Title: COMPARATIVE RENAL EFFECTS OF MIDAZOLAM AND THIOPENTAL

Authors: P.W. Lebowitz, M.D.; M.E. Cote, C.R.N.A.; A.L. Daniels, B.S.; and J. Bonventre, M.D.

Affiliation: From the Anesthesia Services of the Massachusetts General Hospital and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts 02114.

Introduction. Midazolam is a water-soluble benzodiazepine whose quick onset after intravenous injection, short duration of action, lack of airway stimulation, absence of venous irritation, and mild effects on cardiovascular stability have allowed it to be compared favorably with thiopental as an anesthesia induction agent. We proposed to examine the renal effects of midazolam, particularly in comparison with thiopental.

Methods. Sixteen ASA class I-II patients age 18-55 with normal renal function undergoing elective surgery consented to participate in the study as approved by the institutional Human Studies Committee. All patients were premedicated with morphine 0.1 mg/kg IM. After insertion of an indwelling urinary catheter, intravenous fluid loading with 15 ml/kg of lactated Ringer's solution was performed. Priming doses of 10% inulin and 20% para amino hippuric acid (PAH) were administered, immediately followed by a sustaining infusion of inulin and PAH in normal saline. During the establishment of a steady-state diuresis and thereafter, lactated Ringer's solution was given at a rate equal to the volume of urine excreted plus 1 ml/min. Urine was collected over several 10- to 15-min periods with venous blood samples obtained at each midpoint. Midazolam 0.2 mg/kg or thiopental 3.5 mg/kg was then given randomly and in double-blind fashion for induction of anesthesia; N_2O:O_2, 5:3 L/min, was then inhaled spontaneously by mask, with ventilation assisted as needed to prevent hypercarbia. Anesthesia was deepened as needed with increments of either midazolam 0.05 mg/kg or thiopental 0.875 mg/kg, respectively, over the succeeding 30 minutes in the absence of surgical stimulation. Urine was then collected for several 10- to 15-min periods with venous blood samples obtained at each midpoint. Glomerular filtration rate (GFR) was measured for pre- and postinduction periods by inulin clearance: $Cl_{in} = \frac{U_{in} V}{P_{in}}$ [where U_{in} = concentration of inulin in urine, V = urine volume for the period, P_{in} = concentration of inulin in plasma]; effective renal plasma flow (ERPF) by PAH clearance: $Cl_{PAH} = \frac{U_{PAH} V}{P_{PAH}}$; renal blood flow (RBF) by: $\frac{Cl_{PAH}}{(1 - \text{hematocrit})}$; and renal vascular resistance (RVR) by: $\frac{\text{mean arterial pressure}}{RBF}$. Student's *t* test for related samples was applied to each measurement relative to control and the same statistical method was used for independent sample analysis to compare the two drug groups. Differences were considered statistically significant at $p < 0.05$.

Results. The results are summarized in Table 1. Despite minimum declines from baseline in mean arterial pressure (MAP) -- 8% for midazolam *vs* 6% for thiopental -- decreases in GFR (34% *vs* 25%), ERPF (23% *vs* 14%), and RBF (23% *vs* 13%) were of greater magnitude in both groups. Only the reduction in GFR for midazolam was significantly changed from pre-induction values. The decreases in GFR and MAP were also significantly greater than the corresponding changes in patients receiving thiopental.

Table 1

	MAP (mm Hg)			GFR (ml/min)			ERPF (ml/min)			RBF (ml/min)			RVR (mm Hg/L/min)		
	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
MIDAZOLAM	88	81●	-7	107	71★●	-36	539	413	-126	895	686	-209	124	172	+48
	±6	±9	±6	±39	±33	±38	±219	±213	±295	±367	±358	±484	±80	±138	±164
THIOPENTAL	93	87	-6	85	64	-19	478	411	-67	728	637	-91	150	218	+68
	±8	±12	±7	±28	±26	±28	±183	±286	±292	±232	±426	±445	±70	±163	±172

Values reported as Means ± S.D.

N = 8 for MAP, GFR for each drug group
N = 7 for ERPF, RBF, RVR for each drug group
★ $p < 0.05$ relative to pre-induction value
● $p < 0.05$ relative to other drug group

Discussion. Previous studies have consistently shown that all anesthetics, including thiopental-N_2O-narcotic,[1,2] produce a transient depression of RBF and GFR. Likely mechanisms include alteration of the cortical-medullary perfusion ratio or generalized diminution of RBF on the basis of catecholamine-induced preglomerular vasoconstriction or accentuated renin-angiotensin activity. In our study, too, thiopental-N_2O-O_2 anesthesia after morphine premedication caused MAP, RBF, ERPF, and GFR to decrease, and RVR to increase. When midazolam was used in place of thiopental in a similar group of patients, even greater reductions in MAP, RBF, ERPF, and GFR were recorded; the increase in RVR, however, was less pronounced. Our study suggests that midazolam, like all other anesthetics studied, depresses renal hemodynamics and function, at least during the period of anesthetic administration.

References

1. Habif DV, Papper EM, Fitzpatrick HF, *et al.* Surgery 30: 241-255, 1951.
2. Deutsch S, Bastron RD, Pierce EC, *et al.* Br J Anaesth 41: 807-815, 1969.