Amnestic Agents in Pediatric Bronchoscopy*

Anthony D. Slonim, MD, MPH; and Frederick P. Ognibene, MD, FCCM, FACP

Study objective: To assess the risk for complications with the use of sedation and analgesia techniques in pediatric fiberoptic bronchoscopy.

Design: A retrospective case series.

Setting: The ICU of a 325-bed tertiary care research hospital.

Patients: Patients from 1 to 18 years of age who underwent fiberoptic bronchoscopy with BAL or transbronchial biopsy between June 1991 and December 1995 and received IV sedation and analgesia.

Interventions: None.

Methods: A retrospective chart review was performed. Extracted data included anesthetics and sedatives used and their per kilogram dosages, procedure durations, and complications including oxygen desaturations < 90%, vital sign alterations that required intervention, and emergence reactions to ketamine.

Results: A total of 103 bronchoscopies were performed on 64 patients. Ketamine was used as the primary anesthetic in 60 procedures (58%). A combination of fentanyl and midazolam was used in 38 of the 43 remaining procedures. A variety of combinations were used in the five remaining procedures. Complications occurred in 13 procedures and included oxygen desaturations, stridor, cough, apnea, and nasal bleeding. Twelve of the 13 complications occurred in patients with a diagnosis of HIV infection. Eight of the 13 complications involved children ≤ 3 years of age.

Conclusions: Pediatric bronchoscopy is a safe and valuable procedure. However, in this study, anesthetic selection was shown to adversely affect the complication rate in the subsets of children ≤ 3 years of age and with an underlying diagnosis of HIV infection.

(CHEST 1999; 116:1802–1808)

Key words: anesthesia; BAL; bronchoscopy; complications; fentanyl; ketamine; midazolam; pediatrics; procedures; pulmonary disease; sedation

The efficacy of the pediatric flexible bronroscope as a diagnostic and therapeutic tool has been previously demonstrated.1–22 Complications of the procedure that arise may be related to the performance of the procedure itself, to host factors such as age or severity of illness, or to sedation techniques that are used to facilitate the performance of the procedure.1–22

In the three largest pediatric fiberoptic broncoscopy series to date, two single institution studies with a total of > 2,500 procedures reported procedure-related complication rates of 3%.1,3 A large, multi-institutional European study of 51 centers that provided information on nearly 4,600 procedures reported complication rates in < 5% of the procedures in most of the centers.4 Although deaths related to the procedure do occur, they are rare.5 There are additional complications related to the procedure when BAL or transbronchial biopsy needs to be performed.

The relationship of complications to severity of...
illness has not been specifically expounded. Ultimately, a risk-benefit analysis by the operator is used to determine whether the procedure should be performed. However, other host factors, such as age, have been evaluated. The use of the fiberoptic flexible bronchoscope in infants, including those born prematurely, has been assessed. In these groups of patients, the procedure is often used to identify a malformation, to investigate a symptom such as stridor, or to identify complications arising from therapies in the neonatal period.

Sedation and anesthesia have been demonstrated to enhance the safety, technical ease, and comfort of many pediatric procedures. Sedation and anesthesia techniques for pediatric bronchoscopy have also been published. The use of an inhalational anesthetic during fiberoptic bronchoscopy is useful in maintaining physiologic homeostasis during the endoscopic procedure. However, the potential contamination of the procedure room with anesthetic gases and the excessive occupational exposure to personnel may limit the usefulness of inhalational anesthetics. In addition, use of the flexible bronchoscope has allowed the procedure to be moved out of the operating suite. It is now routinely performed in other clinical areas, where additional concerns about the scavenging of gases arise when using inhalational anesthetics. However, the description and systematic assessment of regimens of deep sedation and anesthesia without inhalational agents in pediatric flexible bronchoscopy outside of the operating room has not been previously presented.

In our institution, ketamine, typically in combination with sedatives or narcotics, is often used for analgesia and anesthesia in pediatric procedures. Ketamine has been shown in several large series to be a useful adjunct in the performance of pediatric procedures. However, in repetitive doses, ketamine can lead to the induction of general anesthesia, with its inherent potential for laryngospasm and anesthesia-related complications.

Ketamine, with the addition of a benzodiazepine, has been used successfully for total IV anesthesia in adult patients undergoing endoscopy. The use of ketamine in pediatric bronchoscopy has been limited. A single case series of five patients was reported in 1974. This report highlighted the safety of ketamine in pediatric rigid bronchoscopy performed in the operating room. There are some technical differences between the rigid bronchoscope and the flexible fiberoptic bronchoscope that may alter anesthetic selection. Most notably, the rigid bronchoscope is a hollow tube that allows ventilation to occur through its core. The flexible bronchoscope is a solid bundle of fibers around which the patient must breathe. In addition, there were two reports from the European literature that evaluated ketamine for IV anesthesia in the intubated pediatric bronchoscopy patient. Finally, one study evaluated the use of a combination of ketamine and diazepam in the nonintubated pediatric fiberoptic bronchoscopy patient. This study reports that a "serious" complication occurred in a single patient.

More typically, sedation for pediatric fiberoptic bronchoscopy consists of a benzodiazepine with or without a narcotic. Midazolam and diazepam are two of the more common benzodiazepines used in the studies on pediatric bronchoscopy, whereas meperidine and fentanyl are two of the more common narcotics used for the procedure. Hypnotic agents such as chloral hydrate and droperidol as well as major tranquilizers such as chlorpromazine have also been used.

Consequently, we decided to conduct a retrospective assessment of the complications associated with sedation for pediatric fiberoptic bronchoscopy that used the regimen of ketamine sedation and anesthesia, benzodiazepines, and narcotics in our institution.

Materials and Methods

Patients and Setting

The study was conducted in the ICU of the Warren G. Magnuson Clinical Center, which is the 325-bed tertiary care research hospital of the National Institutes of Health. Pediatric patients between the ages of 1 and 18 years who underwent bronchoscopy from June 1991 to December 1995 were identified from the ICU database. Patients who were intubated and receiving mechanical ventilation at the time of bronchoscopy were excluded from further analysis. The remaining patients who underwent bronchoscopic procedures for diagnostic purposes were included. In our institution, all pediatric procedures including bronchoscopy are performed in the ICU because of the monitoring capability and experience of the physician, nurse, and respiratory therapy staffs.

General exclusion criteria included the aforementioned intubated patients, patients with thrombocytopenia (platelet count < 50,000/μL) or severe hypoxemia (oxygen saturations of < 92% despite the use of supplemental oxygen).

Personnel

The medically responsible bronchoscopists were senior staff physicians with credentials in critical care with additional training in the management of the pediatric airway and the administration of parenteral sedatives and anesthetics for the performance of pediatric procedures. Each procedure was also performed in the presence of a critical care physician in fellowship training, a designated nurse who was responsible for patient monitoring and medication administration, and a respiratory therapist, with additional qualifications in the technique of bronchoscopy, who was present throughout the procedure to provide technical support and assist with patient monitoring.
Bronchoscopic Procedures

Informed consent and assent were obtained before each procedure. Institutional and departmental policies, developed in accordance with the recommendations of the American Academy of Pediatrics and the American Thoracic Society, were adhered to for patient monitoring, performance of bronchoscopy and transbronchial biopsies, and administration of anesthetics.15,35 The procedures were performed with continuous cardiopulmonary monitoring, blow-by aerosolized oxygen, and pulse oximetry. Patients had been without oral intake for at least 6 h before the procedure, and all had functional IV catheters in place.

Topical 1% lidocaine was applied to the posterior pharynx for local anesthesia. The lidocaine was delivered by a nebulizer attached to a simple face mask for children who were unable to cooperate with a hand-held nebulizer or atomizer. Lidocaine jelly was administered to the nares when a nasal approach was anticipated. Additional aliquots of 1% lidocaine were administered via the bronchoscope to the posterior pharynx, trachea, carina, and major bronchial divisions as the bronchoscope was advanced.

Sedation and anesthetic selection and dosage were determined by the bronchoscopist on the basis of the patient’s age, underlying disease, and physiologic status. They were administered in divided doses and titrated to the desired effects. Atropine, when given as an antisialagogue, was administered with the first doses of sedation. This often occurred while the topical anesthetics were being applied and the patient was being prepared for the procedure.

The bronchoscopy procedure was performed with either a 3.6- or 4.9-mm external diameter Olympus pediatric bronchoscope with video adaptor (Olympus America Incorporated; Melville, NY). BALs were performed with aliquots of 0.9% NaCl with the bronchoscope in the wedge position. Total amounts of 0.9% sodium chloride for lavage did not exceed 3 mL/kg. Transbronchial biopsies were performed under direct fluoroscopic guidance.

The procedures were terminated at the discretion of the senior bronchoscopist if there were oxygen desaturations below baseline that did not readily respond to removing the bronchoscope, manipulating the airway, or increasing the inspired oxygen concentration. In addition, increases in the work of breathing manifested as tachypnea, retractions, or nasal flaring, accessory breath sounds such as wheezing or stridor, vomiting, and the failure to attain adequate levels of sedation were all considered complications of the procedure.

Data Collection

This project was reviewed by the Office of Human Subjects Research of the Office of Intramural Research, National Institutes of Health. The investigators reviewed the charts. The weight, in kilograms, of the patient at the time of each procedure was identified from the chart. The drugs administered as well as their total doses were identified from the order sheets and verified in the nurses’ medication administration records. A dosage per kilogram of each drug was calculated and tabulated. The total duration of the bronchoscopy procedure was defined as the time from the first set of vital signs to the time of transfer to the ward or clinic. Total duration was identified from the notes of the dedicated nurse and recorded in minutes. Per clinical protocol, at the time of transfer, the child was awake, following commands, and able to take sips of liquid while protecting his or her airway. Finally, the progress notes and nurses’ notes were examined to identify whether any complications occurred during the procedure or postbronchoscopy follow-up period and what interventions were needed. Potential complications assessed in addition to the procedure-related complications mentioned above were aspiration, cough, rash, and the occurrence of an emergence reaction to ketamine. Emergence reactions are drug-related psychological phenomena that occur in some patients as the effects of ketamine are wearing off.

For the purpose of statistical analysis, each procedure was considered an independent event. As a result, demographic variables between groups were compared using the two-tailed Student’s t test. Primer of Biostatistics, a statistical software package (McGraw Hill; New York, NY), was used for computations.57 A p = 0.05 was used as the significance level in all circumstances.

Results

Sixty-four patients were identified. These 64 patients underwent 103 bronchoscopy procedures during the study period. There were 72 procedures (70%) performed in boys and 31 procedures (30%) performed in girls during the study period. The mean ± SD age for all patients was 9.2 ± 5.1 years, and the median age was 8 years (range, 1 to 18 years). Nearly half of the procedures (n = 46) were performed in patients who had HIV infection. Other diagnoses included chronic granulomatous disease (n = 20; 19%), Wegener’s granulomatosis (n = 12; 12%), and sarcoma (n = 7; 7%). Other diagnoses each contributed to <5% of the total procedures.

Forty-five patients had one bronchoscopy performed during the study period. Eleven patients had two bronchoscopic procedures performed. Four patients had three procedures, two patients had four procedures, and one patient had five procedures performed. One patient had 11 procedures performed.

Ketamine was used as the primary anesthetic in 60 of the procedures performed. Forty-five (75%) of these procedures used the combination of ketamine and midazolam for sedation. Fourteen procedures (23%) used other sedation combinations. In 11 of these 14 procedures, three drugs (ketamine, midazolam, and fentanyl) were given. Ketamine was used in combination with fentanyl in two procedures. Ketamine was used as single-drug therapy in an additional two procedures. Seventy percent of these ketamine procedures (n = 42) included pretreatment with atropine, in an appropriate dose based on weight, in an effort to decrease secretions and to prevent paradoxical vagal-mediated bradycardia.

The mean dose of ketamine was 1.9 ± 1.0 mg/kg (range, 0.5 to 6.4 mg/kg). The mean dose of midazolam, when used, was 0.07 ± 0.09 mg/kg (range, 0.01 to 0.15 mg/kg). In the 14 procedures that included fentanyl, a mean dose of 1.8 ± 1.7 μg/kg (range, 0.5 to 7.5 μg/kg) was used. All doses were given in divided aliquots and titrated to effect. The mean procedure duration was 178 ± 97 min (range, 30 to 515 min).
There were 43 procedures in which ketamine was not used as the primary anesthetic. In 38 of these 43 procedures (88%), the combination of fentanyl and midazolam was used for sedation. In the remaining five procedures, various combinations of medications were used. The combination of midazolam and morphine was used in two procedures, midazolam, fentanyl, and droperidol were used in one procedure, propofol alone was used in one procedure, and midazolam alone was used in one procedure. Pre-medication with atropine for the other regimens was not as common as when ketamine was used as the anesthetic; it was used in only one procedure. For regimens without ketamine, the mean dose of fentanyl was $2.2 \pm 1.4 \mu g/kg$ (range, 1 to 5.5 $\mu g/kg$). The mean dose of midazolam, when used, was $0.07 \pm 0.04\,mg/kg$ (range, 0.01 to 0.15 $mg/kg$). These doses were also given in divided aliquots and titrated to effect. The mean procedure duration was 195 $\pm$ 163 min (range, 60 to 770 min).

The overall complication rate was 13% ($n = 13$). However, for drug combinations that included ketamine as the anesthetic, there were 12 complications. One complication occurred in a patient who received midazolam alone as the sedative. There were no complications in the patients who received the narcotic and benzodiazepine combinations. Table 1 lists the patient demographics, drug dosages of the sedation regimen, complications, and therapeutic interventions required for each of the 13 complications. Of the 12 complications that involved ketamine, all patients had been pretreated with atropine.

The complications that occurred included symptoms that were referable to the respiratory system in 10 of the 13 procedures. These included apnea, desaturations, cough, retraction, and stridor. Vomiting occurred in one patient, and nasal bleeding occurred in two additional patients. Although there may be more than one reason for nasal bleeding to occur during bronchoscopy, inadequate sedation in the pediatric age group is one possibility that has specific relevance to this report on sedation in pediatric bronchoscopy.

Of interest, 12 of the 13 procedures associated with complications occurred in patients with HIV infection as the underlying diagnosis. Eight of the 13 procedures (62%) in the complication group involved children who were $\leq 3$ years of age.

### Discussion

Flexible fiberoptic bronchoscopy is routinely used for therapeutic and diagnostic purposes in the pediatric population, especially for immunosuppressed patients. Although the use of hypnoanalgesia improves patient tolerance and allays fears, sedation with pharmacologic agents can be of benefit to enhance the safety and comfort of the procedure.\(^1,24\)

There has been considerable controversy in the adult bronchoscopy literature about whether sedation is useful.\(^45-51\) In general, pediatric endoscopists seem to agree about the usefulness of sedation in bronchoscopy. However, sedation for pediatric fiberoptic bronchoscopy has not been well scrutinized.

Sedation in bronchoscopy is unique from sedation for other procedures. First, the pathologic process to be diagnosed and treated is either in the tracheobronchial tree or the pulmonary parenchyma and

**Table 1—Sedation Regimen and Therapeutic Interventions in 13 Pediatric Patients Who Experienced Complications During Bronchoscopy**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Diagnosis</th>
<th>Sedation (Dose)†</th>
<th>Time, min</th>
<th>Complications</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>HIV</td>
<td>Ketamine (2.0), atropine (0.06)</td>
<td><strong>275</strong></td>
<td>Transient apnea</td>
<td>Resolved</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>HIV</td>
<td>Ketamine (2.0), midazolam (0.05), atropine (0.02)</td>
<td>?</td>
<td>Desats</td>
<td>Bag ventilation 20–30 s</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>HIV</td>
<td>Midazolam (0.04), atropine (0.06)</td>
<td><strong>265</strong></td>
<td>Desats to low 80s</td>
<td>Oxygen and airway maneuvers</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>HIV</td>
<td>Ketamine (2.0), midazolam (0.1), atropine (0.02)</td>
<td><strong>360</strong></td>
<td>Transient desats</td>
<td>Blow-by oxygen</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>HIV</td>
<td>Ketamine (2.0), midazolam (0.1), atropine (0.03)</td>
<td><strong>90</strong></td>
<td>Rash/desats</td>
<td>Blow-by-oxygen</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>HIV</td>
<td>Ketamine (1.5), midazolam (0.06), atropine (0.02)</td>
<td><strong>165</strong></td>
<td>Cough</td>
<td>Albuterol</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>HIV</td>
<td>Ketamine (1.0), fentanyl (0.5 $\mu g/kg$), atropine (0.02)</td>
<td>?</td>
<td>Stridor</td>
<td>Racemic epi and ICU admission</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>HIV</td>
<td>Ketamine (6.0), midazolam (0.1), atropine (0.03)</td>
<td><strong>195</strong></td>
<td>Stridor/desats</td>
<td>Racemic epi/oxygen with bagging</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>HIV</td>
<td>Ketamine (2.0), midazolam (0.04), atropine (0.02)</td>
<td><strong>180</strong></td>
<td>Retractions</td>
<td>ICU admission</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>HIV</td>
<td>Ketamine (3.0), midazolam (0.075), atropine (0.02)</td>
<td><strong>165</strong></td>
<td>Nasal bleeding</td>
<td>Controlled with pressure</td>
</tr>
<tr>
<td>11</td>
<td>8</td>
<td>HIV</td>
<td>Ketamine (2.5), midazolam (0.08), atropine (0.02)</td>
<td><strong>30</strong></td>
<td>Nasal bleeding</td>
<td>Controlled with pressure</td>
</tr>
<tr>
<td>12</td>
<td>9</td>
<td>HIV</td>
<td>Ketamine (1.0), midazolam (0.01), fentanyl (1.0 $\mu g/kg$), atropine (0.02)</td>
<td><strong>90</strong></td>
<td>Apnea/desats</td>
<td>Bag ventilation 20 s</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
<td>CGD</td>
<td>Ketamine (1.5), atropine (0.01)</td>
<td><strong>170</strong></td>
<td>Vomited</td>
<td>Intubated for procedure</td>
</tr>
</tbody>
</table>

*CGD = chronic granulomatous disease; Desats = oxygen desaturations; epi = epinephrine.
†Doses are in milligrams per kilogram, unless otherwise stated.
may be altering the individual’s ability to oxygenate and ventilate. Secondly, the bronchoscope is in the airway and may further compromise the patient’s ventilatory function. Transient coughing and desaturation occur in bronchoscopy procedures even in patients without significant tracheal or pulmonary disease. Finally, sedation, regardless of drug classification, may add another insult to a pulmonary system that may already be compromised.

The current study demonstrates how the complication rate associated with the performance of pediatric bronchoscopy may be adversely affected by the anesthetic selected. Ketamine was associated with adverse events in 12 of the 60 bronchoscopy procedures (20%) in which it was used. Most of these occurred in two subsets of patients: patients with HIV infection and patients ≤ 3 years of age. The smaller airway size or the severity of the underlying disease may be factors contributing to the number of subsequent complications. In contrast, narcotic and benzodiazepine combinations did not lead to any adverse events.

Pharmacologic combinations have been used with success in our ICU for all types of pediatric sedation including pediatric bronchoscopy, but our results with ketamine as an anesthetic agent in pediatric bronchoscopy have not been uniformly successful. Our bronchoscopists often choose ketamine combinations for use in the younger bronchoscopy patient because of its amnestic, analgesic, and dissociative properties that allow for a more controlled procedure in this population. Older children will often be more amenable to calming and reassurance. Therefore the use of a narcotic and benzodiazepine combination will provide adequate sedation for these older patients in most instances.

In the majority of our study population, bronchoscopy was clinically indicated to diagnose pulmonary infections in an immunocompromised patient. This is different from most other general pediatric series in which the major indications for the procedure include the evaluation of stridor and wheezing and the assessment of airway anatomy and unresolved pneumonia. The severity of underlying disease may play a role in causing complications from any sedative or anesthetic.

It is not entirely clear why such a large proportion of HIV-infected patients (29%) experienced complications in our study. It is possible that the severity of lung disease or hypoxia before the procedure, in conjunction with ketamine anesthesia, may have contributed to the higher complication rate. Several other series, in which pediatric HIV-infected patients underwent bronchoscopy, have demonstrated at least six complications in a total population of 118 patients (5%). Many of the complications were similar to those seen in our series ie, tachypnea and transient problems with respiratory function. The patients in the other series received sedation including meperidine alone or in combination with promethazine and chlorpromazine. Nine of those patients were intubated before the bronchoscopy.

Another subset of patients that experienced complications in the present study were those children ≤ 3 years of age. There were 16 patients ≤ 3 years of age, and all of these younger patients had the primary diagnosis of HIV infection. Two studies have focused on the younger AIDS patient (age range, 2 to 54 months). In these two studies, six complications occurred in 45 (13%) patients. The complications observed were similar to those in our population; however, narcotics were used as the anesthetic in these younger patients when ketamine was used for sedation in the setting of cardiac catheterization.

The use of ketamine as an agent to facilitate the performance of pediatric procedures has been well described. Some authors also believe that ketamine may represent the “optimal agent for intravenous sedation during bronchoscopy” in the pediatric patient. The evidence for the safe use of ketamine in pediatric bronchoscopy is limited.

Ketamine has been associated with laryngospasm, increased oral secretions, and alterations in pulmonary artery pressure, pulmonary vascular resistance, oxygen consumption, heart rate, and cardiac output. Respiratory compromise related to ketamine has been specifically assessed in a number of large studies, as well as in a variety of locations, and has been consistently found to occur in approximately 3% of procedures. This is in comparison to complications after ketamine administration in 12 of 60 bronchoscopy procedures (20%) in our present study. As already noted, patients will often undergo bronchoscopy to establish the diagnosis of a pathologic process in the lung or airway. Many patients already required supplemental oxygen because of their lung disease. This may account for the higher frequency of complications observed in our study sample.

Regardless of the anesthetic method selected, basic tenets of care need to be followed. A healthcare professional skilled in the monitoring of a patient’s cardiorespiratory status and able to handle airway emergencies should be present if sedation is administered. Preparation, in terms of education, experience, and equipment, must be guaranteed. The child should not have eaten for 6 h before the procedure, should be monitored by ECG and pulse oximetry, and should have functioning IV access during the procedure. The effect of advanced and ongoing psychological preparation cannot be mini-
mized.1,28,37 When practical, we visit with the child and parent before the procedure to explain the procedure and to obtain assent and consent. A calm reassuring environment, with soothing conversation, is as important in minimizing stress as the sedative agent selected.1,15,16,28

Although numerous reports have found that ketamine is safe and efficacious for the performance of pediatric procedures, our findings indicate that its use in pediatric bronchoscopy may contribute to procedure-associated complications. Controlled, prospective studies, similar to those performed in adult patients, are necessary to sort out the best sedation strategy that also minimizes complications in pediatric patients undergoing flexible fiberoptic bronchoscopy.

ACKNOWLEDGMENT: The authors thank Drs. Murray M. Pollack and Anthony F. Suffredini for their thoughtful and critical review of the manuscript, the nurses and critical care therapists in the 10D ICU in the Warren G. Magnuson Clinical Center at the National Institutes of Health for the compassionate care of these patients, and Shalana Millard and Candise Kurtz for their assistance in manuscript preparation.

REFERENCES

28 Blair KC. Sedation and hypnotalgesia in pediatric endoscopy. Soc Gastrointest Assistants, 1985; Spring:230–233
33 Greene CA, Gillette PC, Fyfe DA. Frequency of respiratory compromise after ketamine sedation for cardiac catheterization in patients < 21 years of age. Am J Cardiol 1991; 67:1116–1117
43 Mueller B, Briest HJ, Optiz J. Experiences using ketamine in pediatric bronchologic studies. Z Erkr Atmungsorgane 1986; 166:221–222
46 Toft P, Romer U. Comparison of midazolam and diazepam to supplement total intravenous anaesthesia with ketamine for endoscopy. Can J Anaesth 1987; 34:466–469