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Cardiovascular Effects of Water-soluble Benzodiazepine as an Anesthesia Induction Agent [1]

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= Abstract = The new benzodiazepine, midazolam, that is water-soluble, shorter-acting, more potent, and less irritating to veins than diazepam, has been suggested use for induction of anesthesia. The induction tme (from the end of injection to spontaneous closing of eyes and to the disappearance of eyelash reflex), cardiovascular effects (mean arterial pressure; MAP, heart rate; HR, cardiac output; CO), and the effect on arterial oxygen saturation (SaO_2) of an induction-sized dose (0.2 mg/kg) of midazolam in ASA class I or II surgical patients (N = 10) premedicated with glycoppyrolate were compared with those in the similar group of patients (N = 10) receiving thiopental (5 mg/kg). The induction time in midazolam group was significantly slower than in thiopental group. In both groups MAP decreased during induction but increased after intubation significantly. HR significantly increased at early induction period in thiopental group, and significantly increased after intubation in both groups. CO significantly decreased in thiopental group but did not change in midazolam group. In both groups Sa O_2 did not change during induction but significantly increased after intubation.

Although induction time was slow, midazolam, from the cardiovascular point of view, appears to offer some advantages over thiopental and, clinically, is at least as good as thiopental as an anesthesia induction agent in healthy surgical patients.

Key words: ***Induction agent, Midazolam, Thiopental, Induction time, Hemodynamic effects***

INTRODUCTION

The benzodiazepines have an established place in anetheitc practice as sedative hyponotics and some have been used as intravenous induction agents (Dundee and Wyant 1988). The commonly used benzodiazepines, diazepam and lorazepam, are not water-soluble, have a wide variability in action and prolonged duration thus making them unsuitable as routine induction agents. In addition, diazepam causes venous thrombosis (Hegarty and Dundee 1977).

The new benzodiazepine, midazolam, is water-soluble when injected in an aqueous solution of pH<4.0 (due to an open benzodiazepine ring conformation) but becomes lipid-soluble at physiologic pH (due to ring closure) (Greenblatt *et al.* 1983). This structural relationship provides a benzodiazepine that is relatively nonirritating to veins and painless on injection, compared with diazepam (Conner *et al.* 1978; Fragen *et al.* 1978). Other characteristics of midazolam include induction of sleep in less than 2 min. (Brown *et al.* 1979), minimal hemodynamic effects in sedative dose (Fragen *et al.* 1979), mild respiratory depression (Forster *et al.* 1979), relief of anxiety (Conner *et al.* 1978), and anterograde amnesia (Dundee and Wilson 1980). Because of high patient acceptance and low incidence of adverse effects when used as a seda-

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tive-hypnotic, midazolam has been suggested for induction of anesthesia as well (Reves *et al.* 1985).

This present study was undertaken to evaluate midazolam as anesthesia induction agent comparing the induction time, hemodynamic effects and the effect on arterial oxygen saturation of midazolam with those of thiopental in healthy surgical patients.

MATERIALS AND METHODS

Twenty ASA (American Society of Anesthesiologists) class I or II patients were assigned to receive thiopental and midazolam intravenously for induction of anesthesia (10 in each group). The mean age and weight of the 6 male and 4 female patients receiving thiopental (thiopental group) were 43 ± 10.6 years and 63 ± 9.7 kg and those of 5 male and 5 female patients receiving midazolam (midazolam group) were 45 ± 9.3 years and 61 ± 7.3 kg (mean ± SD) (Table 1).

Table 1. Dermographic characteristics of patients (mean ± SD)

Variables	Induction agents	
	Thiopental	Midazolam
Age (yr)	43 ± 10.6	45 ± 9.3
Weight (kg)	63 ± 9.7	61 ± 7.3
Sex (male/female)	6/4	5/5

All patients were administered intramuscularly 0.004 mg/kg of glycopyrrolate as premedicant 1 hour prior to induction.

After electrodes for EKG and cardiac output monitor, arterial catheter, and central venous catheter were placed, control measurements of mean arterial pressure (MAP), heart rate (HR) were obtained from the Datascope (Model 2000A, Datascope Corp., USA) monitor using Gould transducer (Model P23XL, USA) and electorocardiogram lead II. Cardiac output (CO) was determined using Bomed cardic output monitor (Model NCCOM3, Bomed Medical MFG, USA). Arterial oxygen saturation (SaO2) was obtained from finger-tip sensor of Nellcor pulse oximeter (Model N-100, Nellcor INC., USA).

Following the control measurements, doses of either thiopental (5 mg/kg) or midazolam (0.2 mg/kg) was given intravenously in about 15 seconds. The times from the end of injection to spontaneous closing of eyes (Tce) and to the disappearance of eyelash reflex (Tde) were measured. After disappearance of eyelash reflex ventilation was assisted by mask with oxygen and 1.0 mg/kg of succinylcholine was given intravenously. After adequate muscle relaxation, intubation was done. Anesthesia was maintained with 1 vol % of halothane mixed with 2 L/min of N_2O and 2 L/min of oxygen, and 0.08 mg/kg of pancuronium was given intravenously.

Additional measurements of MAP, HR, CO, SaO_2 were made at the Tce, Tde, and immediately after intubation (postintubation).

Control (preinduction) values for each patient were compared with individual measurement at the Tce, Tde, and postintubation using Student's t-test for paired samples. Mean changes in each measurement for all patients given thiopental were then compared with corresponding mean changes for all patients given midazolam using Student's t-test for independent samples. Differences were considered statistically significant when P was less than 0.05.

RESULTS

The induction times are summarized in Table 2. Onset of anesthesia in thiopental group was significantly more rapid than in midazolam group. None of the study patients vomited or aspirated during induction.

Table 2. Induction times (mean ± SD, sec)

	Thiopental	Midazolam
Tce	15 ± 9	49 ± 19†
Tde	34 ± 24	95 ± 49†

Tce; the time from the end of injection to spontaneous closing of eyes

Tde; the time from the end of injection to disappearance of eyelash reflex

†; $p < 0.05$ compared with thiopental group at the same time

The cardiovascular changes during induction and immediately after intubations are summarized in Table 3-5. MAP in both groups significantly decrased during induction but significantly increased after intubation. HR in thiopental group significantly increased except during late induc-

Table 3. Mean arterial pressure druing induction with thiopental and midazolam (mean±SD mmHg)

	Thiopental	Midazolam
preinduction	92 ± 12	91 ± 11
Tce	80 ± 14*	83 ± 11*
Tde	82 ± 13*	81 ± 10*
postintubation	132 ± 22*	123 ± 18*

Tce; at the spotaneous closing of eyes
Tde; at the disappearance of eyelash reflex
*; $p < 0.05$ compared with preinduction value.

Table 4. Heart rate during induction with thiopental and midazolam (mean ± SD, beat/min)

	Thiopental	Midazolam
preinduction	83 ± 13	90 ± 24
Tce	96 ± 13*	93 ± 21
Tde	93 ± 12	93 ± 20
postintubation	108 ± 19*	104 ± 18*

Tce; at the spotaneous closing of eyes
Tde; at the disappearance of eyelah reflex
*; $p < 0.05$ compared with preinduction value

Table 5. Cardiac output during induction with thiopental and midazolam (mean±SD, l/min)

	Thiopental	Midazolam
preinduction	5.3 ± 3.0	5.0 ± 2.0
Tce	4.9 ± 2.2*	5.0 ± 1.9
Tde	4.6 ± 2.0*	4.8 ± 1.6
postintubation	4.4 ± 2.2*	4.7 ± 2.2

Tce; at the spontaneous closing of eyes
Tde; at the disappearance of eyelash reflex
*; $p < 0.05$ compared with preinduction value

tion, but HR in midazolam group significantly increased only after intubation. CO in thiopental group significantly decreased during induction and intubation, but CO in midazolam group did not change significantly. SaO_2 in both groups did not change significantly during induction but increased significantly after intubation. (Table 6)

Two groups were similar regard to age and weight. However, except induction time, there were no significant differences between the two groups in any measurements at any time.

Table 6. Arterial O_2 saturation during induction with thiopental and midazolam (mean±SD, %)

	Thiopental	Midazolam
preinduction	98 ± 1	97 ± 1
Tce	97 ± 2	97 ± 2
Tde	98 ± 2	97 ± 2
postintubation	100 ± 1*	100 ± 1*

Tce; at the spontaneous closing of eyes
Tde; at the disappearance of eyelash reflex
*; $p < 0.05$ compared with preinduction value.

DISCUSSION

Thiopental remains the most widely used induction agent even though it is unstable in solution, produces significant cardiovascular and respiratory depression, lacks analgesic properties, readily crosses the placenta, and is associated with a high incidence of postoperative drowsiness (White 1982). Benzodiazepines have been used to induce anesthesia when cardiovascular stability is critical (McCammon *et al.* 1980: Samuelson *et al.* 1981). Unfortunately, currently available benzodiazepines are water-insoluble, with slow onset, and long durations of action, wide variability in terms of central nervous systems effects, and produce high incidences of phlebitis and prolong recovery when used as adjuvants for inducing general anesthesia. Recently, midazolam, a short-acting water-soluble benzodiazepine, similiar to diazepam in its ability to depress the central nervous system (Reves *et al.* 1985), has been evaluated as an altenative to thiopental for inducing general anesthesia.

Induction is accomplished when there is unresponsiveness to command and loss of the eyelash reflex. There are a number of factors that affect the induction of anesthesia. The main factors are dose, protein binding, lipid solubility and ionization (Dundee and Wyant 1988). There are conflicting reports regarding the potency of midazolam as an induction agent. Fragen *et al.* (1978) revealed that the actual induction dose was 0.177 mg/kg (mean weight=68.4 kg and mean induction dose=12.1 mg), and Reves *et al.* (1978) used as an induction dose 0.2 mg/kg. On the other hand, Gamble *et al.* (1981) found that 0.5 mg/kg midazolam did not adequately induce anesthesia in 40 % of young unpremedicated patients. Many investigations (Foster *et al.*

1980a: Sarnquist *et al.* 1980: Reves *et al.* 1981: Kanto *et al.* 1982) have reported that the induction dose ranges from 0.1 mg to 0.4 mg/kg. The median induction dose of thiopental in the study of Dundee *et al.* (1982) was 3.5 mg/kg. Crankshaw and Allt-Graham (1978) found the ED_{50} for thiopental to be 2.63 —2.70 mg/kg and the ED_{100} to be in the region of 3.5 mg/kg but most clinicians would place the single bolus induction dose for adult in the region of 4-5 mg/kg. Sarnquist *et al.* (1980) have equated 0.15 mg/kg midazolam with 3 mg/kg thiopental.

The degree of protein binding of thiopental is 60-85 % but midazolam is greater than 95 %.Because of high degree of protein binding of midazolam induction is slow as well as variable. In addition low lipid solubility and pKa of midazolam make onset significantly slow. Dundee and Kawar (1982) found that, on the average, loss of consciousness occured 11 seconds after rapid injection of thiopental compared with 38 seconds with midazolam. In this present study, compared with thiopental, midazolam produced slower induction by three times. With larger dose midazolam may produce more rapid induction.

The principal hemodynamic effect of thiopental is a decrease in contractility (Seltzer *et al.* 1980: Toner *et al.* 1980), which is due to reduced availability of calcium to the myofibrils. Although this effect in healthy patients is minimal, there is some reduction in CO and MAP, presumably by reducing venous return because of an increase in venous capacitancy. Changes in HR following intravenous barbituarate can be very variable, depending not only on compensatory hemodynamic changes, but also on resting HR and on premedication (Dundee and Wyant 1988). Many studies (Becker and Tonnesen 1978: Seltzer *et al.* 1980: Tonner *et al.* 1980: Fischler *et al.* 1985) revealed the HR significantly increased during induction with thiopental. Tracheal intubation after thiopental may be accompanied by marked hypertension and tachycardia secondary to the lack of analgesic effect (Fischler *et al.* 1985).

The hemodynamic effects of midazolam have been studied thoroughly. In normal humans, midazolam, 0.15 mg/kg intravenously over 15 seconds, produces statistically significant reductions in systolic (5%) and diastolic (10%) blood pressure and increases in HR (18%) (Forster *et al.* 1980a). Fragen *et al.* (1978) found MAP to decrease 25% or more from control values in two of 25 patients and HR to increase 25% or more in four of 25 patients. Many studies reveal consistently that midazolam produces decreases (12-26%) in MAP, but there are some differences in the change of HR according to reports (—14 - 21%) (Reves *et al.* 1987). This present study found that CO did not change in midazolam group although MAP decreased. This effect is the advantage over thiopental and make midazolam more suitable than thiopental in the patients with cardiac disease. A reduction in blood pressure presumably activates the baroreflexes, simultaneously increasing HR and contractility with mobilization of splanchnic and other blood volume into the central circulation (Gelman *et al.* 1983). Although there is some evidence that midazolam attenuated the catecholamine response to hypotensive stress (Glisson *et al.* 1982: Glisson *et al.* 1983), it is clear that preservation of hemodynamic function occured with midazolam (Glisson *et al.* 1982). Midazolam causes a fall in systemic vascular resistance rather than the rise seen with thiopental (Al-Khudhairi *et al.* 1982; Samuelson *et al.* 1981). These effects are evident when vascular resistance is raised, such as in hypertensive patients and in the stressful period immediately before an operation. With marked sedation or loss of consciousness midazolam usually produces peripheral vasodilatation and a slight drop in cardiac output and peripheral resistance, but this is not clinically significant. When intubation follows induction, however, significant increaes in HR and MAP occur (Boralessa *et al.* 1983: Samuelson *et al.* 1981). These increases are less than with thiopental (Boralessa *et al.* 1983). The cardiac index and left- and right-heart filling pressures are usually maintained (Lebowitz *et al.* 1982). Although hemodynamic changes after midazolam, 0.3 mg/kg intravenously, are similiar to those seen with hypnotic doses of thiopental, 3-4 mg/kg according to the report of Al-Khudhairi *et al.* (1982), hemodynamic changes after midazolam, 0.2 mg/kg were more minimal than those after thiopental, 5 mg/kg in this present study.

The respiratory depressive effect of thiopental is well documented. Apart from the transient sti-

mulation produced by very small doses, barbiturates are more potent central depressants of respiration than any other drugs used in modern anesthesia (Dundee and Wyant 1988). midazolam produces some respiratory depression. In healthy humans, midazolam, 0.15 mg/kg, significantly reduces both the ventilatory response and the mouth occlusion-pressure response to CO_2 (Forster *et al.* 1980b) but there is little effect on respiratory mechanics. This seems to be a CNS effect of midazolam (Forster *et al.* 1982). The peak decrease in the slope of the CO_2 response curve occurs 3.5 min after midazolam, 0.2 mg/kg, when given to healthy volunteers (Reves *et al.* 1985). The reported incidence of midazolam-induced apnea ranges from 18 to 78 % but this is significantly ($p<0.05$) lesser than that of equivalant thiopental-induced apnea (Reves *et al.* 1985). A number of workers note that respiratory obstruction rather than depression is more likely to result in the cyanosis (Dundee and Wyant 1988). On the basis of our result both thiopental and midazolam did not alter in SaO_2 during induction. A significant increase after intubation seemed to be due to controlled respiration.

This present study compared the induction time and the hemodynamic effects of midazolam and thiopental in healthy surgical patients. This study shows that induction with midazolam is significantly slower than thiopental. Hemodynamic changes after thiopental and midazolam are generally similiar. Although both drugs produce decreases in blood pressure, HR and CO are maintained after midazolam, but HR increases and CO decreases after thiopental. Hence, from the cardiovascular point of view, midazolam appears to offer some advantages over thiopental and, clinically, is at least as good as thiopental as an anesthesia induction agent in healthy surgical patients.

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= 국문초록 =

수용성 Benzodiazepine 약제의 마취유도중 심폐혈관에 미치는 영향

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김종성 · 김광우

새로 개발된 수용성 benzodiazepine인 midazolam은 diazepam에 비하여 약효의 발현시간이 빠르고 강력하며 주사시 통증이 없어 마취유도제로 사용하게 되었다. 저자들은 midazolam 정주로 마취유도시 심폐혈관에 미치는 영향을 관찰하기 위하여 ASA class I 혹은 II인 수술환자 10명씩을 대상으로 thiopental (5 mg/kg)과 midazolam (0.2 mg/kg) 정주로 마취유도시 마취유도시간(소스로 눈감는 시간과 안검반사 소실시간)을 관찰하였고 마취유도전, 마취유도중, 기관내삽관 직후에 평균동맥압(MAP), 심박수(HR), 심박출량(CO), 말초산소포화도(SaO_2)를 측정하여 비교하였다. 마취유도시간은 midazolam군에서 유의하게 길었으며 MAP는 두군 모두 마취유도시 유의하게 감소되고 기관삽관후 증가하였다. HR은 thiopental군에서는 마취유도초기와 기관내삽관 직후에 유의한 증가가 있었던 반면 midazolam군은 기관내 삽관 직후에만 유의한 증가가 있었다. CO는 thiopental 군에서는 마취유도중, 기관내 삽관후 유의한 감소가 있었으나 midazolam군에서는 유의한 변화는 없었다. SaO_2는 두군 모두 기관내삽관 직후에만 유의한 증가를 보였다.

이상의 결과로 midazolam은 비록 마취유도시간은 thiopental에 비해 길지만 혈역학적 측면에서 이점이 있으며 임상적으로 thiopental에 뒤지지 않는 마취유도제로 사용할 수 있음을 알 수 있다.