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-N₂O-O₂ 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-N₂O-O₂. 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 percent 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-α][1,4]-benzodiazepine—as the hydrochloride is water soluble when maintained at pH less than 4.0 (due to an open benzodiazepine ring conformation) but becomes lipid-soluble at physiologic pH (due to ring closure). Consequently, this benzodiazepine is relatively nonirritating to veins and painless on injection; compared with diazepam, midazolam causes less venous irritation and thrombophlebitis. Midazolam is two to three times more potent than diazepam and has a 15-fold shorter duration of action. Other characteristics of midazolam include relief of anxiety, anterograde amnesia, sedation-hypnosis, and minimal hemodynamic effects at low doses, as well as induction of sleep in less than 2 min after intravenous injection; mild respiratory depression; and mild reductions in mean arterial pressure, cardiac output, and systemic vascular resistance at higher doses.

Methods

Seventeen ASA Class I–II, ages 21–49, male or non-pregnant 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 N₂O (5 l/min) and O₂ (8 l/min) spontaneously by mask, with ventilation assisted as needed to minimize hy-
percabia. 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 postinduction 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}):

\[ \text{Cl}_{\text{in}} = \frac{U_{\text{in}} \cdot V}{P_{\text{in}}} \]

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

\[ \text{Cl}_{\text{PAH}} = \frac{U_{\text{PAH}} \cdot V}{P_{\text{PAH}}} \]

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

\[ \text{RBF} = \frac{\text{Cl}_{\text{PAH}}}{1 - \text{hematocrit}} \]

Estimated renal vascular resistance (RVR) was determined by:

\[ \text{RVR} = \frac{\text{MAP}}{\text{RBF}} \]

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

\[ \text{FE}_{\text{Na}^+}(\%) = \frac{U_{\text{Na}^+} \cdot \dot{V}}{\text{Cl}_{\text{in}} \cdot P_{\text{Na}^+}} \times 100\% \]

\( \text{U}_{\text{Na}^+} \) and \( P_{\text{Na}^+} \) = 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 \( P < 0.05 \).

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 ± 5 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 \( \text{FE}_{\text{Na}^+} \) 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**

<table>
<thead>
<tr>
<th></th>
<th>Urine Flow (ml/min)</th>
<th>Urine Na⁺ (mEq/l)</th>
<th>Fractional Excretion of Sodium (FE_{Na⁺}) (%)</th>
<th>Urine Osmolality (mOsm/l)</th>
<th>Plasma Osmolality (mOsm/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Midazolam</td>
<td>3.5</td>
<td>1.4*</td>
<td>98</td>
<td>121</td>
<td>2.2</td>
</tr>
<tr>
<td>± 0.6</td>
<td>± 0.3</td>
<td></td>
<td>± 14</td>
<td>± 15</td>
<td>± 0.3</td>
</tr>
<tr>
<td>Thiopental</td>
<td>3.9</td>
<td>1.3*</td>
<td>90</td>
<td>124</td>
<td>1.9</td>
</tr>
<tr>
<td>± 0.9</td>
<td>± 0.3</td>
<td></td>
<td>± 26</td>
<td>± 25</td>
<td>± 0.4</td>
</tr>
</tbody>
</table>

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, for nitrous oxide-oxygen-thiopental-narcotic-relaxant anesthesia, and for subarachnoid or epidural block, as well. The magnitude of change is greater at deeper levels of anesthesia and in states of dehydration. 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. 

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 or, to a lesser extent, diethyl-ether, GFR, ERPF, and RBF all decrease. High levels of circulating catecholamines will reduce RBF through renal vasoconstriction, as indicated by deWardener’s study 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.

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. A comparison of the hemodynamic effects of midazolam and thiopental in ASA Class III patients yielded similar results. In this study we have shown that anesthesia consisting of midazolam-N₂O-O₂ (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, 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**

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