Comparative Evaluation of Intravenous Agents for Rapid Sequence Induction—Thiopental, Ketamine, and Midazolam

Paul F. White, M.D., Ph.D.*

The pharmacologic effects of ketamine, midazolam, and a midazolam-ketamine combination were compared with thiopental for rapid induction of general anesthesia. Thiopental, 4 mg/kg, 1.5 mg/kg ketamine, 0.3 mg/kg midazolam, or 0.15 mg/kg midazolam, and 0.75 mg/kg ketamine, were administered intravenously in a randomized fashion to 80 patients undergoing emergency surgery. Adequacy of induction, hemodynamic changes, and postoperative effects were assessed during and after a standardized induction-maintenance anesthetic technique. Midazolam had the slowest onset (15–60 s) and longest duration of action. During induction, thiopental decreased mean arterial pressure (MAP) by 11%, ketamine increased MAP by 10%, while neither midazolam nor the midazolam-ketamine combination significantly changed MAP. Heart rate (HR) increased during induction in all groups; however, the increase was significantly less in the combination group. After intubation, MAP and HR increased to the same extent in all four groups. Significantly more patients who received ketamine for induction were disoriented during emergence. Midazolam most effectively produced anxiolysis and antegrade amnesia. Significantly more patients who received thiopental felt depressed postoperatively, and 95% required parenteral opiates analgesics in the recovery room. Dreaming was highest after ketamine (55%) and lowest after midazolam (0%) and the combination (5%). Thus, midazolam effectively attenuated both the cardiovascular responses and unpleasant emergence reactions associated with ketamine. The author concludes that both midazolam and the midazolam–ketamine combination are safe and effective induction agents for emergency surgery, which may offer an advantage over thiopental in situations where hemodynamic stability is crucial. Furthermore, midazolam effectively attenuates the side effects of ketamine. (Key words: Anesthesia: induction. Anesthetics, intravenous: ketamine; midazolam; thiopental. Anesthetic techniques: rapid sequence induction. Interactions [drug]. Pharmacology: drug interactions. Surgery: emergency.)

A rapid sequence induction is commonly employed in the anesthetic management of patients at risk from vomiting or regurgitation.† The well-known hazards associated with the use of thiopental and succinylcholine for rapid intravenous induction include: hypotension, increased intra-abdominal pressure, inadequate relaxation, and coughing following intubation.‡ Other induction agents are now available which may offer advantages over thiopental in the emergency situation.

Ketamine has been used in critically ill patients where hypotension or apnea could be life-threatening.§ However, ketamine frequently produces marked cardiovas-

cular stimulation and emergence reactions. In critically ill patients, ketamine can also produce a depressor response† which might result in a maldistribution of systemic blood flow. Recently, midazolam, a potent short-acting, water-soluble benzodiazepine has been evaluated as an intravenous induction agent.§ Adequate doses of midazolam can reliably produce loss of consciousness. Except for a slower onset, midazolam compared favorably with thiopental as the hypnotic drug in a balanced anesthetic regimen.¶

Our study was designed to evaluate the pharmacologic and hemodynamic effects of ketamine and midazolam, both alone and in combination, as compared with thiopental when used for induction of general anesthesia in patients requiring emergency surgery.

Materials and Methods

Eighty unpremedicated† ASA physical status IE or IIE adult patients (men or nonpregnant women) who presented for emergency surgical procedures, and who were considered to have a “full stomach,”‡ were randomly assigned to receive thiopental, ketamine, midazolam, or a midazolam and ketamine combination for induction of anesthesia (20 in each group). A double-blind, open parallel protocol design was utilized in this study.§ Approval was obtained from the University Committee on Human Research and informed consent was obtained from the patients.

To evaluate for retrograde amnesia, patients were shown a picture of a dollar bill immediately before their arrival in the operating room. Routine monitoring equipment consisted of a Dinamap® Model 845 monitor/recorder, EKG leads and a precordial stethoscope. A standard “tilt test” was performed and if the mean arterial pressure or heart rate changed by >20% in 15° reverse Trendelenberg, the patient was considered hypovolemic and additional fluids (250–500 ml lactated Ringer’s solution) were administered intravenously before induction. All patients were administered 0.005 mg/kg glycopyrrolate and 3 mg d-tubocurarine intravenously (iv)...

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† Twelve patients receive narcotic analgesics within 4 h of induction for pain secondary to acute orthopedic injuries.

‡ Patients with acute abdominal emergencies and patients who had eaten or drunk up to six hours before the operation.

§ The investigator administered the study drugs; however, neither the anesthesiologist monitoring the patient, the nurse-observer nor the patient were aware of which induction agent was administered.

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TABLE 1. Demographic Characteristics of Patients Undergoing Emergency Surgery Utilizing a Rapid Sequence Induction Technique

<table>
<thead>
<tr>
<th>Variable</th>
<th>Thiopental</th>
<th>Ketamine</th>
<th>Midazolam</th>
<th>Midazolam/Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29 ± 2</td>
<td>31 ± 2</td>
<td>32 ± 2</td>
<td>33 ± 3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 ± 3</td>
<td>75 ± 3</td>
<td>68 ± 2</td>
<td>64 ± 4</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>10/10</td>
<td>15/5</td>
<td>16/4</td>
<td>11/9</td>
</tr>
<tr>
<td>Pain medication†</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Normal &quot;tilt test&quot;</td>
<td>20</td>
<td>19</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>General/gynecologic</td>
<td>15</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>46 ± 4</td>
<td>43 ± 3</td>
<td>50 ± 4</td>
<td>48 ± 3</td>
</tr>
</tbody>
</table>

* Mean values ± SEM (or number of patients).
† Narcotic analgesics administered within 4 h of starting anesthesia.

3–5 min before induction. After preoxygenation, one of the following was rapidly infused intravenously with 1.5 mg/kg succinylcholine; 4 mg/kg thiopental, 1.5 mg/kg ketamine, 0.3 mg/kg midazolam, or a combination of 0.15 mg/kg midazolam and 0.75 mg/kg ketamine. Cricoid pressure was applied continuously from the start of the infusion until the endotracheal tube cuff was inflated in the trachea (80–100 s after administration of the induction agent). Mean arterial pressure (MAP) and heart rate (HR) were measured during induction and intubation, and at one-minute intervals thereafter until completion of the operation. Hemodynamic data recorded after obtaining baseline values were made immediately before direct laryngoscopy and immediately after inflation of the endotracheal tube cuff.

Induction was evaluated clinically by the anesthetist monitoring the patient in terms of smoothness, adequacy of anesthesia, and ease of intubation. After inflation of the endotracheal tube cuff, maintenance anesthesia was started and consisted of enflurane 1–2% inspired and nitrous oxide 70% in oxygen for all cases. The only adjuvant agents used were d-tubocurarine, pancuronium, and neostigmine/glycopyrrolate (if needed). In the recovery room, the patients were closely observed by a nurse-observer who was not aware of which induction agent was used, and the time to recovery, as well as any unusual behavior, were noted (Appendix 1). Recovery time was defined as the time from completion of the operation until the patient was able to respond appropriately to simple verbal commands. Standard psychological tests (e.g., Profile of Mood States assessment, Multi-Affect Adjective checklist, amnesia test) and a postoperative questionnaire (Appendix 2) were administered 1–2 h after the operation (at the time when the patient was judged fit for discharge from the recovery room). The initial phase of the antegrade amnesia testing consisted of showing the patient ten separate pictures of common objects which they were required to identify (the order of presentation was constant in all patients). Level of anxiety, orientation on awakening from anesthesia, pain requiring parenteral narcotic analgesics, and postoperative mood states were evaluated.

Twenty-four hours postoperatively, patients completed a questionnaire (Appendix 2) and follow-up amnesia test which consisted of showing the patient twenty-one pictures, eleven of which had been viewed the previous day (one preoperatively and ten in the recovery room), and the patient indicated which pictures they recognized (the order of viewing was constant for all patients).

The vein into which the induction agent was infused was reexamined by the same nurse-observer approximately 5–7 days postoperatively and any evidence of phlebitis was noted.

Data were analyzed as follows: continuous variables were analyzed using SPSS one-way analysis of variance and Duncan’s multiple range test (P < 0.05). Categorical variables were evaluated with SPSS chi-square analysis (P < 0.05).

Results

The four study groups were comparable with respect to demographic data (table 1). The average duration of the surgical procedures (47 ± 3 min) did not differ significantly among the four groups. Onset of anesthesia was rapid (<30 s) in most patients; however, it required more time (30–60 s) in about one-fourth of the cases when midazolam alone was used. Although induction was smooth in all cases, one patient in the midazolam group displayed signs of inadequate anesthesia and paralysis during direct laryngoscopy, contributing to a difficult intubation. None of the study patients vomited or aspired during induction, and there was no recall of the laryngoscopy or intubation.

The cardiovascular changes during induction (immediately before direct laryngoscopy) and intubation (immediately after inflating the endotracheal tube cuff) are summarized in table 2. Thiopental produced a significant decrease (11%) in MAP, while ketamine significantly increased (10%) MAP during induction. Neither midazolam nor the midazolam/ketamine combination significantly altered MAP during induction. The HR increased in all groups; however, the increase was significantly less following the combination. Both MAP and HR increased significantly in all groups following laryngoscopy and intubation, although the increase in
HR was significantly greater in the group which received ketamine alone. The change from baseline in the cardiovascular variables following extubation of the trachea was the same for all groups; ΔMAP ranged from −5% to −8% and ΔHR ranged from +2% to +4%.

Recovery time from anesthesia was significantly longer in the midazolam group (table 3). Patients who received thiopental required parenteral opiate analgesics more frequently than did patients in the other three groups. Thiopental was also the least effective amnestic agent and produced the highest incidence of postoperative depression of mood as judged by the patients and the observer (table 3). Ketamine, however, produced the highest incidence of postoperative disorientation. Over half of the patients receiving ketamine for induction dreamed, which included a 20% incidence of unpleasant dreams (two patients required parenteral sedative medication in the recovery room). Midazolam produced superior anxiolysis (i.e., decrease in state anxiety), without excessive postoperative depression or disorientation.

Midazolam was highly effective in producing amnesia during the early postoperative period. The midazolam-ketamine combination produced significantly less disorientation and dreaming (no unpleasant dreams were reported) than ketamine and less antegrade amnesia than midazolam.

Patient acceptance was high among all groups; however, the two patients in the ketamine group who experienced unpleasant dreams preferred to have a different anesthetic if they required surgery in the future. The overall incidence of postoperative phlebitis was 5% and did not differ significantly among the four groups. Similarly, other postoperative problems (e.g., nausea/vomiting 3%, confusion 4%, and dizziness 5%) did not differ among the study groups. Although midazolam and the midazolam-ketamine combination were significantly more effective in producing postoperative (antegrade) amnesia than either thiopental or ketamine, retrograde amnesia (i.e., inability to recall dollar bill) did not appear in any of the treatment groups.

**Discussion**

The availability of new intravenous anesthetics, higher patient acceptance, and concern over anesthetic gas pollution in the operating room have increased interest in intravenous induction agents. 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. Ketamine overcomes many of the disadvantages associated with thiopental; however, it produces significant cardiovascular stimulation and an unacceptably high incidence of emergence sequelae, including vivid dream-like experiences.

Benzodiazepines have been used to induce anesthesia when cardiovascular stability is critical. Unfortunately, currently available benzodiazepines are water-

### Table 2. Cardiovascular Effects Following Rapid Intravenous Administration for Induction of General Anesthesia*

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Baseline</th>
<th>Induction†</th>
<th>Induction‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAP (mmHg)</td>
<td>HR (BPM)</td>
<td>ΔMAP (%)</td>
</tr>
<tr>
<td>Thiopental</td>
<td>4.0</td>
<td>99 ± 4</td>
<td>104 ± 4</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1.3</td>
<td>97 ± 2</td>
<td>101 ± 3</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.3</td>
<td>95 ± 2</td>
<td>101 ± 4</td>
</tr>
<tr>
<td>Midazolam/Ketamine</td>
<td>0.15/0.75</td>
<td>97 ± 3</td>
<td>109 ± 5</td>
</tr>
</tbody>
</table>

* Values are means ± SEM.
† Values represent percentage change from baseline.
‡ Differed significantly from thiopental group, P < 0.05.

### Table 3. Post-anesthetic Effects Following Intravenous Administration for Induction of General Anesthesia*

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Recovery (min)</th>
<th>Pain (%)</th>
<th>Disoriented (%)</th>
<th>State Anxiety†</th>
<th>Antegrade Amnesia‡</th>
<th>Dreaming (%)</th>
<th>Depressed (%)</th>
<th>Preference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient</td>
<td>Observer</td>
</tr>
<tr>
<td>Thiopental</td>
<td>26 ± 2</td>
<td>95</td>
<td>10</td>
<td>1.3</td>
<td>8.5</td>
<td>15</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Ketamine</td>
<td>28 ± 2</td>
<td>60§</td>
<td>35§</td>
<td>1.4</td>
<td>7.5</td>
<td>55§</td>
<td>55</td>
<td>35§</td>
</tr>
<tr>
<td>Midazolam</td>
<td>44 ± 3§</td>
<td>65§</td>
<td>10</td>
<td>1.0§</td>
<td>2.9§</td>
<td>0§</td>
<td>10§</td>
<td>45§</td>
</tr>
<tr>
<td>Midazolam/Ketamine</td>
<td>33 ± 2</td>
<td>65§</td>
<td>15</td>
<td>1.2</td>
<td>5.0§</td>
<td>5</td>
<td>20§</td>
<td>60§</td>
</tr>
</tbody>
</table>

* Values are means ± SEM.
† Scaled score: 0 (none) to 10 (recall all ten objects).
§ Scaled score: 0 to 3 (extreme).
‡ Differed significantly from thiopental group (P < 0.05).
insoluble, with slow onsets 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 (t1/2β = 2–3 h) water-soluble benzodiazepine, similar to diazepam in its ability to depress the central nervous system,17 has been evaluated as an alternative to thiopental for inducing general anesthesia.6–8 Although adequate for the rapid sequence induction technique employed in this study, midazolam’s onset of action was slower than thiopental or ketamine. The major advantages of this short-acting benzodiazepine compared to thiopental as an induction agent include minimal cardiovascular depression, amnesia, and less postoperative depression of mood.

Midazolam was significantly more effective as an amnestic agent than the other drugs studied. On at least two occasions, the nurse-observer noted slight agitation during the recovery period in patients who had received midazolam for induction. When questioned, these two patients denied pain; however, they were “surprised to learn” that their operation had been completed. Both patients immediately settled down after empirical administration of narcotic analgesics. Amnesia regarding the surgical procedure may explain, in part, the surprisingly low percentage of patients (equal to that of ketamine) reporting moderate or severe pain in the recovery room.

The use of enflurane for maintenance of anesthesia would be expected to prolong recovery; however, the magnitude of this effect should be similar in all groups since a comparable number of MAC-hours were administered in each of the study groups. Unfortunately, when midazolam is given in doses adequate to induce general anesthesia, recovery can be prolonged significantly following brief surgical procedures8 and this may be further prolonged in the presence of volatile agents. Currently available benzodiazepines attenuate the cardiovascular stimulation and psychic emergence reactions produced by ketamine to varying degrees.18 Thus, the potential advantages of combining ketamine with midazolam (a benzodiazepine possessing a pharmacokinetic profile19 similar to that of ketamine20) led to this evaluation of the effectiveness of midazolam in attenuating the untoward side effects of ketamine. This study reveals that by combining midazolam with ketamine, an adequate anesthetic state can be rapidly achieved with minimal effects on the cardiovascular system and prompt recovery after surgery.

Since the “ideal” intravenous anesthetic is not yet available, combining two relatively short-acting intravenous drugs possessing mutually complementary pharmacologic properties is logical. Dose-response data for the combination are not available; thus, the optimum dosage mixture for midazolam and ketamine is not known. Although a lower dosage of ketamine was used in the midazolam–ketamine combination group, neither the degree of ketamine-induced cardiovascular stimulation nor the frequency of its emergence sequelae are strictly dose-related. Zsigmond and Domino†† have found the changes in heart rate and blood pressure after 0.5 mg/kg ketamine, iv, did not differ significantly from those produced after 1.5 mg/kg ketamine, iv. Similarly, the incidences of unpleasant dreams and emergence delirium after induction with 0.5 mg/kg ketamine, iv, were not significantly lower than those after 2.0 mg/kg ketamine, iv.21

Since midazolam effectively attenuated the cardiostimulatory response to ketamine and prevented unpleasant emergence sequela, it may be the benzodiazepine of choice as an adjunct to ketamine because of its water-solubility and short elimination half-life. Finally, the midazolam–ketamine combination provided a rapid and smooth induction of anesthesia, excellent hemodynamic stability, and a prompt recovery without postoperative complications. This combination offers significant advantages over either ketamine or midazolam alone for rapid intravenous induction of general anesthesia.

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References
9. McNair DM, Lorr M, Droppleman LF: Profile of Mood States. Education and Industrial Testing Service, P.O. Box 7234, San Diego, CA 92107

### APPENDIX 1.

The nurse-observer completed this form describing the patient's behavior in the recovery room.

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Rating Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALM</td>
<td>□ NO □ YES</td>
</tr>
<tr>
<td>AGITATED</td>
<td>□ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY</td>
</tr>
<tr>
<td>CONFUSED</td>
<td>□ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY</td>
</tr>
<tr>
<td>APPREHENSIVE</td>
<td>□ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY</td>
</tr>
<tr>
<td>SUSPICIOUS</td>
<td>□ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY</td>
</tr>
<tr>
<td>VIOLENT</td>
<td>□ NO □ YES</td>
</tr>
<tr>
<td>IRRATIONAL</td>
<td>□ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY</td>
</tr>
<tr>
<td>HALLUCINATING</td>
<td>□ NO □ YES</td>
</tr>
<tr>
<td>RESTLESS</td>
<td>□ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY</td>
</tr>
<tr>
<td>HOSTILE</td>
<td>□ NO □ YES</td>
</tr>
<tr>
<td>DEPRESSED</td>
<td>□ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY</td>
</tr>
<tr>
<td>EASILY UPSET</td>
<td>□ NO □ YES</td>
</tr>
<tr>
<td>EMOTIONALLY UNSTABLE</td>
<td>□ NO □ MILDLY □ MODERATELY □ EXTREMELY</td>
</tr>
<tr>
<td>DELIRIOUS</td>
<td>□ NO □ YES</td>
</tr>
<tr>
<td>RESENTFUL</td>
<td>□ NO □ MILDLY □ MODERATELY □ SEVERELY</td>
</tr>
<tr>
<td>PATIENT TOO DROWSY FOR VALID EVALUATION</td>
<td>□ NO □ YES</td>
</tr>
</tbody>
</table>
Appendix 2.
Postoperative questionnaire completed by the patient at the time of discharge from the recovery room and approximately twenty-four hours after surgery.

**DO YOU RECALL HAVING A DREAM LIKE EXPERIENCE DURING OR AFTER YOUR OPERATION?**
(Check one) □ NO □ YES

**IF YES, WAS IT UNPLEASANT?**
(Check one) □ NO □ YES □ UNABLE TO RECALL

**AFTER YOU WOKE UP FROM YOUR OPERATION:**

A. **DID YOU HAVE TROUBLE SEPARATING THE DREAM WORLD FROM REALITY?**
(Check one) □ NO □ YES

B. **WERE YOU AFRAID?**
(Check one) □ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY

C. **WERE YOU WORRIED?**
(Check one) □ NO □ SLIGHTLY □ MODERATELY □ EXTREMELY

**AFTER YOU WOKE UP FROM YOUR OPERATION DID ANYTHING BOther YOU?**
(Check one) □ NO □ YES  □ IF YES, SPECIFY

**HOW DID YOU FEEL?**
(Check one) □ DEPRESSED □ NORMAL □ GREAT

**WERE YOU IN PAIN?**
(Check one) □ NO □ YES

**DID YOU HAVE A HEADACHE?**
(Check one) □ NO □ YES

**WERE YOU LIGHtheADED?**
(Check one) □ NO □ YES

**DID THE ROOM SEEM TO BE SPINNING?**
(Check one) □ NO □ YES

**SINCE LEAVING THE RECOVERY ROOM HAVE YOU HAD ANY TROUBLE SEPARATING THE DREAM WORLD FROM REALITY?**
(Check one) □ NO □ YES

**IF YOU NEEDED ANOTHER OPERATION WOULD YOU WORRY?**
(Check one) □ NOT AT ALL □ SAME □ MORE WORRIED

**IF YOU NEEDED ANOTHER OPERATION WOULD YOU HAVE THE SAME ANESTHESIA?**
(Check one) □ NO □ YES □ DON'T KNOW