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Frequent Hypoxemia and Apnea after Sedation with Midazolam and Fentanyl

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More than 80 deaths have occurred after the use of midazolam (Versed®), often in combination with opioids, to sedate patients undergoing various medical and surgical procedures. We investigated the respiratory effects of midazolam (0.05 $mg \cdot kg^{-1}$) and fentanyl (2.0 $\mu g \cdot kg^{-1}$) in volunteers. The incidence of hypoxemia (oxyhemoglobin saturation <90%) and apnea (no spontaneous respiratory effort for 15 s) and the ventilatory response to carbon dioxide were evaluated. Midazolam alone produced no significant respiratory effects. Fentanyl alone produced hypoxemia in half of the subjects and significant depression of the ventilatory response to CO_2, but did not produce apnea. Midazolam and fentanyl in combination significantly increased the incidence of hypoxemia (11 of 12 subjects) and apnea (6 of 12 subjects), but did not depress the ventilatory response to CO_2 more than did fentanyl alone. Adverse reactions linked to midazolam and reported to the Department of Health and Human Services highlight apnea- and hypoxia-related problems as among the most frequent adverse reactions. Seventy-eight per cent of the deaths associated with midazolam were respiratory in nature, and in 57% an opioid had also been administered. All but three of the deaths associated with the use of midazolam occurred in patients unattended by anesthesia personnel. We conclude that combining midazolam with fentanyl or other opioids produces a potent drug interaction that places patients at a high risk for hypoxemia and apnea. Adequate precautions, including monitoring of patient oxygenation with pulse oximetry, the administration of supplemental oxygen, and the availability of persons skilled in airway management are recommended when benzodiazepines are administered in combination with opioids. (Key words: Hypnotics, benzodiazepines: midazolam. Anesthetics, opioids: fentanyl. Drug interaction. Complications: hypoxemia/apnea.)

MORE THAN 80 DEATHS have been associated with the use of midazolam (Versed®) to sedate patients undergoing various diagnostic or therapeutic medical and surgical procedures in the United States (Department of Health and Human Resources). In many of these cases, opioids had been simultaneously administered. Most deaths occurred in patients who were breathing spontaneously, usually without receiving supplemental oxygen. In addition, monitoring of patient oxygenation and ventilation, although usually not stated in adverse drug reaction reports, was most likely quite variable. Outside the specialty of anesthesiology, no minimal monitoring standard is established or applied in patients who receive drugs with the potential to cause significant respiratory depression. Thus, there may be one or more possible explanations for these apparently drug-related deaths.

Although hypnotic doses of midazolam and other benzodiazepines have been shown to decrease spontaneous minute ventilation and the slope of the ventilatory response to CO_2,[1] this effect does not consistently occur with sedative doses of these drugs.[2,3] In fact, the respiratory effects of benzodiazepines are quite variable.[4] All opioids, however, consistently produce dose-dependent depression of the ventilatory response to CO_2. In addition, both benzodiazepines and opioids significantly blunt the ventilatory response to hypoxemia.[5–7] Although opioids and benzodiazepines are often used together for preanesthetic medication, there are no available descriptions of the effects of combinations of these two drugs on ventilation and oxygenation. Much of the reported morbidity and mortality associated with the use of midazolam may be related not only to its own respiratory actions, but also to interactions with other drugs given simultaneously. We therefore designed this study to evaluate the respiratory effects of sedative doses of midazolam and analgesic doses of the opioid fentanyl (Sublimaze®), separately and in combination, in healthy young adult volunteers.

Materials and Methods

The investigation was approved by the University of Utah Health Sciences Center Institutional Review Board for Human Research, and written and oral informed consent was obtained from each subject. The subjects were 12 healthy adult males between the ages of 18 and 40 yr. They had no significant medical conditions, were receiving no chronic medications, and had no history of alcohol or tobacco abuse. The subjects refrained from caffeine and aspirin consumption for at least 12 hr and had nothing to eat or drink for at least 8 hr prior to the commencement of the study. All study sessions began at 7:30 AM.

Each subject was evaluated at three separate sessions at least 48 hr apart. During each session, subjects received either fentanyl (2 $\mu g \cdot kg^{-1}$ iv), midazolam (0.05 $mg \cdot kg^{-1}$ iv), or fentanyl (2 $\mu g \cdot kg^{-1}$) plus midazolam (0.05 $mg \cdot kg^{-1}$) iv. The experimental design was completely balanced for the possible sequences of drug administra-

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tion. Two subjects were assigned to each of the six possible permutations of the order of drug administration at the three sessions. Subjects were assigned to their permutation group by a computer-generated, permuted-block, restricted randomization table; block size was six subjects. During each session, both subject and investigators were blinded to the study drug(s) being administered.

On the morning of each study session a 20-G catheter was inserted into an arm vein after the subcutaneous administration of 0.1 ml 1% lidocaine. Intravenous lactated Ringer's solution was then begun at a rate of 125 ml · hr^{-1}. Systemic blood pressure (Critikon Dinamap vital signs monitor) and heart rate and oxyhemoglobin saturation (Sp_{O_2}) *via* pulse oximetry (Criticare Systems, Inc.) were recorded while subjects were breathing room air. Subjects then performed an initial CO_2 rebreathing challenge to familiarize themselves with the test. Subjects wore comfortable head phones emitting white noise to standardize auditory stimuli and soft nose clips to prevent nasal breathing during each CO_2 challenge. Subjects were instructed to keep their eyes closed during each test session. Fifteen minutes later, resting end-tidal carbon dioxide partial pressure (PET_{CO_2} mmHg) was measured by a Beckman LB-2 infrared CO_2 analyzer while the subject breathed room air. This was followed by a control CO_2 rebreathing challenge.

After another 15-minute rest period, the study drug(s) was given intravenously over 1 min while subjects breathed room air. The respiratory rate and Sp_{O_2} were then continuously monitored by visual inspection and finger pulse oximetry, respectively. Hypoxemic episodes were defined as Sp_{O_2} <90% and lasting at least 10 s. Apnea was defined as the absence of any spontaneous respiratory effort for at least 15 s. If apnea occurred, spontaneous respiration was encouraged by vocal or tactile stimuli. After a 5-min observation period for hypoxemia and apnea, a CO_2 rebreathing challenge was performed. Additional CO_2 rebreathing challenges were completed 20, 40, 60, 90, 120, 180, 240, and 300 min after drug administration. Continuous observation for additional hypoxemia and apnea was made between CO_2 challenges.

Rebreathing Circuit and Measurement

We used a modified Read rebreathing circuit as previously described.[4] The rebreathing apparatus has a 7.5-l neoprene rebreathing bag enclosed in a Lucite box; to measure ventilatory flow, a Validyne differential pressure transducer measures the pressure drop across a Fleisch pneumotachograph at the outlet of the box. Flow was directed either into the bag or through the pneumotachograph by a three-way valve located at the mouth of the box, permitting the subject to breathe directly into the room when not rebreathing CO_2. Inspiratory and expiratory limbs of the circuit were separated by a Collins J-Valve. CO_2 concentration was measured by a Beckman LB-2 infrared CO_2 analyzer, which sampled gas at the mouthpiece at a rate of 200 ml · min^{-1} and returned it to the central chamber of the Collins valve. Inspiratory circuit resistance was 1.7 cm $H_2O \cdot l^{-1} \cdot s^{-1}$. Expiratory circuit resistance was 1.7 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ and remained constant between flow rates of 15 and 135 $l \cdot min^{-1}$. Flow and CO_2 were sampled by a microcomputer (Motorola Exorciser II) 12-bit analog-to-digital (A/D) convertor (Burr-Brown MP7208 Data Acquisition System) with a resolution of 4.8 mV per A/D unit and a range of ±10 V.

Rebreathing Data Collection and Analysis

After allowing the subject to breathe quietly through the mouthpiece with the nose clip in place, the resting PET_{CO_2} was recorded and the three-way valve was switched to the rebreathing bag previously filled with 7.0% CO_2 and 93.0% O_2. For each breath, the following data were displayed on the video terminal and stored electronically: inspiratory time (T_I); breath duration (T_{TOT}); fractional inspired CO_2 concentration $\%IN_{CO_2}$ and end-tidal CO_2 concentration $\%ET_{CO_2}$; tidal volume (V_T); minute ventilation ($\dot{V}_E$); and elapsed time since start of CO_2 rebreathing. All gas volumes were corrected to BTPS. Subjects were encouraged to rebreathe as long as possible, but could stop at any time. The desired goal was to reach a PET_{CO_2} of 65 mmHg. The increase in PET_{CO_2} during CO_2 rebreathing tests was always at least 15 mmHg, but not more than 25 mmHg.

After completion of each CO_2 challenge, plots of $\dot{V}_E$ *versus* PET_{CO_2} were displayed on the video display terminal. To ensure that the regression line reflected only data from the linear portion of ventilatory response, data from the first ten breaths were excluded from analysis. Data from all other breaths were used for least-squares linear regression. The slope of the ventilatory response to CO_2 ($\dot{V}_E/CO_2$, $l \cdot min^{-1} \cdot mmHg^{-1}$) and the estimated $\dot{V}_E$ at a PET_{CO_2} of 50 mmHg ($\dot{V}_E50$, $l \cdot min^{-1}$) were the parameters chosen to depict each subject's response to CO_2.

Descriptive and graphic statistics included line graphs of mean ± standard error for the variables slope $\dot{V}_E/CO_2$ and $\dot{V}_E50$ at baseline and 5, 20, 40, 60, 90, 120, 180, 240, and 300 min after drug(s) for each of the three sessions. Inferential statistics were calculated for both frequency counts and continuous variables. A $P < 0.05$ was considered statistically significant. Analysis of the difference in the incidence of hypoxemia and apnea during the three study sessions was made by a small-sample procedure, contingency-table test for three dependent samples.[8] Comparison of $\dot{V}_E/CO_2$ and $\dot{V}_E50$ was by repeated measurement multivariate analysis of variance (ANOVA) us-

ing restricted maximum likelihood estimation. The P5V module of BMDP was used, allowing use of a data matrix with missing values; the test statistic was a Wald chi-squared statistic, X^2_{df}, where df = the degrees of freedom of the test statistic.

Results

Baseline values for $\dot{V}_E/CO_2$ ($X^2_2 = 1.18$; $P = 0.554$) and $\dot{V}_E50$ $X^2_2 = 0.79$; $P = 0.674$) were not significantly different for the three study sessions. There was a significant difference (fig. 1) in drug effects on $\dot{V}_E/CO_2$ ($X^2_2 = 19.59$; $P = 0.000$). Both fentanyl and fentanyl plus midazolam depressed $\dot{V}_E/CO_2$ for at least 60 min ($X^2_2 = 56.08$; $P = 0.000$). There was also a significant difference (fig. 2) in drug effects on $\dot{V}_E50$ ($X^2_2 = 12.55$; $P = 0.002$). Both fentanyl and fentanyl plus midazolam depressed $\dot{V}_E50$ for at least 60 min ($X^2_2 = 87.78$; $P = 0.000$). The effects of fentanyl and fentanyl plus midazolam were essentially similar for $\dot{V}_ECO_2$ ($X^2_1 = 0.96$; $P = 0.326$) and for $\dot{V}_E50$ ($X^2_1 = 0.14$; $P = 0.708$).

No subject receiving midazolam alone became hypoxemic, whereas hypoxemia occurred in half (6 of 12) of those receiving fentanyl and nearly all (11 of 12) of those given both midazolam and fentanyl. All but one episode of hypoxemia occurred within 5 min of drug administration. Differences in the incidence of hypoxemia were statistically significant between midazolam and fentanyl ($P < 0.05$) and between midazolam and fentanyl plus midazolam ($P < 0.05$). Although neither midazolam nor fentanyl alone resulted in apnea, the combination of the drugs resulted in apnea in half (6 of 12) the subjects ($P < 0.05$). All episodes of apnea occurred within 5 min of injection of the drug combination and were always associated with hypoxemia. All hypoxemic and apneic subjects responded to verbal or tactile stimulation.

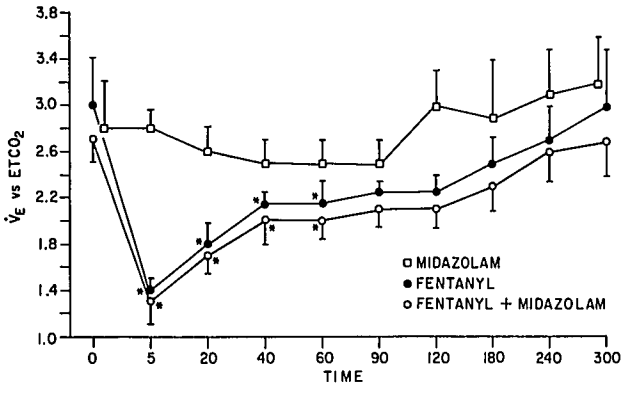

FIG. 1. Slope of the ventilatory response to carbon dioxide ($\dot{V}_E$ *vs.* ET_{CO_2}, l · min^{-1} · mmHg^{-1}) before (time 0) and minutes after midazolam, fentanyl, and midazolam plus fentanyl. (*$P < 0$ 05; see results.)

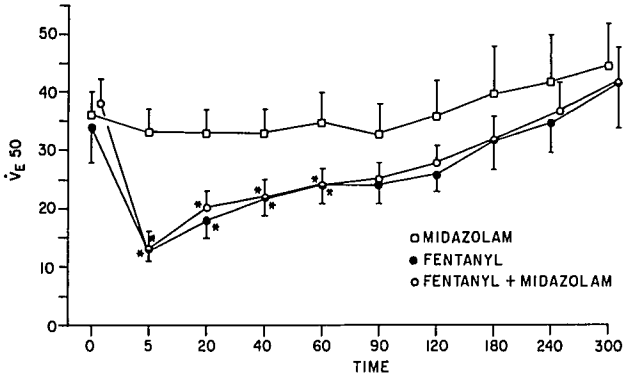

FIG. 2. Minute ventilation at an end-tidal carbon dioxide of 50 mmHg ($\dot{V}_E50$, l · min^{-1}) before (time 0) and minutes after midazolam, fentanyl, and midazolam plus fentanyl. (*$P < 0.05$; see results.)

Discussion

This study evaluated the effects of sedative doses of midazolam and analgesic doses of fentanyl, alone and in combination, on the incidence of hypoxemia and apnea and on the ventilatory response to carbon dioxide in young healthy adult volunteers. Fentanyl alone, 2.0 $\mu g \cdot kg^{-1}$, produced the expected decrease in $\dot{V}_E/CO_2$ and $\dot{V}_E50$ seen with analgesic doses of opioids. On the other hand, midazolam 0.05 $mg \cdot kg^{-1}$ did not produce any change from baseline in $\dot{V}_E/CO_2$ or $\dot{V}_E50$. Combining midazolam with fentanyl produced no greater depression of the ventilatory response to CO_2 than did fentanyl alone. The CO_2 response we observed after midazolam is comparable with the response seen by Power *et al.*,[3] who found that midazolam 0.075 $mg \cdot kg^{-1}$ caused no statistically significant depression of the ventilatory response to CO_2. Gross *et al.*,[1] using higher doses of midazolam (0.2 $mg \cdot kg^{-1}$), found significant depression of the ventilatory response to CO_2 in normal adults. These results suggest that a dose-dependent relationship may exist and that higher (hypnotic) doses of midazolam may be more likely to depress the ventilatory response to CO_2 and spontaneous ventilation than lower doses. In addition, older patients may be more prone to ventilatory depression after any dose of midazolam.[9]

Other investigators have documented changes in respiratory function even after small, sedative doses of midazolam. Using a noninvasive technique to measure ventilatory parameters, Forster *et al.*[2] and Berggren *et al.*[10] documented a decrease in tidal volume and an increase in respiratory rate but no change in $\dot{V}/_E$ in adult volunteers after the administration of midazolam 0.05–0.2 $mg \cdot kg^{-1}$. Both Forster's group and Berggren's group suggested that they were able to identify significant changes in ventilation with small doses of midazolam because their techniques for measuring ventilatory variables

did not stimulate subjects. The presence of a respiratory measuring equipment device, such as a mouthpiece or a nose clip, which is frequently used during CO_2 rebreathing tests, can itself increase ventilation.[11] Thus, our assessment technique may have obscured some of the actions of midazolam on the CO_2 response. However, the effect of nose clips and mouthpieces did not prevent depression of the CO_2 response induced by small doses of fentanyl and therefore is probably of little real significance.

We also documented that low doses of midazolam (0.05 $mg \cdot kg^{-1}$) alone do not produce hypoxemia or apnea in healthy young adults breathing room air. This result was obtained even though our hospital is approximately 5,000 feet above sea level, with an average dry barometric pressure of 593 mmHg. The inspired partial pressure of oxygen is thus significantly lower (125 mmHg) than at sea level (150 mmHg) and would bias our results toward hypoxemia. Again, older subjects or patients may be more prone to hypoxemia. Midazolam did, however, increase the incidence of hypoxemia and apnea produced by fentanyl when these drugs were given in combination. Whereas fentanyl alone produced hypoxemia in 50% (6 of 12) of the subjects studied and apnea in none, the addition of midazolam to fentanyl produced hypoxemia in almost all (11 of 12) and apnea in half (6 of 12) of the subjects. Thus, although we found no further depression of the ventilatory response to CO_2 after combining midazolam with fentanyl, we did document marked increases in hypoxemia and apnea when the two drugs were combined.

The mechanism probably underlying these respiratory effects is the significant blunting of hypoxic ventilatory drive by both benzodiazepines[5] and opioid narcotics.[6,7] Moreover, it appears from our results that depression of hypoxic ventilatory drive occurs sooner and to a greater degree than does the ventilatory response to hypercarbia after combinations of these drugs. This hypothesis is supported by the synergistic effects of the combination of midazolam and fentanyl on hypoxemia and apnea without any alteration of CO_2 responsiveness: whereas midazolam alone did not cause hypoxemia and neither midazolam nor fentanyl alone resulted in apnea, the effects of the drug combination were more than additive. Thus, combining midazolam with fentanyl, and most likely other opioids, can result in an absence of an effective ventilatory response to hypoxemia and can lead to severe arterial oxygen desaturation within 1–2 min in patients breathing room air.[12] In such situations, arterial oxygen partial pressure drops to critically low levels before blood CO_2 tensions can rise adequately to stimulate breathing. Sleep, too, may destabilize ventilation and oxygenation, especially in pain-free individuals receiving sedatives or analgesics.[13]

TABLE 1. The Ten Most Frequently Reported Adverse Reactions to Midazolam*

Reaction	Number of Reports	Per Cent of Total
Apnea	138	9
Hypotension	104	6
Somnolence/stupor	73	5
Cardiac arrest	68	4
Hypoventilation	52	3
Agitation	50	3
Hypoxia/cyanosis	48	3
Hostility	46	3
Bradycardia	46	3
Confusion	35	2
Other	977	60

* Department of Health and Human Services, Office of Epidemiology and Biostatistics, Center for Drug Evaluation and Research, Data Retrieval Unit HFD-737, June 27, 1989.

The clinical significance of our findings is confirmed by review of the adverse drug reactions reported to the Department of Health and Human Services. A total of 1,615 adverse reactions or events (215 types) after use of midazolam have been reported to the Department of Health and Human Services as of June 27, 1989.§ The dose of midazolam reportedly administered most often ranged from 1 to 10 mg. Four patients received higher doses. These reactions ranged in severity from hiccup to death. The single most frequently reported adverse reaction was apnea (table 1). Cyanosis or hypoxia specifically were reported 50 times. However, 17 other types of adverse reactions, totalling 623 events, including agitation, hostility, convulsions (which can be caused by hypoxemia and so may also indicate the occurrence of hypoxemia in these reports), were also reported. A total of 86 deaths occurred in the adverse drug reaction reports in the United States. All but three of these deaths occurred outside the operating room, in clinical situations where patients are typically unattended by anesthesia personnel. Sixty-seven (78%) of these deaths were associated with oxygenation difficulties or ventilation difficulties and in 57% of these respiratory deaths various opioids (most commonly meperidine and fentanyl) had been used with midazolam. It is also possible that cardiovascular depression and hypotension (table 1) also contributed to respiratory insufficiency because of inadequate medullary blood flow.[14]

The clinical implications of our findings are relevant for anesthesiologists and nonanesthesia-trained specialists as well. Midazolam and other benzodiazepines are frequently used in combination with an opioid for sedation, not only during the administration of operative regional

¶ Department of Health and Human Services, Office of Epidemiology and Biostatistics, Center for Drug Evaluation and Research, Data Retrieval Unit HFD-737, June 27, 1989.

anesthesia, but also during many medical office procedures, including gastrointestinal endoscopy. In a recent review of cardiac arrests during spinal anesthesia,[15] over half of the patients who experienced sudden cardiac arrest had received both diazepam and fentanyl. Inadequately recognized hypoxemia and apnea secondary to sedation was believed to be a crucial factor in these mishaps.[15,16] Endoscopists are also beginning to document the risk of hypoxemia in their environment.[17,18] Most of the midazolam-associated adverse drug reaction reports have involved patient care outside the operating room, where standards for the assessment of ventilation and oxygen have not been defined and therefore are variable.

Our results demonstrate that midazolam, when combined with an opioid, is likely to place patients at high risk for hypoxemia and apnea. Adequate precautions, including monitoring of patient oxygenation with pulse oximetry, the application of supplemental oxygen, and the availability of persons skilled in airway management are recommended when these or similar type drugs are combined for patient sedation in any clinical setting.

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