Use of Midazolam Infusion for Sedation following Cardiac Surgery

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A major challenge after cardiac surgery is to provide adequate sedation, analgesia, and hemodynamic stability without prolonging recovery time. Determining the optimal dose of sedative or analgesic medication after cardiac surgery is difficult because the presence of an endotracheal tube and residual neuromuscular blockade complicate efforts to communicate with the patient. The physiologic response to pain includes an increase in sympathetic activity (with tachycardia, hypertension, and increased systemic vascular resistance), which can

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increase myocardial oxygen demand with resultant ischemia. Although sedation and analgesia are important following aorto-coronary bypass surgery, there is no consensus regarding the ideal technique. Intermittent intravenous bolus injections of diazepam and morphine have been used for this purpose. However, diazepam is not ideally suited for use in this situation because it is a veno-irritant with a long elimination half-life (30–90 h). Desmethyl diazepam, its principal metabolite, has an even longer elimination half-life. Midazolam (Versed®) is a water-soluble benzodiazepine with a shorter elimination half-life than diazepam (2–4 h).

This study was designed to evaluate the pharmacokinetics of a constant infusion of midazolam when used for sedation following aorto-coronary bypass surgery. In addition, we determined the effects of two different stable levels of midazolam on the postoperative narcotic requirement, the need for vasoactive drugs, and emergence times.

METHODS

Twenty-seven consenting adults scheduled for elective myocardial revascularization were assigned to one of three treatment groups in a randomized double-blind fashion. For postoperative sedation, the patients received an infusion of either normal saline (group I—control), midazolam 1 mg/ml (group II), or midazolam 2 mg/ml (group III). The protocol was approved by the Institutional Committee for Research on Human Subjects. Criteria for exclusion included significant hepatic, renal, or adrenal dysfunction, history of drug abuse, sensitivity or allergy to benzodiazepines, and use of an intravenous balloon pump.

All patients received a similar narcotic-based anesthetic consisting of a standard premedication (i.e., morphine sulfate 9–10 mg and scopolamine 0.2–0.3 mg im) followed by induction of anesthesia with fentanyl (or sufentanil), thiopental (or etomidate), and pancuronium iv. Maintenance of anesthesia consisted of fentanyl (or sufentanil) supplemented with nitrous oxide and enflurane (or isoflurane). A nitroglycerin infusion, 0.5–1.0 μg·kg⁻¹·min⁻¹, was started after the cardiopulmonary bypass (CPB) period on all patients. The nitroglycerin infusion was adjusted to maintain hemodynamic stability during the post-bypass period, and was discontinued at the end of the operation. Three patients also received low-dose dopamine (1–3 μg·kg⁻¹·min⁻¹) after CPB.

After surgery, patients were transferred to the ICU, and ventilation was controlled with synchronous intermittent mandatory ventilation. Each patient was given a 2 ml loading dose of the assigned solution, followed by a maintenance infusion of 1 ml/h for 8 h using a syringe pump. Blood samples were drawn before the initial (loading) dose, and then every 2 h for the first 12 postoperative hours. Morphine sulfate, 1–2 mg iv, was administered to control pain and agitation by the nursing personnel using subjective criteria. Grimacing, restlessness, and excessive autonomic activity were the most common reasons for administering additional analgesic medication. No other sedative-hypnotic or analgesic drugs were administered.

Heart rate and arterial blood pressure were monitored continuously. Mean arterial pressure (MAP) was maintained between 70–90 mmHg with an infusion of sodium nitroprusside. If the MAP could not be controlled with sodium nitroprusside at a maximal rate of 4 μg·kg⁻¹·min⁻¹ (e.g., widened pulse pressure, tachycardia), an infusion of trimetaphan camyslate was added. Total dosages of morphine sulfate, sodium nitroprusside, trimetaphan camyslate, and dopamine were noted at hourly intervals. Dopamine was the only inotropic agent used during the perioperative period.

Recovery time was assessed every 30 min for first body movement, eye opening, response to verbal commands, and onset of spontaneous ventilation. Arterial carbon dioxide tension (PaCO₂) was noted at the onset of spontaneous ventilation. The criteria used to determine the patient’s suitability for extubation included: 1) responsiveness to verbal commands, 2) respiratory rate > 8 bpm with a tidal volume > 7 ml/kg and a vital capacity > 15 ml/kg, 3) minimum inspiratory pressure of ~20 cm H₂O, 4) PaCO₂ < 45 and PaO₂ > 80 mmHg after 30 min on CPAP with a FIO₂ ≤ 0.4, and 5) no evidence of cardiopulmonary instability.

Serum samples were assayed for midazolam using a Hewlett-Packard® Model 5700A gas chromatograph with an electron capture detector (15 mCi 63Ni source). The extraction procedure described by Greenblatt et al. was used, with an extraction efficiency of 95 ± 2%. The standard curve based on peak height ratio of midazolam to internal standard (Ro 7-9749) was linear from 2.5–100 ng. The variability of the midazolam assay using standardized serum samples was ±5%. A stable ("steady-state") midazolam level was determined for each patient by averaging the concentrations during the maintenance infusion period (2–8 h). Clearance rate values (ml/min) were calculated by dividing the infusion rate (μg/min) by the averaged midazolam level (μg/ml) for each individual patient.

Data were analyzed using one-way analysis of variance, Chi-square analysis, and the Bonferroni test (mean values ± SEM), with P < 0.05 considered statistically significant. The correlation between the morphine requirement and the serum midazolam level was assessed using a standard linear regression analysis.
RESULTS

The three treatment groups were comparable with respect to demographic data and anesthetic technique (table 1). Postoperative requirement for morphine sulfate, trimethaphan camsylate, and sodium nitroprusside are summarized in table 2. The two midazolam treatment groups required significantly less morphine than the control group. No patient in the high-dose midazolam group (group III) required trimethaphan camsylate, although it was required by two patients in group I and four patients in group II. All patients except one in group III required nitroprusside during the early postoperative period. Dopamine was started intraoperatively in three patients in the midazolam groups, and did not have to be increased postoperatively in order to maintain hemodynamic stability. Overall, the requirement for vasoactive drugs during the postoperative period in the two midazolam-treated groups did not differ significantly from the control group. However, the high-dose midazolam group required significantly less vasodilators than the low-dose midazolam group.

Recovery times (as determined by first movement, eye opening, response to commands, and onset of spontaneous ventilation) were prolonged in the midazolam groups as compared to the control group (table 3). Although two different dosages of midazolam were administered, there were no significant differences between these two groups with respect to recovery times. $P_{aCO_2}$ values did not differ significantly among the three groups at the onset of spontaneous ventilation (average $P_{aCO_2}$ equalled 42 ± 6 mmHg). There was no significant difference in the mean time to tracheal extubation (range: 16.2–19.4 h) or the duration of the ICU stay (range: 1.5–2 days) among the three study groups.

Stable serum levels of midazolam were achieved in both midazolam groups (fig. 1). Mean midazolam concentrations during the constant infusion period in group II were 40 ± 6 ng/ml and in group III were 82 ± 4 ng/ml (table 4). Mean levels for individual patients during the 2–8-h infusion period ranged from 30–78 ng/ml in group II (1 mg/h) and from 56–95 ng/ml in group III (2 mg/h). Clearance rates for midazolam were similar in both groups (table 4), with midazolam levels decreasing rapidly following discontinuation of the infusion (fig. 2). For individual patients, there was no correlation between the morphine requirement and the averaged (“steady-state”) midazolam level (fig. 3).

DISCUSSION

An ideal pharmacologic regimen for the postoperative cardiac patient would provide sedation, anxiolysis, and analgesia without producing cardiovascular or respiratory depression. The variety of drugs and techniques used for sedation in the ICU attests to the absence of an ideal drug (or combination of drugs) for patients requiring mechanical ventilation during the postoperative period.6 The use of intravenous infusions has been recommended in the ICU environment because of the enhanced ability to titrate rapid and short-acting sedative and analgesic drugs to produce the desired effect.7–9 We have recently demonstrated that midazolam infusion can provide safe and effective sedation in critically ill patients.7

Our data demonstrate that infusion of midazolam results in a significant decrease in the total morphine dosage requirement. However, postoperative emergence may have been prolonged as a result of residual midazolam-induced sedation. The reported threshold at which midazolam produces a sedative effect is between 30 and 90 ng/ml.10 Both infusion rates produced midazolam serum levels in this range. Interestingly, the postoperative morphine requirement was essentially the same in the two midazolam treatment groups, even though group III received twice as much midazolam as

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (Control)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59 ± 3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86 ± 4</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/1</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>89 ± 6</td>
</tr>
<tr>
<td>Aortic cross clamp (min)</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>289 ± 19</td>
</tr>
<tr>
<td>Sufentanil (µg)</td>
<td>2500 ± 243</td>
</tr>
<tr>
<td>Fentanyl (µg)</td>
<td>5/9</td>
</tr>
</tbody>
</table>

Mean values ± SEM.

TABLE 2. Total Drug Dosages During 8-h Study Period following Coronary Artery Bypass Graft Surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Midazolam (mg)</th>
<th>Morphine (mg)</th>
<th>Nitroprusside (µg/kg)</th>
<th>Trimethaphan (µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>25.3 ± 3.9</td>
<td>0.45 ± 0.10</td>
<td>0.38 ± 0.30</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>11.6 ± 2.3*</td>
<td>0.60 ± 0.13</td>
<td>0.98 ± 0.46</td>
</tr>
<tr>
<td>III</td>
<td>20</td>
<td>10.0 ± 2.2*</td>
<td>0.23 ± 0.06†</td>
<td>0 ± 0†</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

* Significantly different from placebo (group I), P < 0.05.
† Significantly different from group II, P < 0.05.
group II. The absence of a dose-effect relationship with respect to the morphine requirement may relate to the subjective criteria used to determine the need for additional opioid analgesic medication in the ICU setting. In addition, we believe that patients in group II may have been relatively "undermedicated" with morphine, and the resultant pain may have contributed to an increase in the postoperative requirement for vasodilating drugs. Since benzodiazepines do not possess analgesic activity, these data may indicate a minimum opiate requirement for pain control. Fragen and Tobin report a minimum morphine dose (0.1 mg/kg bolus) needed for pain control when used in combination with midazolam (0.05 mg/kg bolus). They found that midazolam and a lower morphine dose (0.05 mg/kg bolus) did not provide adequate pain relief.

Patients receiving the higher infusion rate of midazolam (2 mg/h) required less vasodilator therapy for blood pressure control (compared to group II), which may have been related to an increased level of sedation. Alternatively, this effect may be a result of the vasodilating action produced by midazolam itself.12 Midazolam decreases arterial blood pressure and systemic vascular resistance to a similar (or greater) extent than diazepam. However, when small doses of midazolam (0.05 mg/kg) were administered to patients with coronary artery disease,13 significant depression of the cardiovascular system did not result. Similarly, effective sedation of critically ill patients with a midazolam infusion was not associated with cardiovascular instability.7

Lowry et al.14 reported a lack of accumulation and a short duration of action of midazolam when repeated bolus doses were administered for sedation after cardiopulmonary bypass surgery. In their study, large peak-to-trough differences were seen in midazolam levels with the intermittent bolus technique. Although significant variability was noted among patients (fig. 1), our data demonstrate reasonably linear pharmacokinetics over the 1–2-mg/h dosage range (table 4). However, there is a report of midazolam accumulation after repeated doses in a critically ill ICU patient.15 Our study would indicate that it is possible to achieve reasonably stable plasma concentrations during an 8-h postoperative infusion period (fig. 1). In addition, midazolam concentrations decreased to half of their stable levels within 2–5 h of discontinuing the infusion (fig. 2), consistent with the elimination half-life values reported in the literature.5,10 However, the usual short elimination half-life of midazolam may be prolonged with advancing age and following major operative procedures.16

In our study, the hepatic clearance rate of midazolam after cardiopulmonary bypass was not significantly different from values previously reported for healthy volunteers.5,10 However, our estimate of midazolam clearance is dependent upon achieving stable ("steady-state") levels during the infusion period. Since redistribution of midazolam from the vessel-rich tissues (e.g., brain) to lean muscle and fat during the constant infusion period would lead to an overestimation of midazolam's clearance value, the actual hepatic clearance rate after cardiac surgery may be less than we reported (table 4).

![Serum midazolam concentrations during the 8-h infusion and 4-h post-infusion periods. Individual patient midazolam levels during and after a 1 mg/h (C) or 2 mg/h (O) infusion are shown. Large open circles represent the mean midazolam levels ±SEM at the 1 mg/h infusion rate, while the large closed circles represent the mean values at the 2 mg/h infusion rate.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931384/)
TABLE 4. Plasma Midazolam Levels during the Maintenance Infusion and Calculated Clearance Rate Values

<table>
<thead>
<tr>
<th>Group</th>
<th>Maintenance Infusion Rate (mg/h)</th>
<th>&quot;Steady-state&quot; Level (mg·ml⁻¹)</th>
<th>Clearance Rate (ml·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (±SEM)</td>
<td>Range</td>
<td>Mean (±SEM)</td>
</tr>
<tr>
<td>Group II</td>
<td>1.0</td>
<td>40 ± 6</td>
<td>30–78</td>
</tr>
<tr>
<td>Group III</td>
<td>2.0</td>
<td>82 ± 4</td>
<td>50–95</td>
</tr>
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</table>

A properly conducted dose-response study should clearly define the clinically effective dosage and serum concentration ranges. In an unpublished study involving 18 patients undergoing elective aortocoronary bypass surgery at our institution, a variable-rate midazolam infusion was titrated to produce adequate sedation. During the first 8 postoperative hours, the average dosage requirement of midazolam was 11 mg, with a range between 7 and 15 mg. Thus, it is quite possible that a lower infusion rate (e.g., 0.5 mg/h) or a carefully titrated, variable-rate infusion could produce adequate sedation without delaying recovery. Unfortunately, in the latter situation, it can be extremely difficult to determine whether to administer additional sedative (midazolam) or analgesic (morphine) medication.

The major limitations in the design of this study resulted from our efforts to obtain relevant clinical data in an environment consistent with clinical practice. One such problem was related to the use of highly subjective endpoints to assess recovery after discontinuing the sedative infusions. For example, an attempt was made to extubate the trachea when specific criteria were achieved (see Methods); however, on occasion, patients meeting these criteria did not undergo extubation because the house officer was not immediately available. Furthermore, the morphine dosing intervals were left to the discretion of the nursing/house staff, and the results would suggest that the low-dose midazolam group (group II) may not have received a comparable amount of pain-relieving medication (table 2). Although all three treatment groups received comparable doses of opioid analgesics during the operation (table 1), the residual analgesic effects of these drugs would also be expected to influence the postoperative narcotic requirement. An attempt was made to maintain a similar degree of sedation and analgesia; however, our ability to achieve this endpoint depended on the clinical condition of the patient and the subjective evaluation of the nursing staff involved in each patient’s care.

In summary, midazolam infusion produced stable serum levels which decreased rapidly following discontinuation of the infusion. We found that the infusion of midazolam decreased the total narcotic dosage requirement, while prolonging emergence times. Although midazolam was rapidly eliminated and did not prolong the ICU or hospital stay, the decision to use a benzodiazepine for postoperative sedation depends on whether the potential prolongation of the time to awakening and establishment of spontaneous ventilation is considered.

FIG. 2. Changes in individual patient serum midazolam concentrations (ng/ml) following discontinuation of the midazolam infusion (○ = 1 mg/h; ● = 2 mg/h).
to be offset by the other beneficial effects of the drug (e.g., anxiolysis, sedation, amnesia).

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Regional Anesthesia in a Child with Epidermolysis Bullosa

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Epidermolysis bullosa (EB) is an hereditary disorder with dominant and recessive modes of genetic transmission.1 It is characterized by bullous formation in stratified squamous epithelium that can result in blistering, fusion, and scarring of the lips, oropharyngeal structures, and esophagus. The oropharyngeal involvement may make airway manipulation hazardous during general anesthesia. The use of regional anesthesia in a patient with EB, undergoing correction of syndactyly, is described.

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