Premedication with intramuscular midazolam: Effect on induction time with intravenous midazolam compared to intravenous thiopentone or ketamine

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Our study sought to determine whether premedication with intramuscular midazolam would decrease the time to induction of anaesthesia with intravenous midazolam, and if so whether induction of anaesthesia would be as rapid as with thiopentone or ketamine, intravenously. Eighty-nine patients, ASA physical status I or II, received midazolam 0.2 mg·kg^{-1}, thiopentone 3.0 mg·kg^{-1}, or ketamine 2.0 mg·kg^{-1} intravenously 60–90 min after intramuscular injection of either midazolam 0.07 mg·kg^{-1} or matching placebo. Time to induction of anaesthesia or the dose required to induce anaesthesia with intravenous midazolam was not decreased by midazolam premedication. Both with or without premedication, midazolam induction time was longer than with thiopentone or ketamine. Midazolam induction was associated with a lower incidence of blood pressure increase than with ketamine induction, and a lower incidence of apnea than that with either thiopentone or ketamine.

Key words

ANAESTHETICS, INTRAVENOUS; ketamine, thiopentone; HYPNOTICS: benzodiazepines, midazolam; INDUCTION: anaesthesia; PREMEDICATION: midazolam.

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Introduction

Midazolam, a 1-4 benzodiazepine, has been used intramuscularly (IM) as a preanaesthetic medication, and intravenously (IV) for induction of anaesthesia. With administration of midazolam IV for induction of anaesthesia, loss of lid reflex and loss of response to verbal commands is produced with little change in cardiovascular variables.[1–3] Thus midazolam may offer an advantage over other commonly used induction agents such as sodium thiopentone or ketamine. However, several studies have reported that the time to induction of anaesthesia with midazolam IV may be significantly increased compared to other induction agents and large doses of midazolam may be required.[4–9] Such a time delay may limit the usefulness of midazolam for induction of anaesthesia when a more rapid induction is desired.

Premedication with midazolam IM (0.07 mg·kg^{-1}) previously was reported to shorten the time to induction of anaesthesia with thiopentone.[10,11] The authors speculated that midazolam induction could be facilitated similarly, i.e., that rapid induction

with midazolam IV might be achieved if midazolam 0.07 mg·kg^{-1} was given prior to induction as a preanaesthetic medication IM. Accordingly, the present study was designed to determine whether premedication with midazolam IM would shorten the time to induction of anaesthesia with midazolam IV, and if so whether induction would be as rapid as with other commonly used induction agents, thiopentone and ketamine.

Methods

Eighty-nine adult patients scheduled for elective surgery (non-cardiac, non-neurological) consented to participate in this multi-institutional study. Approval for the study was obtained from the Human Subjects Committee at each participating institution. All aspects of patient selection and study design were similar at each location. Patients were males or non-pregnant females ages 18–61, ASA physical status I or II, with no known sensitivity to benzodiazepines, and had scored > 50 per cent on the Anxiety Visual Analog Test[11] the day before surgery. Patients received no tranquilizers, sedatives, hypnotics, antihistamines, or narcotics within 72 hours of surgery.

Sixty to ninety min prior to surgery patients were premedicated according to random design with either midazolam, 0.07 mg·kg^{-1} IM, or a similar volume of matching placebo (midazolam vehicle) IM from blinded, single dose ampoules. In the operating room, heart rate and rhythm were determined from the electrocardiogram, and blood pressure was determined using a standard blood pressure cuff. After stable preinduction values were recorded, patients breathed 100 per cent oxygen via mask for 5 min prior to induction. For induction of anaesthesia, patients received by random design, either midazolam 0.2 mg·kg^{-1}, thiopentone 3.0 mg·kg^{-1}, or ketamine 2.0 mg·kg^{-1}, IV over a period of 30–60 sec. An investigator/observer prepared the induction medications in unlabeled syringes for administration by an anaesthesiologist. Induction of anaesthesia was defined as loss of lid reflex and/or loss of response to verbal commands. The anaesthesiologist tested for loss of lid reflex and/or response to verbal commands at 10–15 sec intervals following administration of the induction medication. If after 2 min patients remained awake, additional incremental doses of either midazolam 0.05 mg·kg^{-1}, thiopentone 0.75 mg·kg^{-1}, or ketamine 0.5 mg·kg^{-1} IV were administered at 2 min intervals until induction of anaesthesia was achieved. Cardiovascular variables were recorded at 30–60 sec intervals, and patients were observed for occurrence of apnoea. A change in blood pressure or heart rate of > 20 per cent was considered significant. The drug dose required for induction of anaesthesia and the time to induction of anaesthesia were recorded. Thereafter, additional medications for laryngoscopy with intubation and for maintaining anaesthesia were at the discretion of the anaesthesiologist. In the recovery room and at 24 and 48 hours, intravenous and intramuscular injection sites were examined for redness, tenderness, induration or pain.

Comparison between groups regarding time to induction of anaesthesia, drug dose required for induction, and patient characteristics were made using analysis of variance. Fisher's Exact Test was used to compare proportions of patients for change in cardiovascular variables at induction, incidence of apnoea at induction and localized reaction at the intravenous injection sites. A p value <0.05 was considered significant.

Results

Patient characteristics (sex, age, weight, and race; Table I) and preanaesthetic systemic variables (blood pressure and heart rate, not tabulated) were not significantly different between groups. Compared to placebo, premedication with midazolam IM caused no significant change in the time to induction of anaesthesia or the dose required to induce anaesthesia with midazolam IV (Table II). Both with or without premedication, the time to induction of anaesthesia with midazolam IV was significantly longer than with thiopentone or ketamine. At induction, the incidence of elevated blood pressure was increased with ketamine (33 per cent, vs. midazolam seven per cent, and thiopentone five per cent) and the incidence of apnoea was decreased with midazolam (seven per cent vs. thiopental 26 per cent, and ketamine 21 per cent). Otherwise, there were no significant differences between groups at induction regarding incidence of other changes in blood pressure, heart rate, arrhythmias, localized reaction to intravenous injections, or respiratory/diaphragmatic responses (not tabulated). The incidence of redness, tenderness, induration or pain with intramuscular injection of

TABLE I Patient characteristics

		Midazolam IM + midazolam IV	*Placebo IM + midazolam IV*	*Midazolam IM + thiopentone IV*	*Placebo IM + thiopentone IV*	*Midazolam IM + ketamine IV*	*Placebo IM + ketamine IV*
Number of Patients		15	14	15	16	15	14
Sex	Males	5	3	4	3	1	3
	Females	10	11	11	13	14	11
Age	Mean	29.8	34.0	34.1	32.3	29.5	32.6
(years)	Range	(18–61)	(19–61)	(20–60)	(21–51)	(19–53)	(18–61)
Height	Mean	153.7	158.3	156.0	157.3	155.0	154.0
(cm)	Range	(137–175)	(133–180)	(137–170)	(137–207)	(134–169)	(140–165)
Weight	Mean	62.4	76.4	73.3	75.9	71.7	70.9
(kg)	Range	(50–89)	(40–121)	(50–122)	(50–134)	(45–155)	(44–117)
Race	Caucasian	12	10	11	13	12	9
	Black	3	4	4	3	3	5

TABLE II Effects of midazolam IM premedication on induction of anaesthesia with midazolam IV, thiopentone IV, or ketamine IV

	n	*Time to induction (sec), mean ± SEM*	*Induction dose ($mg \cdot kg^{-1}$), mean ± SEM*
Midazolam IM plus midazolam IV	15	148±25*	0.24±0.01
Placebo IM plus midazolam IV	14	128±19*	0.22±0.01
Midazolam IM plus thiopentone IV	15	87±18	3.0±0.2
Placebo IM plus thiopentone IV	16	72±10	3.1±0.2
Midazolam IM plus ketamine IV	15	107±19	2.1±0.2
Placebo IM plus ketamine IV	14	101±20	2.3±0.2

*Significant difference from thiopentone IV or ketamine IV, $p < 0.05$.

midazolam (three per cent) was not significantly different from that with intramuscular injection of midazolam vehicle (two per cent).

Discussion

Our observation that premedication with midazolam IM did not decrease either the time to induction of anaesthesia with midazolam IV, or the dose of intravenous midazolam required for induction is consistent with results of Finucane[9] and Gamble *et al.*[12] In those studies premedication with diazepam caused no change in the time to induction of anaesthesia with midazolam or the dose of midazolam required for induction ($0.28\ mg \cdot kg^{-1}$). Based on our study, and those of Finucane[9] and Gamble *et al.*,[12] it appears that addition of a benzodiazepine as a preanaesthetic medication does not augment induction of anaesthesia with midazolam. In contrast, preanaesthetic medication with narcotics has been reported to augment induction of anaesthesia with midazolam. Fentanyl ($1.5\ mg \cdot kg^{-1}$),[13] papaveretum, 20 mg with hyoscine,[12] or innovar ($0.02\ mg \cdot kg^{-1}$) plus atropine ($0.06\ mg \cdot kg^{-1}$)[14] were observed to significantly decrease midazolam induction time and the dose of midazolam required for induction.

In the present study, that induction of anaesthesia with midazolam IV was associated with minimal cardiovascular changes and minimal venous irritation is consistent with previous studies. Lebowitz *et al.*[3] reported that in healthy patients induction with midazolam 0.25 $mg \cdot kg^{-1}$ intravenously caused more gradual and less pronounced haemodynamic alterations than with thiopentone 4.0 $mg \cdot kg^{-1}$. Both in patients with ischaemic heart disease[1,2,15,16] and in patients with valvular heart disease[15] midazolam 0.2–0.3 $mg \cdot kg^{-1}$ intravenously was reported to provide rapid, haemodynamically stable induction. When compared to induction with diazapam 0.5 $mg \cdot kg^{-1}$, the only statistically significant difference between midazolam and diazepam groups occurred 5 min after induction where heart rates were higher and systolic blood pressure and left ventricular stroke work indices were lower following midazolam.[1] When compared to induction with thiopentone 3.0 $mg \cdot kg^{-1}$, the only statistical difference between midazolam and thiopentone groups occurred 3 min after induction where arterial pressure and peripheral vascular resistance were lower following midazolam.[16]

Regarding discomfort with intravenous injection of midazolam, or redness, tenderness, induration or pain at the intravenous site postoperatively, Samuelson *et al.*[1] reported zero per cent incidence of such complications in 20 patients, and Maltby *et al.*[4] reported no discomfort but a four per cent incidence of thrombosis in 55 patients. Our results (ten per cent incidence of discomfort at injection; five per cent incidence in redness postoperatively) were more similar to those of Jensen *et al.*[17] who reported a six per cent incidence of discomfort and a ten per cent incidence of redness, tenderness, and/or induration postoperatively in 50 patients. In this study the incidence of apnoea (seven per cent) with midazolam induction was less than that observed in previous studies (16–45 per cent)[1,7,18] and likely relates to the slower rate of administration of midazolam used in our study.

Our results with thiopental and ketamine suggest that our patient sample did not respond differently to induction with these drugs or to premedication with midazolam than did previously reported study populations. In our study induction time and dose data for thiopentone IV with and without premedication with midazolam IM were similar to previously reported values.[10,11] Similarly, our induction doses of ketamine IV with and without premedication with midazolam IM were similar to those previously reported.[19]

In summary, under the conditions of this study premedication with midazolam IM did not augment induction of anaesthesia with midazolam IV. While delayed induction may limit the usefulness of midazolam when rapid induction is desired, midazolam induction was associated with a lower incidence of blood pressure increase than ketamine, and a lower incidence of apnoea than with thiopentone or ketamine.

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Résumé

Notre étude cherche à démontrer si une prémédication avec le midazolam IM diminuera le temps d'induction de l'anesthésie avec le midazolam IV et si cette induction sera aussi rapide qu'avec le thiopental ou la kétamine IV. Quatre-vingt-neuf patients, ASA I ou II, ont reçu midazolam 0.2 $mg \cdot kg^{-1}$, thiopental 3.0 $mg \cdot kg^{-1}$ ou kétamine 2.0 $mg \cdot kg^{-1}$ IV 60–90 minutes après une injection IM de midazolam 0.07 $mg \cdot kg^{-1}$ ou de placebo. Le temps d'induction ou la dose requise pour amener l'anesthésie n'ont pas été réduits par la prémédication au midazolam. Avec ou sans prémédication le temps d'induction du midazolam a été plus long que celui du thiopental ou de la kétamine. Le midazolam a été associé à une incidence plus faible d'augmentation de la pression artérielle que la kétamine et à une plus basse incidence d'apnée que le thiopental ou la kétamine.