Arterial oxygen desaturation following intravenous injection of midazolam

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The water soluble benzodiazepine derivative, midazolam, is used almost exclusively at our institution to produce sedation for numerous surgical procedures. Mild arterial oxygen desaturation has been reported in patients who have received as little as .04 mg/kg. A time series design study was undertaken to determine if there was any correlation between the decline in arterial oxygen percent saturation ($\text{SaO}_2$) and the time at which sedation occurred and to establish the presence of any statistical significance in this decline.

Thirty-one ASA I and II patients consisting of 8 females and 23 males requiring various minor orthopedic and general surgical procedures were studied. The total mean age of the population was 32.29 ± 12.43 years (mean ± SD). Fourteen patients had a smoking history, while 15 patients did not (2 patients were eliminated from the study for failure to demonstrate sedation, as characterized by either Verrill's sign or thickened speech following intravenous administration of midazolam). All patients arrived in the operating room unpremedicated and were administered .04 mg/kg midazolam intravenously. Arterial oxygen saturation was measured over a 10-minute period using pulse oximetry. Results were analyzed using regression analysis, a t-test for independent groups, and a one-way analysis of variance.

There was no statistically significant difference in the decline in $\text{SaO}_2$ between smokers and nonsmokers. Our study has shown that the mean onset of sedation using a dose of .04 mg/kg occurred between 3 and 4 minutes, with the peak fall in $\text{SaO}_2$ occurring at the 3-minute interval irrespective of smoking history. The greatest mean drop in $\text{SaO}_2$ was 95.84%.

Midazolam, like its parent drug, diazepam, alters ventilatory mechanics. The mean onset of sedation using midazolam in a dosage of .04 mg/kg occurred between 3 and 4 minutes. Moreover, the peak fall in $\text{SaO}_2$ also occurred at the 3-minute interval irrespective of smoking history. Although the decline in $\text{SaO}_2$ is minimal, even in patients with smoking histories, we feel it is advisable to administer midazolam cautiously to patients with significant tobacco use. Other studies have clearly indicated that the slope of the CO$_2$ response curve is more affected in patients with chronic obstructive pulmonary disease (COPD) when administered midazolam. The population used for this study consisted of essentially healthy individuals. We feel it is prudent to provide supplemental oxygen to all patients who receive midazolam intravenously.
Midazolam, a water soluble benzodiazepine derivative, has essentially replaced valium as the means of producing sedation for patients requiring anesthesia at our institution; it has been found to be an ideal anxiolytic which has a rapid onset of action, provides for decreased recall and has a minimum of side effects. The hydrochloric salt of the drug is soluble at a pH of 4.0 and, therefore, does not require oily solvents such as propylene glycol which is frequently used in diazepam and lorazepam preparations. Consequently, midazolam is virtually void of the burning sensation that often accompanies the other benzodiazepine derivatives. After intravenous administration, midazolam quickly changes to a physiologic pH which makes it very lipid soluble. In fact, it is the most lipid soluble of all currently used benzodiazepines. This high lipid solubility accounts in part for its large volume of distribution and subsequent rapid onset of action with sedation occurring within 30-97 seconds after intravenous injection.

The termination of activity and the recovery time (i.e., the time it takes to become awake, reoriented to time, place and person and to have full cognitive ability) from diazepines depend on the distribution or alpha phase of the drugs and their elimination (clearance). After single intravenous administration of either midazolam or diazepam, the duration of action of either of these drugs is quite short, with the alpha half-lives of midazolam and diazepam being 15 and 30 minutes respectively.

Midazolam has a high hepatic extraction ratio, which means that clearance of this drug depends heavily on blood flow to the liver. In fact, with a clearance of approximately 7.5 ml/kg/min, the hepatic clearance of midazolam lies within the range of 50% of hepatic blood flow. Hence, the elimination half-life is quite short at about 2.8 hours. In contrast, the elimination half-life of diazepam is 21-37 hours. This is because the hepatic extraction ratio is low, which means that hepatic clearance of diazepam is essentially flow independent. Moreover, the desmethyl metabolite of diazepam is produced in clinically relevant amounts, which accumulate if diazepam is given repeatedly. Consequently, recovery from repeated doses of diazepam is slow.

On the other hand, midazolam produces essentially two clinically insignificant metabolites which are rapidly conjugated with glucuronic acid and excreted in the urine. Both metabolites are less lipid soluble and have lower receptor affinity than the parent compound and, thus, even after repeated doses, recovery is quite rapid.

The effectiveness of midazolam as a premedication was evaluated by Connor and associates. The majority of patients in their study reported a wide level of acceptance, with the main side effect being dizziness. Reduction of anxiety and suppression of recall was prevalent in greater than 69% of their patients after 32 minutes. The majority of the patients to whom we administer midazolam also report diminished recall. We have found this to be true even in unpremedicated patients who have received the drug intravenously prior to the surgical experience in a dosage range of .03 mg/kg to .05 mg/kg.

Pulse oximetry is used on all our patients requiring any type of anesthetic intervention. Anecdotally, we have witnessed mild arterial oxygen desaturation in patients who have received midazolam in dosages as little as .04 mg/kg. Other studies have described depression of ventilatory mechanics following intravenous injection of midazolam in a dosage range of .05 mg/kg up to 0.2 mg/kg. Based on these studies, our own observations, and our concern that smoking history might confound these observations, we decided to examine midazolam's effect on SaO2 to see if there was indeed any correlation between the decline in SaO2 and the time at which sedation is produced, and to establish the presence of any statistical significance in this decline.

Methods
To evaluate these reports, a time series design study was undertaken using a group of 31 ASA I and II patients requiring various minor orthopedic and general surgery procedures. The sample population consisted of 8 females and 23 males with a total mean age of 32.29 ± 12.43 years (mean ± SD) and total mean weight of 88.6 kg (± 18.8 kg). The subjects had no previous medical problems nor did they take medication or imbibe alcohol on a regular basis. Informed consent was obtained, and permission for the study was secured from the appropriate institutional authorities.

All patients arrived in the operating room unpremedicated, and while intravenous access was established, SaO2 was determined using a finger probe of a Novametrix 500 Pulse Oximeter (Novametrix Medical Systems, Wallingford, Connecticut), which has an SaO2 range of 0-100% with an accuracy of ± 2% in the 80-100% range. After baseline SaO2 readings were determined, midazolam .04 mg/kg was administered intravenously. The decision to use this dose was based on reports that midazolam is approximately 2.5 times more potent than valium with regard to producing loss of consciousness.
Since we customarily administer valium in 5 mg increments, we concluded that a dose of 2.5 mg midazolam would provide equivalent sedation. In a 70 kg individual this equates to approximately .04 mg/kg. All dosages were rounded down to the nearest 0.5 mg. SaO₂ measurements were determined every minute for 10 minutes, and the onset of sedation as manifested by Verrill's sign (i.e., bisection of the cornea by the upper eyelid) or thickened speech was noted. The 10-minute limit was selected because several studies have heretofore indicated that midazolam's effects on tidal volume, respiratory minute volume and the CO₂ response curve seem to plateau at around 10 minutes postadministration.¹⁵,¹⁶

Regression analysis was used to evaluate changes in SaO₂ over time, to evaluate the onset of sedation and to predict changes in SaO₂ over 10 time intervals as a function of smoking history. Probability of making a Type I error was set at .05.

Next, the SaO₂ was determined for the interval at which sedation was noted (Table I). Seven

| Table I  |
| SaO₂ differences between smokers and nonsmokers |
| Smokers sedation intervals | SaO₂ |
| 1 | 97 |
| 2 | 97,97,93,97,98,93,98,94 |
| 3 | 96,98,97 |
| 4 | 99 |
| 5 | 96 |
| 6 | 95 |
| 7 | 8 |
| 9 | |
| 10 | |

| Nonsmokers sedation intervals | SaO₂ |
| 1 | 98, 97,97,97 |
| 2 | 94,96,93,95,97,97 |
| 3 | 95,98,97 |
| 4 | |
| 5 | 96 |
| 6 | 97 |
| 7 | 8 |
| 9 | |
| 10 | |

Sedation occurred during the first 7 minutes after the administration of midazolam. Changes in SaO₂ were noted for each time interval and separated into two groups, smokers and nonsmokers.

vals (1 through 7) were isolated as the primary times at which the onset of sedation occurred. Peak sedation occurred during the first 7 minutes following administration of midazolam. In 2 cases no sedation occurred. Thus, the mean time for the onset of sedation (n=29) was 2.58 minutes.

The population was then divided into 2 groups: nonsmokers (n=15) and smokers (n=14) (Table I). There were 5 intervals in each group at which sedation occurred during the first 7 minutes after the administration of midazolam. The onset of sedation occurred during the first 7 minutes following administration of midazolam. In 2 cases no sedation occurred. Thus, the mean time for the onset of sedation (n=29) was 2.58 minutes.

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tion occurred, and SaO₂ was noted for each of the 5 intervals. Differences between the means in SaO₂ for each group were analyzed using a one-way analysis of variance (p = .05) (Table I). A comparison of the 2 groups (smokers versus nonsmokers) at intervals 2 and 3 were conducted using a t-test (p = .05) to determine the difference in SaO₂ (Table III). These intervals were selected because Verrill's sign and slurred speech were noted primarily at these intervals.

**Results**

This study revealed a change in SaO₂ over a 10-minute period following the intravenous administration of midazolam in 31 healthy patients. The fact that no further decline in SaO₂ was observed following this 10-minute period correlates with other published reports on the ventilatory plateau affect of the drug. The base mean SaO₂ of our sample population was 97.31, with the greatest mean drop in SaO₂ occurring at approximately 3 minutes postinjection (SaO₂ = 95.84) (Table IV).

Over the 10 intervals of time, regression analysis failed to reveal any statistically significant change in oxygen saturation. Similarly, regression analysis of the onset of sedation in smokers versus nonsmokers also failed to show any significant difference. Table I lists all 10 intervals in which sedation occurred, with smoking history as the independent variable and oxygen saturation as the dependent variable. There was no statistically significant difference for any of the sedation-time intervals due to smoking history. One-way analysis of variance failed to detect any statistically significant difference in oxygen saturation among smokers and nonsmokers resulting from the administration of midazolam.

**Discussion**

Midazolam, like its parent drug, diazepam, alters ventilatory mechanics. Midazolam depresses the mean slope of the CO₂ response curves and significantly reduces the ventilatory response to CO₂ and the mouth occlusion pressure response to CO₂ at a dose of 0.15 mg/kg. Such depression occurs within 2-3 minutes and lasts from 15-30 minutes. Moreover, in doses of .05 mg/kg, 0.1 mg/kg and 0.2 mg/kg, midazolam significantly increases tidal volume. These observations probably account for the decrease in SaO₂ noted on our study, and in Tucker et al., in which they demonstrated that during conscious sedation, SaO₂ is well maintained above 95%. Similarly, our study revealed that throughout 10 time intervals the mean value for SaO₂ remained above 95%. Perhaps the increase in respiratory rate and subsequent maintenance of minute ventilation, as demonstrated in other studies, account for this.

Nonetheless, we have found the greatest mean decline in SaO₂ occurring at 3 minutes postinjection using dosages of .04 mg/kg. This parallels the findings of Forster et al., who demonstrated that respiratory depression peaks in about 2-3 minutes in dosages as low as .05 mg/kg.

Our study has shown that the mean onset of sedation using midazolam in a dosage of .04 mg/kg occurs between 3 and 4 minutes postadministration. Moreover, the peak fall in SaO₂ also occurs at the 3-minute interval, irrespective of smoking history, even in doses as low as .04 mg/kg. We are not implying that one should not be concerned in administering midazolam to patients with a significant smoking history. On the contrary, Gross et al. clearly established that the slope of the CO₂ response curve is more affected in patients with COPD than in normal, healthy patients. We think it is prudent to administer midazolam cautiously to patients with significant tobacco use, since these individuals are more prone to pulmonary changes as a consequence of smoking.

While this study lacks a control group and fails to randomize subjects, thus raising questions about the validity of our findings, we believe that the 10-minute time interval, over which we measured arterial oxygen saturation, strengthens our ability to attribute the change in oxygen saturation to midazolam. Furthermore, although we did not prove any statistically significant arterial oxygen desaturation in our healthy population, we feel that clinically the decline in SaO₂ by 5 or 6 percentage points, which occurred in several members of our population, may be significant, and may be of greater significance in patients who have impaired cardiopulmonary reserve. Therefore, we advocate that all patients who receive midazolam intravenously have supplemental oxygen provided to them during the administration of the drug.

**References**

### Table IV

<table>
<thead>
<tr>
<th>Number of Individuals for Sedation Times 1 through 7</th>
<th>SD = 3.75</th>
<th>N = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. 10-15 min.</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>B. 16-20 min.</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>C. 21-25 min.</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>D. 26-30 min.</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>E. 31-35 min.</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>F. 36-40 min.</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>G. 41-45 min.</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>H. 46-50 min.</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>I. 51-55 min.</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>J. 56-60 min.</td>
<td>4</td>
<td>18</td>
</tr>
</tbody>
</table>

**Demographics**

*Super Age: Male = 1, Female = 0*

**SDO**


AUTHORS

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The opinions stated in this article are the authors' own and do not reflect the official opinions of the Department of Defense or the United States Army.