Cardiovascular Effects of Midazolam and Thiopentone for Induction of Anaesthesia in Ill Surgical Patients

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The cardiovascular effects of midazolam (0.15 mg kg^{-1}) and thiopentone (3.0 mg kg^{-1}) were compared during induction of anaesthesia in 20 American Society of Anesthesiologists class III patients. In patients given thiopentone (N = 11), cardiac output, mean arterial pressure, heart rate, and systemic vascular resistance all decreased significantly over the course of the study period; mean right atrial pressure rose slightly, and stroke volume remained the same. Patients receiving midazolam (N = 9) experienced similar haemodynamic changes which were significant relative to baseline only for the fall in mean arterial pressure and the rise in mean right atrial pressure at ten minutes. There were no significant differences between the two groups. Midazolam thus appears to be at least as acceptable an induction agent as thiopentone in ill patients, from a haemodynamic point of view.

Key Words

ANAESTHETICS, INTRAVENOUS: midazolam, thiopentone; BLOOD PRESSURE: drug effects; HEART: cardiac output, drug effects.

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Because of its relatively rapid onset, short duration of action, effectiveness as a sedative-hypnotic, minimal haemodynamic effects in sedative doses,[1] and favourable patient response, midazolam, a new water-soluble benzodiazepine, has been considered for use as an anaesthetic induction agent.

In contrast to thiopentone,[2] midazolam appears to have few deleterious effects upon ventilation and the airway. Midazolam tends not to produce apnoea of long duration, laryngospasm,[3] or bronchoconstriction;[4] however, the ventilatory depression that does occur lasts longer than that of thiopentone (correlating with midazolam's longer-acting sedative effect).[5,6] It has been thought that, as a benzodiazepine, midazolam might have less haemodynamic effect than thiopentone. The present study was undertaken to detail further the cardiovascular effects of induction doses of midazolam in surgical patients with severe systemic illness, particularly as compared to equipotent doses of thiopentone in similar patients under identical conditions.

Methods

Twenty male or non-pregnant female patients, aged 18 or older, determined to be American Society of Anesthesiologists class III (but excluding patients with symptomatic or suspected cardiac disease) and scheduled to undergo elective surgical procedures for which arterial and central venous catheters would customarily be placed, consented to participate in this study, as approved by the institution's Subcommittee on Human Studies. Such surgical

TABLE I Cardiovascular Effects of Midazolam and Thiopentone

	Minutes	*CO* *(L min^{-1})*	*MAP* *(KPa)*	*MRAP* *(KPa)*	*HR* *(b min^{-1})*	*SVR* *(KPa/L min^{-1})*	*SV* *(ml)*
Midazolam	0	8.3 ± 3.5	12.6 ± 1.7	0.9 ± 0.5	88 ± 13	1.6 ± 0.5	96 ± 38
N = 9	2	8.3 ± 3.3	12.2 ± 1.7	1.2 ± 0.7	85 ± 15	1.5 ± 0.4	94 ± 28
	5	7.9 ± 3.5	11.3 ± 2.9	1.3 ± 0.7	81 ± 16	1.5 ± 0.4	93 ± 30
	10	7.5 ± 3.6	10.6 ± 2.3*	1.3 ± 0.7*	81 ± 17	1.3 ± 0.4	87 ± 31
Thiopentone	0	8.6 ± 3.4	11.8 ± 2.1	0.8 ± 0.4	83 ± 24	1.5 ± 0.4	105 ± 28
N = 11	2	7.4 ± 4.6	11.0 ± 2.5	0.9 ± 0.7	79 ± 22	1.5 ± 0.6	103 ± 36
	5	8.5 ± 3.9	10.6 ± 1.7*	1.0 ± 0.7	78 ± 22	1.3 ± 0.4	108 ± 32
	10	7.9 ± 3.0	10.0 ± 1.6*	1.0 ± 0.7*	79 ± 23	1.2 ± 0.4*	105 ± 34

Results reported as Means ± S.D.
*p less than 0.05 as compared to baseline.

procedures included abdominal aortic grafting for asymptomatic aneurysm or aorto-iliac occlusive vascular disease, pulmonary lobectomy, hepatic lobar resection, excision and grafting of burn wounds, and total hip replacement. Following morphine (0.05 mg kg^{-1} i.m.) premedication and additional morphine (up to 0.2 mg kg^{-1} i.v.) for sedation during arterial and central venous catheterization, patients were given 67 per cent N_2O in O_2 to inhale spontaneously by mask.

After a stable baseline of sedation and cardiovascular stability was achieved, control measurements of mean arterial pressure (MAP), mean right atrial pressure (MRAP), and heart rate (HR) were obtained from the strip recording of a Hewlett-Packard 8-channel monitor (model 7758), employing Statham transducers (model P 23) and ECG lead 2. Cardiac output (CO) was determined using a Lexington Instruments cardiodensitometer (model R509045) through computerized integration of radial arterial indocyanine green dye concentration following rapid injection of 5 mg of dye into the central venous circulation. Stroke volume (SV) and systemic vascular resistance (SVR) were derived from the measured data.

Following the baseline measurements, an equipotent dose of either midazolam (0.15 mg kg^{-1}) or thiopentone (3.0 mg kg^{-1}), selected randomly, was given i.v. as a bolus injection in double-blind fashion. Upon induction of anaesthesia, ventilation was assisted by mask where needed so as to approximate baseline respiratory gas exchange. Additional measurements of MAP, MRAP, HR, and CO were made at two, five, and ten minutes after administration of the study drug. The patients were not otherwise manipulated until the study period had ended, after which an endotracheal tube was inserted, maintenance anaesthetics added, and surgery begun.

Baseline controls for each patient were compared to individual measurements at two, five, and ten minutes, using Student's t test for paired samples. Mean changes in each category for all patients in the thiopentone group (N = 11) were then compared with corresponding mean changes for all patients in the midazolam group (N = 9) using Student's t test for independent samples. Two-way analysis of variance was used to confirm the reported t statistics and the equivalence of the starting populations for each haemodynamic parameter. Differences were considered significant for p less than 0.05.

Results

The two groups of patients were nearly identical with regard to age (mean: 52 years for midazolam and 55 years for thiopentone), weight, morphine dose, and physical condition. Oxygenation was adequate at all stages of the study in both groups. During the transition from spontaneous breathing to assisted ventilation following induction, $Paco_2$ increased slightly (mean change: 4.8 mmHg for midazolam and 7.5 mmHg for thiopentone); the two groups were similar in this regard as well. Patients with symptomatic or suspected cardiac disease, as well as those taking medications affecting cardiovascular performance, were excluded from the study.

Patient data are summarized in Table I. Among patients anaesthetized with thiopentone, MAP, HR, CO, and SVR all decreased from baseline over the

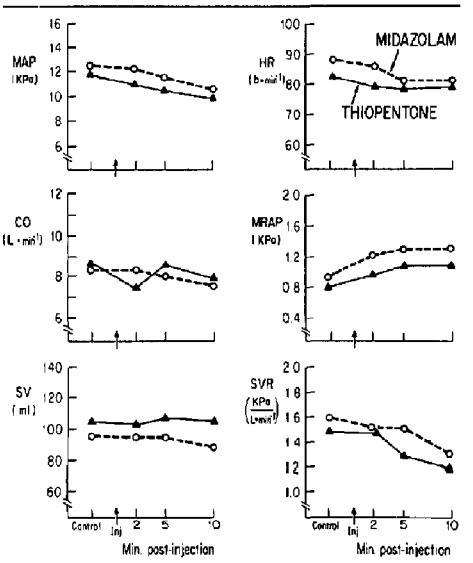

FIGURE 1 Graphic representation of the cardiovascular effects produced by either midazolam (N = 9) or thiopentone (N = 11) administration. Significant changes from control measurements were noted for MAP and MRAP at ten minutes in the group given midazolam, as well as MAP at five and ten minutes, MRAP at ten minutes, and SVR at ten minutes in the group given thiopentone.

ten minutes of the study. During this time MRAP rose slightly while SV did not appreciably change. Significant differences from control included the decline in MAP at five minutes and at ten minutes, the rise in MRAP at ten minutes, and the fall in SVR at ten minutes.

In the group anaesthetized with midazolam, MAP, HR, CO, SVR, and SV all fell with induction of anaesthesia; MRAP rose slightly. Significant changes from baseline were recorded among these patients only for the ten-minute lowering of MAP and the ten-minute rise of MRAP.

Comparison of the patients receiving midazolam with those given thiopentone is depicted graphically in Figure 1. In comparing the two groups, we could find no significant differences in any measured or derived parameter for any corresponding point in the study. The maximum decrease in MAP from control was 15.7 per cent in both groups. The maximum decline in CO was 8.1 per cent in patients given thiopentone and 9.6 per cent in patients given midazolam; HR decreased 4.8 and 8.0 per cent, respectively. The greatest rise in MRAP was comparable between groups (33.3 and 42.8 per cent, respectively) as was the reduction in SVR (18.1 and 16.7 per cent, respectively). Although SV decreased 9.4 per cent in patients given midazolam but did not change in patients given thiopentone, the differences were not significant.

Discussion

Midazolam – 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a] [1,4]-benzodiazepine – as the hydrochloride assumes an open ring conformation in an aqueous solution of pH less than 4.0 and is thus water-soluble. This structural relationship forms the basis for the clinical finding that midazolam is relatively non-irritating to veins and painless on injection.[7] At physiologic pH the benzodiazepine ring closes, and midazolam becomes lipid-soluble and therefore CNS-active.[8] Midazolam is additionally characterized by induction of sleep in less than two minutes after intravenous injection,[9] an excretion half-life of two hours with no known active metabolites,[10] relief of anxiety,[11] and anterograde amnesia.[12] Coupled with a high degree of patient acceptance and a low incidence of adverse sequelae,[13] midazolam has proven efficacious both as a preoperative sedative-hypnotic and as an anaesthetic induction agent. Comparisons of midazolam and diazepam for anaesthetic induction stress midazolam's approximately twice greater potency[14] and fifteen-fold duration of action,[10] as well as its lower incidence of venous irritation.[14,15]

Thiopentone, the standard for comparison among induction drugs, has been extensively studied, particularly with regard to hemodynamic effects.[16] Evidence for a primary myocardial depressant mechanism includes the findings of CO reduction coupled with MRAP elevation in dog heart-lung preparations,[17] as well as a decrease in myocardial contractile force both in dog heart-lung preparations[18] and in intact dogs.[19] Similar conclusions were reached for thiopentone in human subjects.[20,21] Other clinical studies[22,23] additionally support the concept of thiopentone as a vasodilator with venous pooling leading to decreased blood return to the right atrium and subsequent decline in CO.

As a benzodiazepine, midazolam might conceivably exert less cardiovascular effect than thiopen-

tone when given in equi-effective doses. In dogs at doses as high as 10 mg kg^{-1} midazolam produced negligible changes in MAP, HR, CO, SV, or SVR.[24] In surgical patients, midazolam (0.15 mg kg^{-1}) caused little change in MAP or HR.[3] Patients with ischaemic heart disease whose anaesthesia was induced with midazolam (0.2 mg kg^{-1}) after morphine–scopolamine premedication experienced significant decreases in MAP, SV, and SVR with a significant increase in HR. Cardiac output, as well as MRAP, mean pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP), did not differ significantly from pre-induction values.[25] A similar group of patients whose anaesthesia was induced with midazolam (0.2 mg kg^{-1}) but were also given 50 per cent N_2O in O_2 instead of 100 per cent O_2, developed significant reductions from pre-midazolam levels only for PAP, PCWP, and SV.[26] In a double-blind study of midazolam (0.25 mg kg^{-1}) and thiopentone (4.0 mg kg^{-1}) for induction of anaesthesia in healthy patients, midazolam produced significant changes from baseline only for MAP (16 to 18 per cent), while thiopentone caused reductions in MAP and CO, as well as an elevation of MRAP.[27]

The present study sought to compare in double-blind fashion induction of anaesthesia with midazolam or thiopentone in sicker patients. In the setting of morphine premedication/sedation and 67 per cent N_2O in O_2 the cardiovascular effects of thiopentone administration indicated elements of both myocardial depression and peripheral vasodilation. Similar changes were noted for midazolam. The reductions in MAP and CO coupled with the elevated MRAP point to myocardial depression, but the decreased SVR implies some degree of vasodilation. Anxiolysis and the interruption of heightened sympathetic tone – the induction of anaesthesia – may be responsible through mechanisms in the central nervous system for the combined influences of myocardial depression, arterial impedance reduction, and possible venous pooling. These effects appear to be more clearly discernible in sicker patients, whose sympathetic reserve is usually less than in healthy patients, even at the smaller induction doses used in this study.

We conclude that, from a haemodynamic viewpoint, midazolam is at least as good an induction agent as thiopentone, but not significantly better. Its selection over thiopentone for induction of anaesthesia will in all likelihood, therefore, be made on the basis of its other pharmacologic effects.

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Résumé

On a comparé les effets cardiovasculaires obtenus pendant l'administration de l'anesthésie avec le midazolam (0.15 mg kg^{-1}) et le thiopentone (30 mg kg^{-1}) chez 20 patients appartenant à la Classe III (American Society of Anesthesiologists). Chez les patients recevant le thiopentone (N = 11), on a observé que le débit cardiaque, la fréquence cardiaque, la résistance vasculaire générale et la tension artérielle ont baissé sensiblement durant le cours de notre recherche. La pression moyenne de l'auriculaire cardiaque droite haussa faiblement tandis que le débit systolique resta le même. Les patients auxquels on administra le midazolam (N = 9) ont éprouvé des changements hémodynamiques significatifs par rapport à la valeur de base où l'on observa seulement une baisse de la pression artérielle moyenne et une hausse à dix minutes de la pression moyenne de l'auriculaire cardiaque droite. Il n'y a donc pas de différences significatives entre les deux groupes. Le midazolam apparaît être un agent d'induction aussi acceptable que le thiopentone chez les malades, au point de vue hémodynamique.