Use of Dynamic Negative Airway Pressure (DNAP) to Assess Sedative-induced Upper Airway Obstruction

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Background: Traditional methods of assessing ventilatory effects of sedative agents do not measure their propensity to cause upper airway obstruction (UAO). The primary objective of this study was to develop a method, using dynamic negative airway pressure (DNAP), for replicating UAO during deep sedation.

Methods: A state of deep sedation (defined as an Observer Assessment of Alertness and Sedation score of 3 and a bispectral index < 80) was attained in 10 healthy volunteers, aged 19–41, using midazolam. Volunteers breathed through a chamber connected to a regulated source of negative pressure that was gradually adjusted downward to produce UAO based on maximal inspiratory flow. The study consisted of three phases: A control phase while awake, a study phase during midazolam deep sedation, and a recovery phase after flumazenil administration.

Results: During the control phase no subject demonstrated airway obstruction at negative pressures to −30 cm H2O. All subjects exhibited complete UAO during DNAP episodes while sedated. Negative pressures required to cause complete UAO (Pcrit) ranged from −2 to −14 cm H2O. After administration of flumazenil, all subjects attained full consciousness within 5 min and did not demonstrate UAO at negative pressures to −30 cm H2O.

Conclusions: Dynamic Negative Airway Pressure is a useful method for provoking midazolam-induced UAO, and may potentially be used to compare the potential for different sedatives and patient factors to cause UAO. Flumazenil was completely effective in reversing the potential for midazolam to cause UAO.

The use of sedatives to treat pain and anxiety during medical procedures and diagnostic tests has assumed increasing importance in recent years. The most important side effect that limits the use of sedatives is respiratory depression. Respiratory depression is manifested as decreased respiratory drive and, more importantly, the inability to maintain a patent upper airway, which can lead to life-threatening hypoxemia. The goal of establishing the safety of a particular sedative agent would be to ensure that its deleterious effects on upper airway patency and respiratory drive are minimal at doses producing the desired level of sedation.

Traditionally, the ability of a drug to cause respiratory depression has been quantitatively described by measuring its effects on resting carbon dioxide levels and its ability to alter the normal respiratory response to hypoxia and hypercarbia.1 Although sedatives often produce dose-dependent depression of these parameters, their utility to assess respiratory risk during sedation remains unclear because their relationship and predictive value for apnea and upper airway obstruction (UAO) are not known. In addition, UAO may be a more common and important cause of hypoxemia. For example, with a patent airway, and only a modest increase in F1O2 (40%), there must be extreme hypoventilation (je, PaCO2 > 100) for hypoxemia to occur. But when UAO occurs, hypoxemia will develop rapidly, even with an increased F1O2.2 While transient mild to moderate hypercapnia and respiratory acidosis are generally not harmful to healthy patients, rapid onset of hypoxemia because of airway obstruction is potentially devastating.3–5 Therefore, a technique that could determine the tendency of a drug or drug combination to cause UAO under various patient and procedure-related circumstances during sedation would be extremely useful for determining associated respiratory risk.

The primary objective of this study was to develop an experimental method involving application of dynamic negative airway pressure (DNAP) to replicate UAO during sedation in healthy volunteers. A similar technique has been used for studying upper airway patency in adults with obstructive sleep apnea syndrome (OSAS)6 and susceptibility to UAO during partial neuromuscular block.7 In this study we used midazolam to induce a state of deep sedation. A secondary objective was to assess the ability of flumazenil to reverse midazolam-induced UAO.

Methods

The Research Subjects’ Review Board of the University of Rochester approved this study; written and verbal consent was obtained from all subjects studied. Healthy subjects were recruited from the University community. Exclusion criteria included obesity (greater than 150% ideal body weight), sleep apnea, significant medical disease, tobacco use, chronic alcohol or drug use, and men with beards (impedes facemask seal). Occult sleep apnea was ruled out by ensuring an Epworth Sleepiness Score of less than 11 in each subject,8 a neck circumference...
less than 16 inches, and absence of hypertension. Subjects fasted overnight before the day of the study, which took place in the Department of Anesthesiology’s respiratory physiology laboratory. Subjects lay supine with their heads in the neutral position, resting on a small folded blanket. Monitors included an electrocardiograph, pulse oximeter, automated blood pressure device, bispectral index (BIS monitor; Aspect Medical Systems Inc., Nattow, MA), capnograph, and respiratory inductance plethysmography (RIP) (Ambulatory Monitoring Inc., Ardsley, NY). The RIP consists of two coils of Teflon-insulated wire that are sewn onto elastic bands that encircle the rib cage and abdomen. Changes in cross-sectional areas of the rib cage and abdominal compartments alter the self-inductance of the coils and are displayed graphically as waveform patterns. During unobstructed breathing, the chest wall and abdominal cavities expand and contract almost simultaneously and the patterns obtained with the RIP are nearly synchronous. When UAO occurs, the normal outward movement of the rib cage and abdomen during inspiration is then replaced by asynchronous or even paradoxical motion, and is displayed graphically by waveforms that travel in opposite directions. For uniformity, subjects listened to classical music via headphones to minimize auditory stimuli during the nonsedated phases of the study. Each subject had an intravenous catheter inserted and lactated Ringer solution infused at a normal maintenance rate.

Respiratory measurement techniques have been described in detail before. The volunteers breathed from an anesthesia facemask (Vital Signs, Totowa, NJ), secured in place by a rubber facemask strap, that was connected to a gas-mixing breathing chamber designed to deliver oxygen (50%) and air, and connected to a regulated source of negative pressure. The total flow of this system was 60 l/min. A transducer continuously measured the pressure under the mask. A pneumotachometer (Hans Rudolph Inc., Model 4700B, Kansas City, MO) continuously measured ventilatory flow. To apply negative pressure, the breathing chamber was connected to the central hospital vacuum supply by polyvinyl chloride tubing with an interspersed manual regulator. Negative pressure levels were not adjusted to the phase of breathing. All data were stored automatically into a previously described computerized data acquisition program. The study consisted of three phases:

1. Control phase: Before sedation, and after familiarizing the subject to the breathing apparatus, DNAP was applied to the subject’s airway, beginning at a pressure of −5 cm H₂O. The negative pressure was held for 15 breaths and then released. After a 1 min recovery period without negative pressure application, the pressure was lowered to −10 cm H₂O and held for 15 breaths and then released. This process was repeated in decrements of −5 cm H₂O until either UAO occurred or a maximum negative pressure of −30 cm H₂O was attained.

2. Study phase: After a 15 min rest period, the subjects received midazolam, which was titrated to achieve a state of deep sedation in each subject. The standardized method consisted of a 1 mg bolus every 2 min. Every 1 min the subject was asked in a normal tone of voice to open his or her eyes. Bolus administration of midazolam stopped when the subject no longer responded to a normal tone of voice but was responsive to loudly calling their name. This is defined as a score of 3 on a modified Observer Assessment of Alertness and Sedation (OAA/S) scale. In addition, we required the subject’s BIS level to be less than 80. At this time a midazolam infusion, 0.25 μg·kg⁻¹·min⁻¹, was begun. This dose was based on previously published pharmacokinetic parameters for this subject population. The negative pressure protocol was then applied in a similar manner as in the control phase, except that mask pressure was lowered in decrements of −2 cm H₂O (instead of −5) to a maximum negative pressure of −20 cm H₂O or until complete UAO occurred. Both sedation criteria (OAA/S score and BIS value) were reconfirmed before each subsequent DNAP challenge, so that occasionally more than 1 min elapsed between DNAP challenges. The midazolam infusion was discontinued upon completion of this phase.

3. Recovery phase: Twenty minutes after the first midazolam DNAP event, flumazenil, 0.5 mg, was administered. Five minutes later, the DNAP protocol was repeated in a manner similar to the initial control phase.

For safety, the study would have been immediately terminated if any of the following occurred: dysphoria, decrease in blood pressure more than 30% of baseline, oxyhemoglobin saturation less than 90% for more than 3 min, or < 85% at any time. At the conclusion of the study the subjects were observed and monitored for at least 60 min and until reaching baseline hemodynamic and mental status before discharge (always with an attendant). The study participants were instructed not to drive or operate hazardous equipment for the remainder of that day.

Data and Statistical Analysis

For each subject, the DNAP episodes were examined using graphic analysis (Origin 6.0, Microcal Software, Northampton, MA). Complete UAO was defined by the absence of flow and end tidal carbon dioxide, along with continuation of abdominal movements on inductance plethysmography. The negative pressure at which complete UAO occurred was called the critical closing pressure of the pharynx (Pcrit). Means and standard deviations for the individual results were calculated using a spreadsheet software program (Microsoft Excel 97, Redmond WA). Linear correlation of Pcrit versus body mass
index was determined using Origin 6.0 (Microcal Software, Northampton, MA).

Results

Twelve subjects initially enrolled. One subject was excluded because of insufficient sedative effect after 17 mg midazolam; another had persistent episodes of partial airway obstruction during deep sedation before the application of DNAP. Therefore, data are presented on 10 subjects: 6 men and 4 women, between the ages of 19 and 41. Table 1 lists the individual Pcrit values for all subjects.

During the awake, control phase no subject demonstrated flow-limiting airway obstruction at any negative pressure tested. This is an expected result for healthy, conscious subjects.15

During the study phase, the initial doses of midazolam required to attain a state of deep sedation ranged from 4 to 10 mg. All subjects exhibited complete UAO during DNAP episodes while sedated. Pcrit ranged from $-2$ cm H$_2$O to $-14$ cm H$_2$O. Seven of the 10 subjects had arousal episodes during complete UAO and were able to spontaneously relieve their obstruction. A representative tracing of complete UAO followed by a spontaneous arousal is illustrated in Figure 1.

Following administration of flumazenil, all subjects attained full consciousness (OAA/S score = 5) and BIS > 95 within 5 min. As with the control phase, we were unable to obtain flow-limiting airway obstruction at any level of negative pressure tested.

There were no episodes of hypoxemia, or other adverse events in any subject at any time during the study.

Discussion

The first major finding in this study was the ability to cause complete UAO in sedated patients with the use of DNAP, and to quantify the propensity of the subject’s airway to collapse by the Pcrit value. Researchers in the field of sleep apnea have validated the reproducibility of this value in individual subjects and have used it to determine the response to specific therapeutic maneuvers.16,17 Although this method has also been used by anesthesiologists to determine Pcrit during partial neuromuscular blockade,7 Pcrit values have not previously been determined in sedated healthy subjects at similar levels of depressed consciousness.

The range of Pcrit values we observed during deep sedation with midazolam was similar to that found in

![Figure 1](attachment:image.png)

**Fig. 1.** Dynamic negative airway pressure with complete upper airway obstruction and a spontaneous arousal in a sedated subject. The bottom panels refer to the abdominal and rib cage components of the plethysmograph.
healthy subjects during REM and non-REM sleep, and healthy paralyzed subjects. The arousal patterns were also similar. During sleep in healthy subjects, and in those with obstructive sleep apnea, these arousals are associated with the sudden reopening of the collapsed pharynx. They are likely triggered by pharyngeal reflexes related to increasing ventilatory effort. The mechanism of arousals during sedative-induced UAO would likely be the same but have not been investigated. Since arousals are potentially protective against life-threatening hypoxemia, future studies should elucidate differences in arousal characteristics of sedated patients.

The variability of the Pcrit values that we observed in our subjects led us to examine the relationship between Pcrit and body mass index (BMI), a consistent predictor of the severity of OSAS. Our analysis revealed an inverse correlation between Pcrit and BMI (r = 0.6, P = 0.005), such that as BMI increased, Pcrit became more negative, indicating that larger subjects were more resistant to upper airway collapse during sedation. The inverse correlation is an unexpected finding, since BMI is often directly correlated with severity of OSAS. However, a recent investigation did not find a consistent relationship between Pcrit and either BMI or neck size in patients with OSAS and these parameters have not been investigated in non-OSAS subjects. Although the statistical significance of this inverse correlation in our subjects was strong, our number of subjects was relatively small, and there is no existing evidence that patients with larger BMIs are more resistant to the airway obstructing effects of sedatives. It may be that in subjects without OSAS, the larger BMI correlates with a larger airway that is more resistant to collapse. However, in OSAS patients, the increased BMI could correlate with an excess fat deposition in the upper airway. Further studies in both normal and OSAS patients will have to be made before definite conclusions as to the cause of this provocative correlation can be made.

The second major finding was the ability of flumazenil to completely reverse the tendency for midazolam to cause complete UAO during deep sedation. Although flumazenil reverses midazolam’s sedative and airway obstructive effects, its ability to reverse midazolam’s effect on upper airway patency has not been completely elucidated with a provocative test.

In summary, this study represents an important starting point for the investigation of one of the most important complications related to administration of drugs that depress consciousness. Dynamic Negative Airway Pressure is a useful method for provoking midazolam-induced UAO, and may potentially be used to compare the potential for different sedatives and patient factors to cause UAO.

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