plasma concentrations of midazolam and albumin in the patients who received 0.15 mg·kg^{-1} IM midazolam

	Men (n = 10)	Women (n = 10)
Midazolam (ng·ml^{-1})	171.3 (30.1)*	137.4 (31.0)
Albumin (g·dl^{-1})	4.1 (0.2)	4.0 (0.2)

Values are expressed as mean (SD).
* $P < 0.05$ *vs.* women.

sedation and respiratory depression, was found in men than in women.

Discussion

The relationship between the patient's sex and the response to IM midazolam has not been well investigated. Our findings in the present study indicate that a sex difference exists in sedative and respiratory effects of IM midazolam which is attributed to an actual difference in plasma concentration of midazolam between men and women following administration of the some dose.

Fragen et al. mentioned that there were no evident sex differences in sedation with IM midazolam 0.08 mg·kg^{-1}, although the number of male subjects was insufficient for definitive statistical evaluation [4]. In the present investigation, a greater degree of sedation was found in men than in women even after the 0.075 mg·kg^{-1} dose of IM midazolam. An IV midazolam study revealed apparently lower response to midazolam in women according to the following neurological scoring system: duration of the subjective tranquilizing sensation, degree of suppression of eyelash reflex, and duration of sleep [2]. This finding of sex difference in the neurological action of midazolam is consistent with our results although the scoring system is different.

Montravers et al. demonstrated that IV administration of midazolam 0.1 mg·kg^{-1} induced apnea within a few minutes, followed by upper airway obstruction accompanied by sleep [6]. Also, IV midazolam 0.15 mg·kg^{-1} produced apnea more frequently in men than in women [2]. In our study, all breathing disturbances started with an obstruction of the upper airway, except for a male patient who had apnea after the 0.15 mg·kg^{-1} dose of IM midazolam. The sex difference in respiratory depression of IM midazolam was essentially compatible with the results of IV study.

A pharmacokinetic study of IM midazolam by Holazo et al. indicated that the absorption rate of midazolam was not affected by sex [7]. The intensity and duration of the action of midazolam after a single dose injection depend much more on the volume of distribution (V_d) than on the rate of elimination and metabolic clearance [3]. The V_d is probably larger in women than in men due to a greater degree of adiposity in women [3,7]. As midazolam is highly lipophilic at physiological pH [1], its distribution to neurologically nonfunctioning tissues will be enhanced in women. Greenblatt et al. recommend that midazolam, when administered as a single IV dose in obese subjects, should be increased in proportion to total body weight because of the increment of V_d [3]. Since we selected the dose of midazolam according to the body weight, more men were given more midazolam than women. The same dosage of IM midazolam per unit body weight in men and women would explain the higher plasma concentration of midazolam in men.

Some studies on IV, IM, and oral administration of midazolam demonstrated that the subjective or objective psychomotor effects correlated positively with the plasma concentration of midazolam [8–12], which was attributed to the rapid equilibration of midazolam between plasma level and concentration at the receptor [11]. The mechanism responsible for the sex difference in sedation with IM midazolam would be related to the disparity in the plasma concentration of midazolam between men and women.

White et al. demonstrated that men had a higher upper airway resistance than women. Furthermore, it appeared that upper airway resistance increased with age in men, but no such trend was observed in women [13]. Upper airway resistance also increased with IV

midazolam at sedative doses [6]. The higher plasma concentration of midazolam in men may have induced the higher upper airway resistance than in women.

The possible mechanism involved in lower sensitivity to midazolam in women than in men was addressed by Forster et al. [2] who speculated that there may be a sex difference between the sites of action of midazolam. It is still unknown whether our findings can be explained by either hormonal influences to the benzodiazepine receptors or other factors; however, it is out of the scope of this article to explore physiological mechanisms of sex factors in midazolam effects.

In conclusion, we have demonstrated that men are more sensitive to IM midazolam than women regarding sedation and respiratory depression. This finding will have an important implication in determining the dosage of IM midazolam for premedication. IM midazolam dose per unit body weight should be reduced in men to avoid unexpected excessive sedation and respiratory depression.

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