A Small Dose of Midazolam Decreases the Time to Achieve Hypnosis Without Delaying Emergence During Short-term Propofol Anesthesia

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Study Objective: To evaluate the effect of a small dose of midazolam (10 μg kg⁻¹) on induction and emergence during short-term propofol anesthesia and to investigate the effects of subsequent administration of flumazenil.

Design: Double-blinded, prospective, randomized study.

Setting: Operating room of a medical college hospital.

Patients: 30 male ASA physical status I and II patients (ages 51 to 75) scheduled for minor surgery under spinal anesthesia.

Interventions: Patients were randomly allocated to one of three groups: the placebo-propofol-placebo (PP) group, the midazolam-propofol-placebo (MP) group, or the midazolam-propofol-flumazenil (MF) group. After administering placebo or midazolam (10 μg kg⁻¹), propofol 250 μg kg⁻¹ min⁻¹ was infused. Immediately after confirming that the patient was hypnotized, we terminated the propofol infusion and administered placebo or flumazenil (5 μg kg⁻¹).

Measurements: The dose and the times required to achieve hypnosis (the first endpoint) and to emerge from anesthesia (the second endpoint). The plasma concentration at each endpoint was determined.

Main Results: Midazolam significantly decreased the dose and time needed to achieve hypnosis (PP vs. MP, 66 ± 14 vs. 48 ± 15 mg, 260 ± 55 vs. 179 ± 44 sec, respectively (mean ± SD)). Thus, the plasma concentration of propofol at hypnosis was significantly lower (PP vs. MP, 3.31 ± 0.78 vs. 2.41 ± 0.57 μg mL⁻¹). The time to emerge from anesthesia was not prolonged by midazolam, and was further shortened by administration of flumazenil (PP, MP vs. MF, 237 ± 77, 207 ± 71 s vs. 126 ± 56 sec, respectively). Flumazenil also reversed the reduction in propofol concentration induced by midazolam at emergence (PP, MP, and MF, 0.54 ± 0.17, 0.37 ± 0.15, and 0.59 ± 0.22 μg mL⁻¹, respectively).

Conclusions: Coadministration of 10 μg kg⁻¹ midazolam decreases the dose and time required to achieve hypnosis with propofol induction without delaying emergence from anesthesia. Additional administration of flumazenil further shortens the time to emerge from midazolam-propofol anesthesia. © 2001 by Elsevier Science Inc.
Keywords: Drug interactions, emergence, flumazenil, hypnosis, midazolam, propofol.

Introduction

Propofol is widely used for general anesthesia and sedation. Its characteristic ability to induce the rapid onset of, and clear emergence from, anesthesia makes it suitable for both induction and maintenance of clinical anesthesia. However, an overdose of propofol can prolong emergence from anesthesia. An anesthesiologist is sometimes required to perform a brief anesthetic induction followed by a rapid emergence for minor procedures such as minor ambulatory surgery or examinations. Some physicians perform many procedures a day, and it is actually important to shorten the time used for anesthesia, even if only by a small amount. Midazolam, which is a benzodiazepine tranquilizer, is reported to show a synergistic effect when co-administered with propofol. Thus, we expect that the administration of a small dose of midazolam at the induction of propofol anesthesia might reduce the required propofol dose and the time for induction. Midazolam premedication was reported to increase sedation without taking any medication at the beginning of this study. However, an overdose of propofol can prolong emergence from anesthesia. Anesthesiologists sometimes report the rapid emergence for minor procedures such as minor surgery. Midazolam is closely related to propofol anesthesia. Both midazolam and propofol are benzodiazepine derivatives, and the two drugs compete for benzodiazepine receptor binding sites. We also administered flumazenil to investigate its reversible effects on emergence and evaluate whether the effect of midazolam was present at emergence.

Materials and Methods

After obtaining approval from the National Defense Medical College Ethics Committee of Departments and written informed consent from each patient, we recruited patients for this prospective, double-blinded study. All participants were scheduled for minor urological surgery with spinal anesthesia. The patients were ASA I and II males, ages 51–75, and weighing 47 to 80 kg. The sample size was determined using the results of our previous investigation. We sequentially randomized the patients into three groups: a placebo-propofol-placebo (PP) group, a midazolam-propofol-placebo (MP) group, and a midazolam-propofol-flumazenil (MF) group. None of the patients studied had any psychological problems or were taking any medication at the beginning of this study.

Standard monitors including continuous electrocardiography (ECG), heart rate (HR), noninvasive arterial blood pressure (BP), and pulse oximetry were applied immediately after the patient entered the operating room (OR). Without any premedication, the patients received spinal anesthesia while placed in the lateral position. A 25-gauge spinal needle was inserted and 2.0 to 2.3 mL of 0.5% dibucaine solution was injected at the L3–L4 interspace. Then patients were turned to the supine position and the degree of analgesia at the level of S10–Th10 was confirmed. Oxygen was administered at a rate of 3 L min⁻¹ via facemask.

After BP, HR, and analgesic level were stabilized, patients in the PP group received 2 mL of saline, whereas patients in the MP and MF groups received 10 μg kg⁻¹ of midazolam. Subsequently, all patients received propofol at 250 μg kg⁻¹ min⁻¹ with Ringer’s acetate solution at 20 mL min⁻¹ through an antecubital venous catheter using an infusion pump (Terufusion, Terumo, Tokyo, Japan). The anesthesiologist in charge was blinded as to which drugs, except for propofol, were administered to the patient. Complete hypnosis was defined as failure to open the eyes in response to a verbal command with light stimuli (tactile) by the anesthesiologist in charge. Each patient’s response was evaluated every 10 seconds, and the dose and time for achieving hypnosis were measured.

Immediately after achieving the endpoint for hypnosis, we discontinued the propofol infusion, and a 2-mL venous blood sample was withdrawn from the left dorsal pedal vein. Then, the surgical procedure was started, and 2 mL of saline was administered to patients in the PP and MP groups, and 5 μg kg⁻¹ of flumazenil was given to the MF patients. The time of emergence from hypnosis was determined by noting the first response to the verbal command and stimulus described above. The command and stimulus were repeated every 10 seconds until a response was observed. At the emergence endpoint, a 2-mL blood sample was collected from each patient. When the operation needed to be continued at emergence from anesthesia, propofol was immediately readministered at the dose designated for the operation.

The blood samples were centrifuged for 15 minutes at 3,500 rpm, and the plasma was stored frozen until it could be assayed. The concentration of propofol was determined using a high-performance liquid chromatograph with fluorescence detection. Analysis of variance was used to evaluate differences in mean values among groups. Significant differences (p < 0.05) were further explored using the Newman-Keuls multiple comparison posthoc test. Post hoc power analysis was performed and the power value greater than 0.8 was considered sufficient to reject the null hypothesis when it was false. All calculations were performed using a statistical software package (NCSS 2000, Number Cruncher Statistical Systems, Kaysville, UT).

Results

There were no significant differences in background parameters (age, weight, and height) among the three treatment groups (Table 1). In the PP group, the mean dose was higher, the time to achieve hypnosis was longer, and the propofol plasma concentration at the endpoint was higher than in the MP or MF groups (Table 2). At the time of emergence from hypnosis, the mean time required for recovery was significantly shorter in the MF group than in the PP or MP groups. There was no significant difference between the PP and MP groups in emergence times. The time from the
start of induction to emergence was significantly different among the three groups. The plasma concentration of propofol was significantly lower in the MP group at emergence. The post-hoc power analysis showed that the power values were above 0.8 for all results except the plasma concentration of propofol at emergence (that power value was 0.66).

Blood pressure and HR showed no statistically significant differences among the three groups at any time point. Oxygen saturation (SpO₂) under 95% as measured by pulse oximetry was not observed in any of the patients.

### Discussion

The aim of this investigation was to evaluate the effect of a small dose of midazolam, a synergistic benzodiazepine derivative, on the propofol dose and the times required for hypnosis and emergence. This study clearly showed that 10 μg kg⁻¹ midazolam decreased the necessary propofol dose and the time to achieve hypnosis without unpleasantly prolonging the time to emergence. The dose and time for hypnosis were significantly decreased by approximately 30%. The administration of flumazenil produced more rapid emergence from midazolam-propofol anesthesia.

In our previous investigation, a midazolam dose of 20 μg kg⁻¹ decreased the hypnotic dose of propofol at anesthesia induction.6 In the present investigation, we reduced the dose of midazolam to 10 μg kg⁻¹ to avoid a prolongation of emergence, and found significant decreases in the dose of propofol needed and the time for achieving hypnosis. Oxorn et al.11 administered midazolam at 30 μg kg⁻¹, a dose threefold higher than ours, immediately before the induction of propofol anesthesia, and they found no decrease in the hypnotic dose of propofol. Since propofol is known to induce anesthesia in an infusion-rate dependent manner,12,13 the slow-rate infusion may gradually increase propofol concentration. Indeed, the infusion rate of the present investigation might prove a suitable method for evaluating the drug interaction between a small dose of midazolam and propofol.6 The degree of the reduction in hypnotic dose of propofol was similar to the result of our previous investigation, despite the fact that the dose of midazolam was reduced. The differences of patients’ background and the anesthetic methods might have an effect on the results.

The time necessary to emerge from anesthesia was not prolonged by co-administration of midazolam in this study. This result was consistent with that of Richardson et al.7 or Fredman et al.8 but inconsistent with that of Bevan et al.9 The plasma concentration of propofol at the end of emergence was significantly lower in the MP group than in the PP or MF groups. In addition, administration of flumazenil might accelerate emergence from midazolam-propofol anesthesia. Although the additive effect of midazolam on propofol hypnosis was shown in the recovery phase, the time to emergence was not prolonged. Thus, the reduced dose of propofol that is necessary when co-administering midazolam might account for the faster emergence.14 Administering flumazenil further decreased the total procedure time by reversing the concentration threshold of propofol for emergence. However, flumazenil, which is a benzodiazepine antagonist, is expensive.

### Table 1. Demographic Details

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Age (yrs)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP (placebo-propofol-placebo)</td>
<td>10</td>
<td>65.3 ± 6.6</td>
<td>60.2 ± 6.4</td>
<td>161.3 ± 5.2</td>
</tr>
<tr>
<td>MP (midazolam-propofol-placebo)</td>
<td>10</td>
<td>65.1 ± 6.3</td>
<td>61.5 ± 9.1</td>
<td>161.9 ± 7.9</td>
</tr>
<tr>
<td>MF (midazolam-propofol-flumazenil)</td>
<td>10</td>
<td>66.2 ± 5.1</td>
<td>62.3 ± 8.3</td>
<td>163.1 ± 5.9</td>
</tr>
</tbody>
</table>

Note: Age, height, and weight of patients are expressed as means ± S.D. There was no statistically significant differences among the patient groups.

### Table 2. Dose and Time to Achieve Hypnosis and Emergence, and Plasma Concentration of Propofol

<table>
<thead>
<tr>
<th></th>
<th>Required Dose (mg)</th>
<th>Required Time (sec)</th>
<th>Concentration of Propofol (μg mL⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For Hypnosis</td>
<td>To Hypnosis</td>
<td>To Emergence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>262 ± 53</td>
<td>240 ± 75</td>
</tr>
<tr>
<td>PP (placebo-propofol-placebo)</td>
<td>66 ± 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP (midazolam-propofol-placebo)</td>
<td>48 ± 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF (midazolam-propofol-flumazenil)</td>
<td>52 ± 10</td>
<td>188 ± 31</td>
<td>125 ± 54</td>
</tr>
</tbody>
</table>

Note: Data are expressed as means ± S.D. *

* Statistical significance among groups (p < 0.05).
and its cost-effectiveness should be weighed in the clinical setting.

We administered propofol to patients using a low-rate, fixed infusion protocol instead of target-controlled infusion techniques. Although use of a low-rate, fixed infusion of propofol may not achieve the rapid induction desired in the typical clinical setting, in some cases, anesthesiologists may administer a drug incrementally until the required clinical effect appears, thus avoiding inappropriate drug administration. Surgeons performing an operation prefer to start the procedure after confirming hypnosis, and they desire quick emergence from anesthesia immediately after the end of the surgery. In this study, midazolam administration shortened the entire duration of the procedure with the use of a low-rate infusion.

The limitations of our experimental design should be addressed. We only studied patients under spinal anesthesia, but local anesthetics may affect hypnosis. Another limitation was that the participants were all male and were relatively elder patients. Gan et al. reported that women emerge from general anesthesia faster than men do. The population used here, however, might be more sensitive to the effects of treatment than would another population consisting of both genders, or of various aged patients. We determined the sample size using the result of our previous investigation by limiting the gender and age of our study patients. Power analysis demonstrated reliability of the results in spite of the study’s small sample size. Statistical analysis using age as a covariant was performed. However, age was not a significant parameter for all analysis of covariance in the population of the present investigation.

In summary, we demonstrated that a small dose of midazolam, 10 μg kg⁻¹, decreased the necessary hypnotic dose of propofol and the time to achieve hypnosis without prolonging the time to emergence. In patients given spinal anesthesia, additional flumazenil administration accelerated the reversal of midazolam’s effects on propofol hypnosis. The combination of a small dose of midazolam and propofol may be a useful technique for minor ambulatory surgery or examinations.

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References