Supplementation by Continuous Infusion for Ambulatory Surgical Procedures

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Many surgical procedures in ambulatory patients are performed under regional anesthesia or local anesthesia with monitored anesthesia care. Half of the anesthetic effect is derived from the local anesthetic agent and the other half from the supplemental medications that are given to increase patient comfort. Two drugs widely used for supplementation by infusion are midazolam and alfentanil.

Sedation

Midazolam is a benzodiazepine that probably is the most commonly used intravenous (IV) sedative. The redistribution half-life of midazolam is approximately 15 minutes and the elimination half-life is approximately 2.0 to 2.5 hours in healthy adults. For short surgical procedures, midazolam may be given for supplementation using incremental bolus doses. Doses for sedation may be administered in increments of 1 to 2 mg, to a total dose of 0.07 to 0.15 mg/kg or about 4 to 10 mg for a 70-kg adult. Onset of significant sedative effect is within two to three minutes, which is consistently more rapid than with the older benzodiazepine, diazepam.

When midazolam is used for sedation, there is a large interindividual variability in the dose-response relationship. Magni and associates studied patients who received 75 to 100 μg/kg of midazolam during upper gastrointestinal endoscopy, and reported that the clinical responses ranged from mild sedation to complete sleep.

Midazolam has a high patient acceptance. Reinhart and colleagues studied patients undergoing spinal anesthesia who were given midazolam or diazepam and then asked to assess their own sedation. After midazolam 0.1 mg/kg, 81% of the patients assessed their sedation as very good and 15% as good. After diazepam 0.2 mg/kg, 4% rated their sedation as very good, 20% as good, and 40% as sufficient. For comparison, 65% of patients who received saline placebo also assessed their sedation as sufficient (Table 1). Hanno and Wein provided benzodiazepine sedation to equivalent clinical endpoints during cystoscopy under local anesthesia. All patients given 0.12 mg/kg midazolam rated their sedation as excellent, whereas after 0.14 mg/kg diazepam, only 30% rated their sedation as excellent and 65% as good to fair.

Amnestic Effects

Another clinical property of midazolam is its ability to generate amnesia. After 5 mg of IV midazolam, the peak effect is seen at three minutes, with significant amnesia lasting 20 to 30 minutes. At peak effect, 67% of the patients experienced total amnesia and 93% experienced at least partial amnesia for picture recall.

When compared with diazepam, midazolam causes a higher incidence of amnesia at equivalent sedative endpoints. In the study by Hanno and Wein, the patients who received midazolam showed total anterograde amnesia for both the introduction and withdrawal of the cystoscope, whereas recall was 80% and 70%, respectively, with diazepam. These differences in amnesia persisted during the two hours of recovery studied.

Midazolam also causes more complete amnesia than does diazepam. Magni and associates sedated patients undergoing endoscopy with either midazolam or diazepam. Among the patients who had amnesia after midazolam, 80% had total amnesia, whereas among the patients who had amnesia after diazepam, only
Table I. Patient self-assessment of sedation after midazolam (0.1 mg/kg), diazepam (0.2 mg/kg), or placebo (0.9% NaCl).*

<table>
<thead>
<tr>
<th>Degree of Sedation</th>
<th>Midazolam</th>
<th>Diazepam</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Very good</td>
<td>81</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Good</td>
<td>15</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Sufficient</td>
<td>0</td>
<td>40</td>
<td>65</td>
</tr>
<tr>
<td>Insufficient</td>
<td>4</td>
<td>36</td>
<td>35</td>
</tr>
</tbody>
</table>

*Data from Reinhart et al.*

33% had total amnesia. The authors also were able to demonstrate that with midazolam, complete amnesia can occur without deep sedation. Among the patients who showed total amnesia after midazolam, about one third were asleep, but one third were moderately sedated and one third were drowsy. With midazolam, the sedative and amnestic benzodiazepine effects are separated.

**Recovery Times**

An important aspect of a drug's clinical utility is the rapidity of recovery from its effects. This recovery is faster with midazolam than with diazepam. Three hours after surgery under heavy benzodiazepine sedation, five of ten patients who had received midazolam, but one of ten who had received diazepam were completely awake.

Barclay and colleagues looked at patients' sleep patterns at home after sedation with midazolam or diazepam for oral surgery. Fewer patients who had received midazolam reported residual sleepiness either the afternoon or the night after surgery. In another study of oral surgical patients by Barker and associates, each patient received either midazolam or diazepam at one treatment session, and received the other at the next session. Patients assessed their recovery, and reported that their ability to work on the day after surgery was the same with both sedatives. However, significantly more patients reported being able to drive the day after midazolam sedation than after diazepam ($P<0.05$).

**Sedative Dose-Responses**

There is, in general, a separation of benzodiazepine effects with increasing doses, and this order is different for different benzodiazepines. For midazolam, a low dose causes anxiolysis and slight sedation. Increasing the dose produces amnesia and intense sedation; a high dose is required to produce sleep. Administration of the benzodiazepine antagonist flumazenil reverses the effects of midazolam in the order opposite to that of appearance, so that low doses of flumazenil reverse sleep, whereas high doses are needed to reverse slight sedation.

This separation of effects has been shown to correlate with different blood midazolam concentrations. Persson and associates studied clinical responses during recovery from midazolam infusion. At blood midazolam concentrations of 200 to 150 ng/ml, patients were arousable; at 150 to 100 ng/ml, patients were drowsy; and at 100 to 75 ng/ml, patients were awake (Figure 1). Interestingly, the range of blood midazolam concentrations associated with amnesia overlapped the concentrations seen not only when patients were drowsy, but also when they appeared to be awake. With the separation of effects by concentration, we can titrate a steady infusion level to achieve the desired clinical effects, individualized to each patient. Midazolam can, therefore, be administered by infusion to provide supplementation for ambulatory surgical procedures.

To administer midazolam by infusion, the proper technique consists of giving both a loading dose, to reach the desired concentration rapidly, and a maintenance infusion. Determinants of the total midazolam dose include the level of sedation desired, the presence of other drugs such as opioids or analgesia from a regional block, and the level of concurrent surgical stimulation. It is important to titrate the infusion rate down whenever clinically appropri-
FIGURE 1. Clinical responses at various blood midazolam concentrations. (Reprinted, with permission, from Persson et al.\textsuperscript{10})

ate, and, if deeper sedation is chosen, to terminate the infusion before the end of the procedure to enhance recovery.\textsuperscript{11}

**Sedation Levels**

The levels of sedation must be defined before comparing drug doses. A convenient scoring system has been suggested by Wilson and associates.\textsuperscript{12} A score of 1 is given to the patient who is fully awake and oriented; 2 to the patient who is drowsy; 3 if eyes are closed, but the patient is arousable to verbal command; and 4 if eyes are closed, but the patient is arousable with mild physical stimulation. The authors\textsuperscript{12} also list a score of 5, at which the patient is unarousable to mild physical stimulation, but many practitioners would describe this as light general anesthesia (Table II).

The range of midazolam doses that have been reported may reflect the level of sedation desired under differing circumstances. Our sedation goals were patients who were drowsy, but who would respond easily to verbal stimuli (Wilson level 2). To achieve these goals, we supplemented local and regional anesthesia with an initial IV dose of midazolam totalling from 1 to 5 mg. Most patients required 3 to 5 mg; the very low doses were given to elderly patients.\textsuperscript{13} The infusion rate ranged from 1 to 5 mg/hr, with typical rates of 3 to 5 mg/hr or approximately 0.7 to 1.2 \( \mu \)g/kg/min. An initial estimate of the infusion rate needed may be taken from the loading dose in mg given per hour (mg/hr). The total doses given ranged from 1.5 to 18 mg for procedures lasting 0.5 to 5.25 hours. Urquhart and White\textsuperscript{4} gave sedative infusions during regional anesthesia. Their sedation goals were patients who were sleepy and responsive to verbal stimuli (Wilson level 3). This required a loading dose of \( 3.7 \pm 1.5 \) mg of midazolam, followed by a maintenance infusion rate of \( 7.5 \pm 4 \) mg/hr for procedures lasting 53 \( \pm 28 \) minutes; this higher infusion rate probably reflected the deeper level of sedation desired. The level of sedation was stable during the procedure, as demonstrated by the low number of rate changes needed.

Urquhart and White\textsuperscript{4} evaluated patient recall of perioperative events, comparing sedation with midazolam, methohexital, and etomidate infusions. Patients who received midazolam in-

<table>
<thead>
<tr>
<th>Score</th>
<th>Degree of Sedation</th>
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<tbody>
<tr>
<td>1</td>
<td>Fully awake and oriented</td>
</tr>
<tr>
<td>2</td>
<td>Drowsy</td>
</tr>
<tr>
<td>3</td>
<td>Eyes closed but rousable to command</td>
</tr>
<tr>
<td>4</td>
<td>Eyes closed but rousable to mild physical stimulation (earlobe tug)</td>
</tr>
<tr>
<td>5</td>
<td>Eyes closed but unrousable to mild physical stimulation</td>
</tr>
</tbody>
</table>

*Data from Wilson et al.\textsuperscript{11}
Supplementation by Continuous Infusion

Infusions had significantly ($P<0.05$) less recall of surgical incision, intraoperative events, and entry to the postanesthesia care unit (PACU) than did patients who received methohexital or etomidate infusions. When amnesia was assessed at the time of PACU discharge two hours later, the amnestic effect of all infusions had dissipated and all patients had complete recall. Residual sedation also was assessed. At the time of arrival in the PACU, patients who received midazolam were significantly more sedated than patients who received methohexital or etomidate; this is compatible with midazolam's slower kinetics. At 30 minutes after arrival, the midazolam-treated patients remained drowsier than the methohexital-treated patients only; at 60 and 90 minutes, there were no differences in residual sedation between the three groups. There also were no significant between-group differences in discharge times, which ranged from 129 to 143 minutes. Clinical recovery from sedation with midazolam infusion was similar to that with methohexital or etomidate, despite the slower rate of midazolam clearance. This suggests the importance of careful dose titration to produce optimal recovery.

White and Negus also reported that a midazolam loading dose of $4.2\pm1.4$ mg and a maintenance rate of $8.6\pm5.4$ mg/hr produced a Wilson level 3 to 4 sedation. They also compared differences in the midazolam dose needed for local versus regional anesthesia techniques. Patients who received regional anesthesia required less midazolam for both loading dose and maintenance infusion rate. This may reflect more suppression of noxious stimuli with regional anesthetic techniques.

White and Negus also compared infusions of midazolam and propofol for supplementation of ambulatory surgical procedures. They found that pain on injection occurred with both drugs, although significantly ($P<0.05$) more often with propofol. Furthermore, there was significantly ($P<0.05$) more recollection of pain with propofol (15%) than with midazolam (0%). Short-term recovery, including eye opening, response to verbal command, and orientation, was significantly ($P<0.05$) faster with propofol than with midazolam (Figure 2). However, intermediate recovery, as determined by the ability to sit and stand, and readiness for discharge, was not significantly different between the two agents. Overall, recovery time was related not to the drug used for infusion but rather to the choice of local or regional anesthetic technique. When Wilson and colleagues compared infusions of midazolam and propofol to achieve level-4 sedation, they reported faster immediate recovery after propofol, but significantly greater amnesia after midazolam.

![Figure 2](image-url)  
**Figure 2.** Recovery times after midazolam and propofol infusions. *$P<0.05$. (Reprinted, with permission, from White and Negus.*)
Analgesia is the other component of supplementation for ambulatory surgical procedures. The opioid most commonly used by infusion is alfentanil, which has a redistribution half-life of 11.6 minutes and an elimination half-life of 92 minutes. This shorter elimination half-life, compared with the older compound fentanyl, is due to its smaller volume of distribution and lower lipid solubility. Bolus doses of 5 to 10 μg/kg alfentanil can be used for supplementation. However, the pharmacokinetic properties of alfentanil suggest that it is appropriate for supplementation by infusion. These properties include rapid equilibration between plasma and site of action, rapid redistribution from the brain to nonresponsive tissues, and rapid elimination from the body without the formation of active metabolites.

The clinical pattern that emerges after bolus doses of alfentanil has been described by Ausems and associates. Repeated bolus doses of alfentanil were needed to achieve the desired level of analgesia, leading to repeated motor and hemodynamic responses. Alfentanil then was given by continuous variable-rate infusion, and a marked reduction in responses was seen. Administration of alfentanil by variable infusion also affects recovery time. White and colleagues compared the administration of alfentanil by infusion or intermittent bolus technique for ambulatory gynecologic procedures. They found significantly shorter recovery times for both awakening and orientation when alfentanil was given by infusion; times to ambulation were not different.

At the Brigham and Women's Hospital, we use supplementation with alfentanil by infusion. Our technique consists of an initial bolus of 5 μg/kg and an initial infusion rate of 0.5 μg/kg/min. Incremental boluses of 2.5 to 5 μg/kg are given, with incremental changes in the infusion rate of 0.25 to 0.5 μg/kg/min. The dose should be titrated up and down to match surgical stimulation and to facilitate rapid recovery. Clinically, the sedative quality of alfentanil is different from that of fentanyl. Alfentanil produces more euphoria and sedation than fentanyl, and thus appears more similar to the other mu opioid receptor agonist, morphine. Alfentanil infusion may be given alone if the patient desires predominantly analgesia, or with other sedative hypnotics such as midazolam, methohexital, or propofol.

Respiratory Depression

When using supplementation with alfentanil by infusion, the most important side effect is respiratory depression. Respiratory depression does occur after alfentanil infusion, but it is shorter in duration than after infusion of fentanyl. However, of more concern are the delayed respiratory depression and respiratory arrests that have been reported up to 70 minutes after cessation of high-dose alfentanil infusions given during general anesthesia. The plasma alfentanil concentrations at the time of two of the respiratory arrests were 87 and 95 ng/ml. In another study, Auscare and colleagues determined the alfentanil plasma concentration associated resumption of spontaneous ventilation was 226 ± 10 ng/ml. The low alfentanil concentrations during the respiratory arrests indicate that a secondary peak in alfentanil blood level was not the cause. More likely, the contributory factor was decreased stimulation in the PACU, as well as the development of sleep psyche. Several patients also received naloxone. An adequate period of postoperative observation and monitoring is mandatory for patients who have received prolonged alfentanil infusions for supplementation.

White and associates assessed opiate side effects, including respiratory depression and muscular rigidity when alfentanil has been given by infusion or bolus techniques. They defined respiratory depression as a rate less than five breaths per minute requiring assistance, and muscular rigidity as sufficient to require succinylcholine 5 to 10 mg. They found that both respiratory depression and muscular rigidity occurred less frequently when alfentanil was given by infusion rather than bolus doses. This reduction in side effects may be related to the lower average alfentanil dose administered, which was 0.77 ± 0.07 μg/kg/min in the infusion group and 1.30 ± 0.16 μg/kg/min in the bolus group.

Drug Interactions

Benzodiazepines and opioids are often used together to provide supplementation for ambulatory procedures. Given in combination, these drugs interact, and have additional effects and side effects. One effect is increased respiratory depression, which is seen during supplementation with benzodiazepine-opioid combinations. Bailey and colleagues evaluated the interac-
tion of midazolam and fentanyl. They gave midazolam 0.05 mg/kg or fentanyl 2 μg/kg, or both drugs together. They assessed the occurrence of hypoxemia, defined as a pulse oximetry saturation of less than 90% for ten seconds. Among the subjects who received midazolam alone, none developed hypoxemia; among those who received fentanyl alone, 50% developed hypoxemia. However, among those who received both midazolam and fentanyl, 92% became hypoxemic. The authors also assessed the occurrence of apnea, defined as 15 seconds without spontaneous respiration. Among the subjects who received midazolam alone or fentanyl alone, none developed apnea. However, among those who received both drugs in combination, 50% developed apnea.

The combination of benzodiazepine and alfentanil also causes increased postoperative respiratory depression. Silbert and colleagues gave alfentanil for anesthesia induction at two doses, 100 and 200 μg/kg. At each dose, an additional group of patients was premedicated with diazepam 0.125 μg/kg. The authors assessed the occurrence of postoperative respiratory depression, defined as a respiratory rate of less than 10 breaths per minute, and found that five of the six patients who experienced postoperative respiratory depression had received diazepam premedication.

Another clinical effect seen when benzodiazepines and opioids are given together is enhanced sedation. Persson and colleagues compared patients who had received midazolam infusion alone to provide sleep during epidural anesthesia with a group of patients who had also received alfentanil by infusion for total intravenous anesthesia. Blood midazolam concentrations were measured at different clinical levels of sedation response during recovery. The patients who had received midazolam plus alfentanil were more sedated at similar midazolam blood concentrations, with a shift to the left in the midazolam plasma concentration–effect curve (Figure 3).

Benzodiazepines also interact with opioids to augment their sleep-inducing effect. Dundee and colleagues premedicated patients with 150 or 300 μg of alfentanil before induction of general anesthesia with midazolam 0.3 mg/kg. They found that the mean induction times were significantly shorter after alfentanil premedication, and even shorter with higher-dose alfentanil (Table III). The authors also evaluated the effectiveness of induction, which they defined as the percentage of patients asleep at three minutes. Again, a significantly higher percentage of patients who had also received alfentanil premedication were asleep at three minutes, and the improvement was dose-related.

Vinik and colleagues studied the interaction of midazolam and alfentanil for anesthesia induction. The dose required to induce anesthesia with midazolam alone was 0.22 mg/kg. When alfentanil was given with saline, the dose to induce sleep was 0.13 mg/kg. When alfentanil

![Figure 3. Blood midazolam levels and sedation responses after midazolam alone (●) and after midazolam plus alfentanil (■). (Reprinted, with permission, from Persson et al.)](image-url)
Table III. Mean induction times and sleep responses in patients induced with midazolam (control) and when premedicated with alfentanil.*

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean Induction Time (seconds ± SEM)</th>
<th>% Asleep at Three Minutes</th>
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<tbody>
<tr>
<td>Control</td>
<td>110</td>
<td>113.7 ± 1.07</td>
<td>60</td>
</tr>
<tr>
<td>Alfentanil</td>
<td></td>
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<tr>
<td>150 µg</td>
<td>40</td>
<td>76.4 ± 5.16</td>
<td>85</td>
</tr>
<tr>
<td>300 µg</td>
<td>40</td>
<td>55.9 ± 5.48</td>
<td>90</td>
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*Data from Dundee et al.*

was given with 0.07 mg/kg of midazolam, the alfentanil induction dose was reduced to 0.028 mg/kg. Therefore, when both drugs were given together, only 21% of the full alfentanil induction dose and only 33% of the full midazolam induction dose were needed. This interaction is synergistic. Synergism has also been reported\(^*\) using subanalgesic doses of alfentanil 3 µg/kg with midazolam to induce unconsciousness.

The ability of opioids to enhance the hypnotic effects of benzodiazepines is of particular concern when the anesthetic plan is local or regional anesthesia. The change from conscious to “unconscious” sedation carries with it increased risk of loss of protective reflexes and inability to maintain a patent airway. When opioids are given with benzodiazepines to supplement local and regional anesthesia, particular attention must be given to administer doses in small, titrated increments, and to allow time to observe effects that may develop.\(^*\)

CONCLUSIONS

The two agents midazolam and alfentanil complement each other to provide supplementation by infusion for ambulatory surgical procedures. The dose must be carefully titrated to achieve the desired clinical effect. Then, the combination of midazolam and alfentanil can produce highly acceptable sedation, amnesia, and analgesia, with minimal side effects and without prolongation of recovery.

REFERENCES


13. Philip BK. Infusion in regional blocks. In: Vinik HR, ed. *Midazolam infusion for anesthesia and*


