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Comparative Renal Effects of Midazolam and Thiopental in Humans

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Midazolam is a water-soluble benzodiazepine whose quick onset after intravenous injection, short duration of action, absence of venous irritation, and mild cardiovascular and respiratory effects suggest its use for induction of anesthesia. The renal effects of midazolam-N_2O-O_2 anesthesia, as determined by renal clearance of injected inulin and para-aminohippuric acid (PAH), in hydrated ASA Class I–II surgical patients (N = 8) were compared in a double-blind fashion with a similar group of patients (N = 9) anesthetized with thiopental-N_2O-O_2. Except for glomerular filtration rate, there were no significant changes in any of the measured variables (blood pressure, effective renal plasma flow, renal blood flow, and renal vascular resistance). The per cent reduction in glomerular filtration rate in patients given thiopental differed significantly from that in patients given midazolam. This study suggests that midazolam, as opposed to thiopental, offers minimal advantage in maintaining renal performance at least during the period of anesthetic administration. (Key words: Anesthetics, intravenous: midazolam; thiopental. Kidney: blood flow; function.)

MIDAZOLAM—8 chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine—as the hydrochloride is water soluble when maintained at *p*H less than 4.0 (due to an open benzodiazepine ring conformation) but becomes lipid-soluble at physiologic *p*H (due to ring closure).[1] Consequently, this benzodiazepine is relatively nonirritating to veins and painless on injection[2]; compared with diazepam, midazolam causes less venous irritation and thrombophlebitis.[3,4] Midazolam is two to three times more potent than diazepam[3] and has a 15-fold-shorter duration of action.[5] Other characteristics of midazolam include relief of anxiety,[6] anterograde amnesia,[7] sedation-hypnosis,[8] and minimal hemodynamic effects at low doses,[9] as well as induction of sleep in less than 2 min after intravenous injection[10]; mild respiratory depression[11]; and mild reductions in mean arterial pressure, cardiac output, and systemic vascular resistance at higher doses.[12,13]

Regarding regional circulation, cerebral blood flow[14] and splanchnic blood flow[15] have been shown to decrease following midazolam administration. The present study was undertaken to determine the effects of anesthesia induced and maintained with midazolam on renal blood flow and function, particularly as compared with the changes produced by anesthesia induced and maintained with thiopental.

Methods

Seventeen ASA Class I–II, ages 21–49, male or nonpregnant female patients with normal renal function, undergoing elective surgical procedures requiring placement of an indwelling urinary bladder (Foley) catheter, consented to participate in the study as approved by the institution's Subcommittee on Human Studies.

All patients received morphine 0.1 mg/kg intramuscularly as premedication. After an indwelling urinary bladder catheter was inserted, intravenous fluid loading was accomplished with administration of lactated Ringer's solution (15 ml/kg over 30 min). Priming doses of 10% inulin (American Critical Care) and 20% para-aminohippuric acid (PAH) (Merck Sharp & Dohme) then were given intravenously and were followed immediately by a sustaining infusion of inulin and PAH in normal saline solution. During the establishment of a steady-state diuresis and thereafter, lactated Ringer's solution was administered at a rate equal to that of urine flow plus 1 ml/min. Control preinduction samples of urine were collected over several 10- to 15-min periods, with venous blood samples obtained at the midpoint of each collection period.

Induction of anesthesia then was performed, initially using either midazolam (0.2 mg/kg) or thiopental (3.5 mg/kg), selected randomly and given in double-blind fashion. Incremental doses of the respective study drug, either midazolam (0.05 mg/kg) or thiopental (0.875 mg/kg), subsequently were given at intervals of 2 or more minutes, as needed to induce or maintain anesthesia over the succeeding 30 min, during which time there was no surgical stimulation. Following induction, the patient inhaled N_2O (5 l/min) and O_2 (3 l/min) spontaneously by mask, with ventilation assisted as needed to minimize hy-

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TABLE 1. Renal Hemodynamics and Function

MAP (mmHg)			GFR (ml/min)			ERPF (ml/min)			RBF (ml/min)			RVR (mmHg · l^{-1} · min)		
Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
Midazolam														
88	81	−7	110	77	−33	591	487	−103	978	808	−169	105	161	+56
± 2	± 3	± 2	± 12	± 13	± 15	± 74	± 102	± 111	± 125	± 172	± 183	± 17	± 49	± 54
Thiopental														
92	90	−2	94	59*†	−35	531	363	−167	815	558	−256	133	295	162
± 3	± 5	± 4	± 12	± 9	± 15	± 66	± 106	± 114	± 95	± 155	± 175	± 24	± 91	± 98

N = 9 for MAP, GFR in thiopental group; N = 8 for ERPF, RBF, RVR in thiopental group; N = 8 for MAP, GFR in midazolam group; N = 7 for ERPF, RBF, RVR in midazolam group.

Values reported as means ± SE.
* $P < 0.05$ relative to preinduction value.
† $P < 0.05$ relative to other drug groups.

percarbia. Postinduction urine collections were carried out over several 10- to 15-min periods, with venous blood samples obtained at each midpoint. The initial postinduction collections were not included in the calculation of the mean inulin and PAH clearances in order to avoid the predictable errors produced by the presence of preinduction urine in the dead space of the renal collecting system, ureters, and bladder.

Glomerular filtration rate (GFR) was measured for preinduction and postinduction periods by inulin clearance (Cl_{in}):

$$Cl_{in} = \frac{U_{in}\dot{V}}{P_{in}},$$

where U_{in} = concentration of inulin in urine, $\dot{V}$ = urine flow rate during the collection period, and P_{in} = concentration of inulin in plasma. Effective renal plasma flow (ERPF) was determined by PAH clearance (Cl_{PAH}):

$$Cl_{PAH} = \frac{U_{PAH}\dot{V}}{P_{PAH}},$$

where U_{PAH} = concentration of PAH in urine and P_{PAH} = concentration of PAH in plasma. Renal blood flow (RBF) then was estimated by the expression:

$$RBF = \frac{Cl_{PAH}}{1 - \text{hematocrit}}.$$

Estimated renal vascular resistance (RVR) was determined by:

$$RVR = \frac{MAP}{RBF},$$

where MAP = mean arterial pressure by arm sphygmomanometric determination. Fractional excretion of sodium (FE_{Na^+}) expressed as percentage was determined by:

$$FE_{Na^+}(\%) = \frac{U_{Na^+} \cdot \dot{V}}{Cl_{in} \cdot P_{Na^+}} \times 100\%,$$

where U_{Na^+} and P_{Na^+} = respective urinary and plasma concentrations of sodium. Plasma and urine osmolalities were determined by the freezing point depression method.

Results are expressed as mean ± SE. Analysis of variance was used to compare the two drug groups with regard to changes from control measurements. Mean postinduction measurements then were compared with preinduction controls within each drug group by paired Student's *t* test analysis. Differences were considered statistically significant at *P* is less than 0.05.

Results

The results of the study are summarized in table 1. The patients in the thiopental group and those in the midazolam group were comparable with respect to age (36 ± 3 yr in each group) and weight (62 ± 4 kg *vs.* 64 ± 3 kg, respectively).

The only significant change by paired analysis from preinduction measurements was the reduction in GFR in patients anesthetized with thiopental. Despite downward trends, postinduction changes for GFR in patients given midazolam and postinduction changes in ERPF and RBF in both groups were not statistically significant. Similarly, the postinduction increases in estimated RVR did not possess statistical significance. In a comparison between groups, only the percentage decrease in GFR in patients receiving thiopental was significantly greater than the corresponding change in patients receiving midazolam. In other comparisons, differences between groups were not statistically significant.

Adequate hydration of the patient population at all times in the study was reflected by the urinary flow rate, the high urine Na^+ concentration, and the FE_{Na} greater than 1% (table 2). Urinary output decreased significantly following induction to approximately the same degree in both groups of patients.

TABLE 2. Water and Solute Excretion

Urine Flow (ml/min)		Urine Na^+ (mEq/l)		Fractional Excretion of Sodium ($FE_{Na}+$) (%)		Urine Osmolality (mosm/l)		Plasma Osmolality (mosm/l)
Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Midazolam								
3.5 ± 0.6	1.4* ± 0.3	98 ± 14	121 ± 15	2.2 ± 0.3	1.7 ± 0.3	368 ± 43	444 ± 31	284 ± 3
Thiopental								
3.9 ± 0.9	1.3* ± 0.3	90 ± 26	124 ± 25	1.9 ± 0.4	1.7 ± 0.3	313 ± 90	402 ± 74	280 ± 3

N = 8 for midazolam group; N = 9 for thiopental group.
Values reported as means ± SE.

* $P < 0.05$ relative to preinduction value.

Discussion

Previous studies consistently have shown that anesthesia, with or without accompanying surgery, produces a transient depression of renal perfusion and glomerular filtration. These effects have been documented for individual anesthetic agents,[16–25] for nitrous oxide-oxygen-thiopental-narcotic-relaxant anesthesia,[26,27] and for subarachnoid[28] or epidural[29] block, as well. The magnitude of change is greater at deeper levels of anesthesia[19,30] and in states of dehydration.[31] Likely mechanisms for the observed effects include 1) anesthetic-induced depression of cardiac output and systemic blood pressure with consequent reduction in blood flow to the kidneys, an effect perhaps exacerbated by loss of renal autoregulation of blood flow; 2) reduction in renal blood flow due to catecholamine- or angiotensin-induced vasoconstriction; and 3) redistribution of the existing renal blood supply from the cortex to the medulla, thus altering the cortical-medullary perfusion ratio. The release of antidiuretic hormone (ADH) as part of the generalized stress response to surgery also may contribute to observed changes in renal function.[32] Clinical manifestations of these physiologic influences include a decrease in urine output, lowered free water clearance, and a reduction in total urinary sodium excretion. Upon discontinuation of anesthesia, RBF, GFR, urine output, and urinary sodium excretion all increase to approach preanesthetic levels.

Most studies of renal hemodynamics during anesthesia have shown that minor decreases in systemic perfusion are associated with proportionately greater decreases in renal perfusion. Even when MAP increases or remains unchanged, as observed in patients anesthetized with cyclopropane[16–18,22] or, to a lesser extent, diethylether,[16–18] GFR, ERPF, and RBF all decrease. High levels of circulating catecholamines will reduce RBF through renal vasoconstriction, as indicated by deWardener's study[18] in which infused norepinephrine caused MAP to increase by 64% at the same time that RBF decreased by 18%. The influence of ADH to induce renal vasoconstriction also has been suggested.[20]

In a study of their cardiovascular effects in healthy surgical patients, midazolam and thiopental each caused reductions in cardiac output and MAP to nearly the same degree (less than 20%) without increasing systemic vascular resistance.[33] A comparison of the hemodynamic effects of midazolam and thiopental in ASA Class III patients yielded similar results.[34] In this study we have shown that anesthesia consisting of midazolam-N_2O-O_2 (morphine premedication) caused no significant changes in GFR, ERPF, RBF, or RVR. Only the decrease in GFR in patients receiving thiopental differed significantly from both the control values and the patients given midazolam. The degree of change induced by either midazolam or thiopental was either unmeasurable or minimal and generally not as marked as that resulting from use of exclusively inhalational anesthetics,[16–25] although varying study protocols make quantitative comparisons unreliable.

In conclusion, the selection of midazolam, as opposed to thiopental, for induction or maintenance of anesthesia appears to offer minimal advantage in maintaining renal performance. Clinically, however, the two drugs appear to be very similar in their effects upon kidney function, at least under the conditions of this study.

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References

1. Dundee JW: New I.V. anaesthetics. Br J Anaesth 51:641–648, 1979
2. Pagano RR, Graham CW, Galligan M, Conner JT, Katz RL: Histopathology of veins after intravenous lorazepam and RO 21-3981. Can Anaesth Soc J 25:50–52, 1978
3. Reves JG, Corssen G, Holcomb C: Comparison of two benzodi-

azepines for anaesthesia induction: Midazolam and diazepam. Can Anaesth Soc J 25:211–214, 1978
4. Dundee JW, Samuel IO, Toner W, Howard PJ: Midazolam: A water-soluble benzodiazepine. Anaesthesia 35:454–458, 1980
5. Sarnquist FH, Mathers WD, Blaschke TF: Steady-state pharmacokinetics of midazolam maleate. ANESTHESIOLOGY 51:S-41, 1979
6. Conner JT, Katz RL, Pagano RR, Graham CW: RO 21-3981 for intravenous surgical premedication and induction of anesthesia. Anesth Analg 57:1–5, 1978
7. Dundee JW, Wilson DB: Amnesic action of midazolam. Anaesthesia 35:459–461, 1980
8. Reves JG, Vinik R, Hirschfield AM, Holcomb C, Strong S: Midazolam compared with thiopentone as a hypnotic component in balanced anaesthesia: A randomized, double-blind study. Can Anaesth Soc J 26:42–49, 1979
9. Fragen RJ, Meyers SN, Barresi V, Caldwell NJ: Hemodynamic effects of midazolam in cardiac patients. ANESTHESIOLOGY 51:S-103, 1979
10. Brown CR, Sarnquist FH, Canup CA, Pedley TA: Clinical electroencephalographic and pharmacokinetic studies of a water-soluble benzodiazepine, midazolam maleate. ANESTHESIOLOGY 50:467–470, 1979
11. Carel WD, Zebrowski ME, Gardner S, Smith TC: Ventilatory depression following midazolam induction. ANESTHESIOLOGY 53:S-408, 1980
12. Reves JG, Samuelson PN, Lewis S: Midazolam maleate induction in patients with ischaemic heart disease: Hemodynamic observations. Can Anaesth Soc J 26:402–409, 1979
13. Samuelson PN, Reves JG, Dole K, Smith LR, Linnan M: Midazolam-N_2O induction in ischemic heart disease patients. ANESTHESIOLOGY 51:S-104, 1979
14. Forster A, Juge O, Morel D: Effects of midazolam on cerebral blood flow in human volunteers. ANESTHESIOLOGY 55:A-263, 1981
15. Gelman S, Reves JG: Splanchnic circulation and midazolam in chronic experiments. ANESTHESIOLOGY 55:A-192, 1981
16. Burnett CH, Bloomberg EL, Shortz G, Compton DW, Beecher HK: A comparison of the effects of ether and cyclopropane anesthesia on the renal function of man. J Pharmacol Exp Ther 96:380–387, 1949
17. Habif DV, Papper EM, Fitzpatrick HF, Lowrance P, Smythe CM, Bradley SE: The renal and hepatic blood flow, glomerular filtration rate, and urinary output of electrolytes during cyclopropane, ether, and thiopental anesthesia, operation, and the immediate postoperative period. Surgery 30:241–255, 1951
18. deWardener HE: Renal circulation during anaesthesia and surgery. Anaesthesia 10:18–33, 1955
19. Mazze RI, Schwartz FD, Slocum HC, Barry KG: Renal function during anesthesia and surgery. 1. The effects of halothane anesthesia. ANESTHESIOLOGY 24:279–284, 1963
20. Papper S, Papper EM: The effects of preanesthetic, anesthetic, and postoperative drugs on renal function. Clin Pharmacol Ther 5:205–215, 1964
21. Deutsch S, Goldberg M, Stephen GW, Wu W-H: Effects of halothane anesthesia on renal function in normal man. ANESTHESIOLOGY 27:793–804, 1966
22. Deutsch S, Pierce EC, Vandam LD: Cyclopropane effects on renal function in normal man. ANESTHESIOLOGY 28:547–558, 1967
23. Gorman HM, Craythorne NWB: The effects of a new neuroleptanalgesic agent (Innovar) on renal function in man. Acta Anaesthesiol Scand (Suppl) 24:111–118, 1966
24. Mazze RI, Cousins MJ, Barr GA: Renal effects and metabolism of isoflurane in man. ANESTHESIOLOGY 40:536–542, 1974
25. Cousins MJ, Greenstein LR, Hitt BA, Mazze RI: Metabolism and renal effects of enflurane in man. ANESTHESIOLOGY 44:44–53, 1976
26. Deutsch S, Bastron RD, Pierce EC, Vandam LD: The effects of anaesthesia with thiopentone, nitrous oxide, narcotics and neuromuscular blocking drugs on renal function in normal man. Br J Anaesth 41:807–814, 1969
27. Jarnberg P-O, Santesson J, Eklund J: Renal function during neurolept anaesthesia. Acta Anaesthesiol Scand 22:167–172, 1978
28. Kennedy WF, Sawyer TK, Gerbershagen HU, Everett GB, Cutler RE, Allen GD, Bonica JJ: Simultaneous systemic cardiovascular and renal hemodynamic measurements during high spinal anaesthesia in normal man. Acta Anaesthesiol Scand (Suppl) 37:163–171, 1970
29. Kennedy WF, Sawyer TK, Gerbershagen HU, Cutler RE, Allen GD, Bonica JJ: Systemic cardiovascular and renal hemodynamic alterations during peridural anesthesia in normal man. ANESTHESIOLOGY 31:414–421, 1969
30. Miles BE, de Wardener HE, Churchill-Davidson HC, Wylie WD: The effect on the renal circulation of pentamethonium bromide during anaesthesia. Clin Sci 11:73–79, 1952
31. Barry KG, Mazze RI, Schwartz FD: Prevention of surgical oliguria and renal-hemodynamic suppression by sustained hydration. N Engl J Med 270:1371–1377, 1964
32. Philbin DM, Coggins CH: Plasma antidiuretic hormone levels in cardiac surgical patients during morphine and halothane anesthesia. ANESTHESIOLOGY 49:95–98, 1978
33. Lebowitz PW, Cote ME, Daniels AL, Ramsey FM, Martyn JAJ, Teplick RS, Davison JK: Comparative cardiovascular effects of midazolam and thiopental in healthy patients. Anesth Analg 61:771–775, 1982
34. Lebowitz PW, Cote ME, Daniels AL, Martyn JAJ, Teplick RS, Davison JK, Sunder N: Cardiovascular effects of midazolam and thiopentone for induction of anaesthesia in ill surgical patients. Can Anaesth Soc J 30:19–23, 1983