

Original Articles

THE DILEMMA OF HEMODYNAMIC INSTABILITY DURING INDUCTION OF ANESTHESIA: CAN MIDAZOLAM SERVE AS A SUITABLE SUBSTITUTE FOR THIOPENTONE?

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ABSTRACT

Both midazolam and thiopental sodium are being used as induction agents and for maintenance of anesthesia. In contrast to other benzodiazepines such as diazepam, midazolam has a rapid onset of action and fast distribution and causes few cardiovascular or respiratory effects. Being water soluble, midazolam is also associated with a low incidence of venous irritation.

The purpose of this study was to see whether midazolam is a suitable substitute for thiopental sodium as an induction agent. To compare the hemodynamic changes associated with midazolam and thiopental sodium as induction agents, this study was conducted in two groups each comprising of 30 patients. No significant hemodynamic changes regarding heart rate and blood pressure could be noticed in the two groups ($p < 0.05$). All patients in the midazolam group exhibited anterograde amnesia but in the thiopental group, 20% of the patients had recall for operative events one hour after completion of surgery.

To arrive at more conclusive results, preferably multi-center studies involving large numbers of cases are recommended.

MJIRI, Vol. 16, No. 4, 183-187, 2003.

Keywords: Hemodynamic instability, Induction of Anesthesia, Midazolam, Thiopental sodium.

INTRODUCTION

In spite of the continued introduction of intravenous

anesthetics to clinical practice, thiopental remains the most commonly used anesthetic for the intravenous induction of anesthesia in Western countries.¹ Thiopentone, first used approximately 60 years ago, remains the standard intravenous anesthetic induction agent. For the past 20 years it has also become the standard neuroprotective agent in the treatment of severe head injury complicated by uncontrolled intracranial hypertension, refractory sta-

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Midazolam Instead of Thiopentone

tus epilepticus and acute brain insults associated with cerebral ischemia. Midazolam (MDZ) is a benzodiazepine agonist that has a rapid onset of action and fast distribution with few cardiovascular or respiratory effects. Being water soluble^{1,5} and having a low incidence of venous irritation^{3,4} after intravenous (IV) injection make MDZ a good choice for conscious sedation, induction and for maintenance of anesthesia.^{2,6,7}

Postoperative recall has always been an unpleasant experience following anesthesia and MDZ curtails this lamentingly sad episode by providing anterograde amnesia.^{5,7,8,9,10} Although MDZ is used in a wide variety of clinical conditions, investigators have urged caution of its use in patients with hypovolemia and impaired left ventricular function due to the negative inotropic effects of the drug in animals and humans.¹² MDZ possesses a muscle relaxing effect. Among other effects, the muscular relaxation is attributed to the interaction of MDZ with the γ -amino butyric acid (GABA_A) receptor.¹³

This study was undertaken to evaluate the hemodynamic effects of thiopental sodium and MDZ during the induction of anesthesia. The study aims at comparing the use of MDZ as an induction agent to that of thiopental, noteworthy to say that the latter enjoys widespread reputation.

Temporal profile of amnesia was also evaluated in the two groups of patients enrolled in the trial.

PATIENTS AND METHODS

Written informed consent was obtained from 60 pa-

tients (ASA₁ and ASA₂) scheduled to undergo elective abdominal surgery under general anesthesia. Patients' age ranged between 20-50 years including both sexes.

After insertion of an I.V. cannula and placement of routine intraoperative monitors, all patients were randomly assigned to one of the two groups. All the patients were requested to memorize four names prior to premedication. Group 1 received 0.5 mg atropine and 100 μ g fentanyl intravenously as premedication. Thiopental sodium 5 mg per kg body weight (BW) was subsequently given as an induction agent followed by succinylcholine 1.5 mg per kg BW to facilitate endotracheal intubation. In group II again the same armamentarium of drugs was adopted except that MDZ was substituted for thiopental sodium as an induction agent in a dose of 0.15 mg per kg BW.

Mean systolic blood pressure (MSBP) and mean heart rates (MHR) were monitored and recorded before initiating anesthesia, 2 minutes after premedication, during endotracheal intubation and subsequently 2,5 and 10 minutes after intubation. The data was analysed using pooled t-test. A *p* value <0.05 was considered to be significant.

RESULTS

A total of 60 patients were enrolled in the study and each group was comprised of 30 patients. There were no significant differences regarding demographic variables among the two groups. Also the preoperative hemodynamic variables tallied between patients of either group.

The MSBP and MHR before starting anesthesia, 2

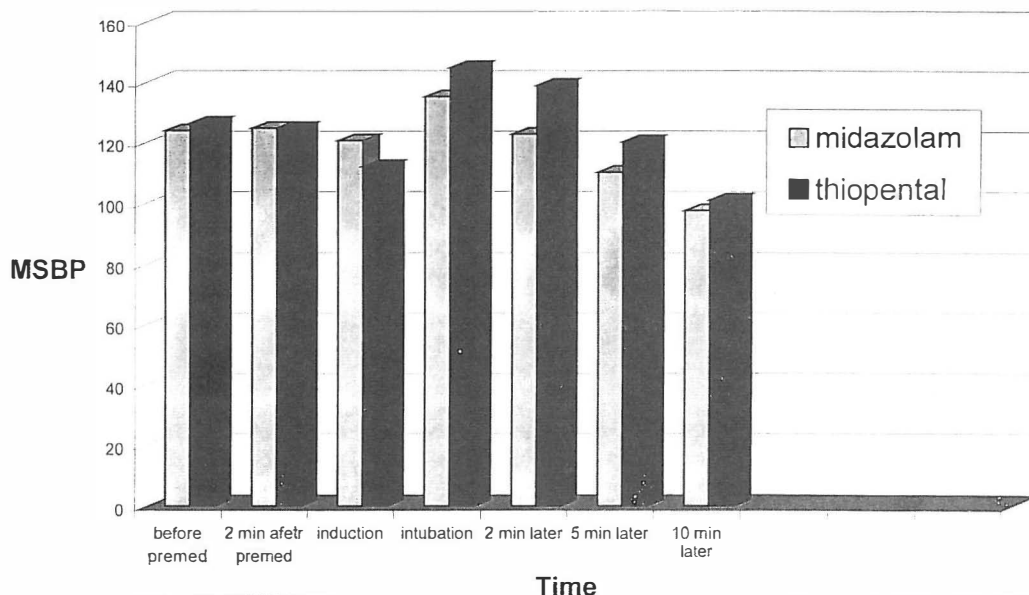


Fig. 1. Blood pressure variations in the two groups. MSBP= mean systolic blood pressure.

minutes following premedication, during induction and endotracheal intubation and subsequently 2,5 and 10 minutes after intubation are depicted separately for the two groups (Table I). No significant differences could be found in the hemodynamic variable between the two groups (Fig. 1 and 2, $p < 0.05$).

An hour after completion of surgery, all patients in both groups could at least remember three of the memorized four items. No patient in the MDZ group had a recall for intraoperative events, whereas this recall was observed in 6 (20%) of the patients in the thiopental group.

DISCUSSION

Induction of anesthesia has always been associated

with undesirable hemodynamic changes which many a time prove to be a source of embarrassment for even the hard task anesthesiologists. To circumvent these problems, various protocols are advocated with varying results and outcomes.

Benzodiazepines are administered prior to surgery to provide anxiolysis, amnesia and sedation.² These drugs facilitate binding of γ -aminobutyric acid (GABA) to GABA_A receptors in the central nervous system. This enhances GABA-mediated neuronal inhibition in the cortex and the limbic system, the latter having a critical role in central integration of emotion.¹³ MDZ impairs acquisition of new information without affecting retrieval of previously stored information^{6,7,8,11} which render the drug unique and promising. The absence of retrograde

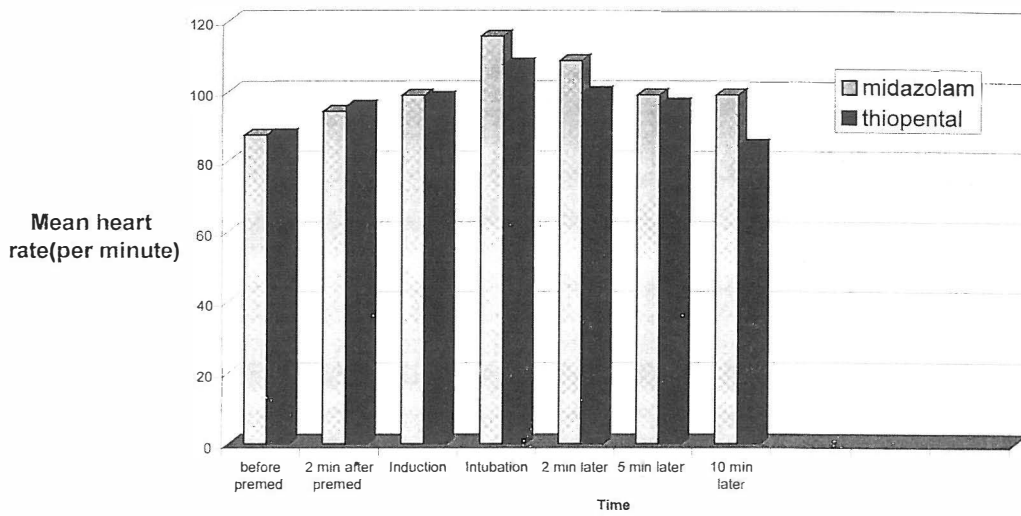


Fig. 2. Heart rate variations in the two groups.

Table I. Blood pressure and heart rate variations before induction and thereafter.

Time	Midazolam		Thiopental	
	Mean systolic blood pressure	Mean heart rate	Mean systolic blood pressure	Mean heart rate
Before premed.	123.87±9.99	87.43±18.70	126.37±10.58	87.53±10.07
2 min after premed.	124.67±9.83	94.17±11.0	124.67±9.09	95.63±11.32
Induction	120.47±13.67	98.77±12.40	111.83±9.77	98.13±10.47
Intubation	135.17±10.35	115.43±12.71	144.70±14.44	107.47±12.73
2 minutes later	122.67±10.97	108.47±13.38	138.87±12.27	99.50±20.28
5 minutes later	109.93±12.04	98.90±11.99	120.13±9.19	96.27±11.46
10 minutes later	97.33±12.77	98.90±11.99	100.8±6.82	84.57±11.11

amnesia and presence of anterograde amnesia in most of the patients in the MDZ group corroborates with the afore-mentioned findings.

When used in combination with narcotics or during cardiopulmonary bypass, MDZ can cause severe hypotension accompanied by a reduction in systemic vascular resistance. This hypotension may possibly be caused by a direct vasodilating effect of MDZ. The mechanism underlying the vasodilating action of MDZ involves its interference with the transmembrane influx of Ca^{++} in a way similar to that of Ca^{++} antagonists, and its enhancement of nitric oxide synthesis from endothelium.¹⁴ The negative inotropic effects attributed to MDZ could be caused by inhibition of the L-type Ca^{++} channels and therefore some authors have urged caution of its use in patients with hypovolemia or impaired left ventricular function.¹⁶ No noticeable differences in the hemodynamic variables between the two groups were detected in our study, probably because of the relatively small dose of fentanyl that we employed in our patients and moreover because our patients were in ASA class 1 and 2 and as such enjoyed good ventricular functional status. Except for a small rise of blood pressure in group I at 5 and 10 minutes after induction, other variables did not show a statistically significant difference. Studies conducted elsewhere pertaining to the cardiovascular effects of MDZ have yielded conflicting results. Surprisingly, some authors have reported enhanced cardiovascular stability associated with MDZ in their set of patients^{4,10} but at least in one of these studies larger doses of thiopental had been administered for induction¹⁵ thus exaggerating the cardiovascular stability associated with MDZ.

Since in this study, both induction agents produced almost the same hemodynamic changes, it had been difficult to demarcate clearly their effective utility in our set of patients. However, under certain circumstances, one drug might be preferred over the other. Although in our series, MDZ group patients revealed less venous irritation and recall for the surgery, nevertheless the higher cost for MDZ could be a potential drawback in unprivileged patients undergoing surgery in some centers.

As our patients enjoyed a good physical status, the negative inotropic effects of both induction agents were easily and effectively compensated for by splanchnic blood mobilization to the central circulation and a baroreceptor mediated increase in the heart rate and contractility; of course, these results could not be generalized to ASA class III and IV patients.

Moreover in our study, there were no significant differences as far as demographic variables were concerned and also the hemodynamic variables were again more or less identical in the two groups before the start of anesthesia emphasizing that our groups matched. It can therefore be stressed that hemodynamic effects in the two

groups were not influenced by other confounding factors thereby granting this study sufficient validity.

Although it has been stated that the apparent myocardial depression caused by MDZ is offset by similar decreases in left ventricular afterload in patients with either decreased or normal preoperative ejection fraction,¹⁶ in our opinion it is prudent to avoid MDZ and circumvent any deleterious effects under circumstances where left ventricular function is in jeopardy. With advancing age, both lean body mass and cardiac output decrease,¹⁷ therefore dose requirements for thiopental should be preferably curtailed to overcome an exaggerated response. Again where doubt exists regarding myocardial performance, the decision to administer additional MDZ should be delayed for 2-3 minutes, until the depressant effects of previous doses have reached their peak.¹⁸

In summary, we unequivocally state that both MDZ and thiopental sodium can be safely used as induction agents in any age group provided the indices of myocardial function are not jeopardized due to hemorrhage or defective adrenergic stimulation. However preferring one drug over the other depends upon individual discretion since both drugs have been incriminated in decreasing myocardial performance in susceptible and high risk patients.

REFERENCES

1. Stone DJ, Moscicki JC, Difazio CA: Thiopental reduces halothane MAC in rats. *Anesth Analg* 74: 542-6, 1992.
2. Reves JG, Fragen RJ, Vinik HR, Greenblat DJ: Midazolam: pharmacology and uses. *Anesthesiology* 62 (3): 310-24, 1985.
3. Forster A, Gardaz JP, Suter PM, Gemperle M: IV Midazolam as an induction agent for anesthesia: a study in volunteers. *Br J Anesth* 52 (9): 907-11, 1980.
4. Luo A, Huang Y, Liu Y, Ren H, Jia N: Midazolam as a main anesthesia induction agent-a comparison with thiopental and diazepam. *Chin Med Sci J (Abstract)* 6(3): 172-4, 1991.
5. Kanto JH: Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. *Pharmacotherapy* 5 (3): 138-55, 1985.
6. Koht A, Moss JJ: Does midazolam cause retrograde amnesia and can flumazenil reverse that amnesia? *Anesth Analg* 85: 211-2, 1997.
7. Twersky RS, Hartung J, Berger BJ, McClain J, Beaton C: Midazolam enhances anterograde amnesia but not retrograde amnesia in pediatric patients. *Anesthesiology* 78 (1): 51-5, 1993.
8. Fuse A, Hosokawa T, Kume T, Hayashi K, Toujo H, Tanaka Y: Amnestic effect of oral midazolam as premedication in children. (Abstract) *Masui* 41 (7): 1109-12, 1992.

9. Izuro KL, Foulkes-Crabbe DJ, Kushimo OT, Orumwence TO, Lawani-Osunde AS, Chukwuani CM: Open comparative study of the efficacy, safety and tolerability of midazolam versus thiopental in induction and maintenance of anaesthesia (Abstract). *West Afr J Med* 13 (2): 73-80, 1994.
10. Driessen JJ, Boij LH, Vree TB: Comparative study of thiopental and midazolam for induction of anesthesia. *Anesthesist* 32 (10): 478-82, 1983.
11. Reitan JA, Porter W, Braunsein M: Comparison of psychomotor skills and amnesia after induction of anesthesia with midazolam or thiopental. *Anesth Analg* 65 (9): 933-7, 1986.
12. Reves JG, Kissen I, Fournier S: Negative inotropic effects of midazolam. *Anesthesiology* 60: 517-8, 1984.
13. Khan LC, Lustik SJ: Treatment of paradoxical reaction to midazolam with haloperidol. *Anesth Analg* 85: 213-5, 1997.
14. Yamguchi S, Kanmura Y, Yoshimura N: Effects of midazolam on contractions in smooth muscle of the rabbit mesenteric artery. *Anesth Analg* 84: 199-205, 1997.
15. Berggren L, Eriksson I: Midazolam for induction of anesthesia in outpatients: a comparison with thiopentone. *Acta Anesthesiol Scand* 25 (6): 492-6, 1981.
16. Messina AG, Paranicas M, Yao FS, Illner P, Roman MJ, Saba PS, Devereux RB: The effects of midazolam on left ventricular pump performance and contractility in anesthetized patients with coronary artery disease: effects of preoperative ejection fraction. *Anesth Analg* 81: 793-9, 1995.
17. Avram MJ, Sanghvi R, Henthorn TK, et al: Determinants of thiopental dose requirements. *Anesth Analg* 76: 10-17, 1993.
18. Pound WW, Hartman M: Ventilatory depression and midazolam (Letter). *Anesth Analg* 75: 312, 1992.

