A case report: The use of ketamine and midazolam intravenous sedation for a child undergoing radiotherapy

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The combination of ketamine hydrochloride and midazolam was used to successfully provide intravenous sedation for a child requiring daily radiation treatments. During the radiation therapy treatments, the anesthesia provider was not in direct contact with the patient. Traditional monitoring was complemented by the addition of closed-circuit television monitoring. The drug combination provided consistent cardiac and respiratory stability, as well as patient immobility, for each radiation treatment.

Key words: Ketamine, midazolam, radiotherapy.

Introduction
The anesthesia staff at the U.S. Air Force Medical Center, Wright Patterson Air Force Base, Ohio, has been involved in the care of a child requiring sedation for radiotherapy. The combination of ketamine hydrochloride and midazolam has been used successfully to provide intravenous sedation during the child's 6-week course of daily radiotherapy treatments.

The patient was a 32-month-old, 15-kg male with a history of an intracranial medulloblastoma, which was initially debulked in September 1990. In October 1990, the patient had a ventriculoperitoneal shunt placed. He then received chemotherapy. Although a followup magnetic resonance imaging (MRI) in March 1991 revealed remission of the residual tumor, in May 1991 he had a grand mal seizure. Phenytoin was used to control the seizure disorder. A repeat MRI showed regrowth of the tumor, which was felt to be unresectable, so radiotherapy was initiated in July 1991.

The radiotherapy procedure required the patient to be placed in a preformed body mold in the prone position (Figure 1). The facial portion of the mold was cut out and padded to provide access for an oxygen mask. The patient was then aligned for the radiotherapy treatments using a laser for guidance.

The anesthetic challenge was to keep the child completely immobilized during the radiotherapy.
treatments, provide amnesia for the procedure, insure appropriate oxygenation and ventilation, and maintain cardiovascular stability. Ideally, intubation and mechanical ventilation could be avoided by maintaining spontaneous respirations. Each of the 30 treatments lasted 15-35 minutes.

The setup

The radiotherapy chamber was readied to give general endotracheal anesthesia, should it become necessary. An anesthesia machine was brought into the chamber as well as standard monitoring that included an electrocardiograph (ECG), pulse oximeter, and noninvasive blood pressure monitor. Mask oxygenation precluded the use of capnography.

Since no one could be with the child in the chamber during the radiotherapy treatment, a series of television cameras were used. Two cameras allowed direct visualization of the patient. One camera was trained on the child, providing a lateral view. A second camera provided a view from above, focusing on the thorax. The images portrayed on the closed-circuit monitor were so clear that the child’s chest could be seen rising and falling with each breath. A third camera was focused on the ECG, noninvasive blood pressure monitor, and pulse oximetry monitor readouts (Figure 2).

The television monitoring and pulse oximeter allowed continuous monitoring of the patient’s ventilation and circulation, as required by the Harvard Criteria published in 1986. While the means to monitor temperature were available, temperature monitoring was not done because the procedures were short and the patient was covered with a blanket from his shoulder blades to his feet.

Consideration also was given to using a radio-transmitting precordial stethoscope to provide redundancy in monitoring heart rate and ventilation. Some of the information gained from a precordial stethoscope cannot be duplicated by other monitors. Heart tones and quality of ventilation may be difficult to assess without a precordial stethoscope. A continuous ECG tracing and a corresponding pulse oximeter reading were used to indicate pulsatile flow and the absence of electromechanical dissociation. Visualization of the thorax rising and falling and the continuous hemoglobin saturation reading from the pulse oximeter yielded information concerning the adequacy of ventilation. Therefore, a radio-transmitting precordial stethoscope was not used.

Contingencies for emergencies were discussed in advance. A dry run of emergency access to the chamber was completed before the radiotherapy treatments began. The time from emergent termination of the radiation treatments to patient access was 15 seconds. In the event of a respiratory or cardiac arrest, equipment was available for immediate intubation and implementation of advanced cardiac life support.

Case summary

Before each of the treatments, the child and his parents were met in the radiation holding area. The patient had a previously established central venous catheter for intravenous access. Each treatment was scheduled for 7:30 am, with the child having nothing by mouth after midnight. The patient willingly allowed access to the central venous catheter, and a balanced salt solution was initiated. This was followed by sequential administration of atropine 0.02 mg/kg, midazolam 0.1 mg/kg, and ketamine 2 mg/kg intravenously as a bolus.

The onset of sedation was rapid. Within 60 seconds the child appeared “dissociative”; both eyes were open with nystagmus present, spontaneous regular respirations continued, and the patient’s heart rate increased 10% above baseline. The patient was then taken into the radiation chamber and positioned prone in the body mold. Next, warm blankets were used to cover him from his shoulder blades to his feet. Oxygen by face mask was initiated at 5 L/min, and all monitors were applied. If the child exhibited spontaneous movement during the initial portion of positioning for the procedure, an additional bolus of ketamine 2 mg/kg was given. Sedation was maintained by an infusion of ketamine and midazolam. In a volutrol with 50 mL of fluid, 150 mg of ketamine and 2 mg of midazolam were added. The initial rate of the infusion was 2 mL per minute. The infusion rate was adjusted if the pa-
tient demonstrated spontaneous movement, an increase in blood pressure or heart rate, or an increase in respiratory rate. The infusion was immediately discontinued at the conclusion of the radiotherapy treatment, the intravenous line was flushed, and the child was taken to a recovery area. The child was awake and discharged from recovery in 60-90 minutes after discontinuation of the infusion.

**Discussion**

Ketamine has been used alone for sedating children for radiotherapy.\(^1,2\) The combination of ketamine and midazolam was chosen intentionally in hopes of complementing the action of each drug. Although this is not intended to be a comprehensive review of ketamine and midazolam pharmacokinetics and pharmacodynamics, a review of some of the salient features of each drug is indicated in order to appreciate the complementary nature of this combination.

Ketamine is a phencyclidine derivative that produces dissociative anesthesia, characterized by electroencephalographic evidence of dissociation between the thalamus and the limbic system.\(^3\) Ketamine has been in clinical use since 1970. Its mechanism of action for analgesia is depression of the medial thalamic nuclei. The drug also interferes with transmission of the affective-emotional component of pain.

Ketamine resembles thiopental in terms of its rapid onset of action, relatively short duration (elimination half-time 1-2 hours), and high lipid solubility pKa of 7.5 at pH 7.4. It is a potent cerebral vasodilator capable of increasing cerebral blood flow 60% in the presence of normocapnea.\(^4\) The child's existing neurologic status—awake, alert, without evidence of increased intracranial pressure, and presence of a functioning ventriculoperitoneal shunt—indicated that this drug combination could be used safely.

Ketamine does not produce significant depression of ventilation. The ventilatory response to PaCO\(_2\) is maintained during ketamine anesthesia. Upper airway skeletal muscle tone is well-maintained, and upper airway reflexes remain relatively intact.\(^5\) Despite preserving airway reflexes, ketamine does not negate the vigilance necessary to prevent aspiration. The increase in salivary and tracheobronchial mucus gland secretions associated with ketamine requires an antisialogogue to be administered prior to its use. Therefore, atropine was included in the regimen.

The cardiovascular effects of ketamine resemble sympathetic nervous system stimulation in adults. There is an increase in systemic and pulmonary arterial blood pressure, cardiac output, cardiac work, and myocardial oxygen requirements. In contrast, ketamine administered to mildly sedated infants fails to produce hemodynamic changes in either systemic or pulmonary circulation.\(^6\)

Ketamine is metabolized extensively by hepatic microsomal enzymes. A major pathway of metabolism is by cytochrome P-450 enzymes to form norketamine, a metabolite one-fifth to one-third as potent as ketamine. Chronic administration of ketamine results in stimulation of these enzymes which are responsible for its metabolism.\(^6\)

There is a case report of tolerance developing with repeated administration of ketamine.\(^7\) There was concern about tolerance at the onset of the anesthetic procedure, since it was assumed enzyme induction already existed from weeks of therapy using phenytoin, a drug known to induce the cytochrome P-450 system. Depending on the length of the procedure, the child received as much as 190-400 mg of ketamine, which is 12-26 mg/kg and 2-4 mg of midazolam, which is 0.15-0.30 mg/kg.

The emergence delirium reported with ketamine appears to be prevented by the prior administration of benzodiazepines. Documentation of emergence delirium in children is rare. Children are thought to possibly experience this phenomenon with the same frequency as adults, but are unable to verbalize the experience. Midazolam was added to this anesthetic to provide the additional benefits of a benzodiazepine:

1. Production of amnesia.
2. Minimal depression of ventilation.
3. Relative safety in overdose.
4. Rare development of tolerance.

The disadvantage of administering benzodiazepines prior to the advent of midazolam was their long elimination half-life. Diazepam (elimination half-life 21-37 hours) and lorazepam (elimination half-life 10-20 hours) had been the only choices available.\(^6\) Midazolam, with an elimination half-life of 1-4 hours, appears to be an excellent choice of adjunctive therapy with ketamine. The potential benefit of this drug combination was postulated as early as 1982.\(^3\)

Midazolam is a water-soluble benzodiazepine with an imidazol ring in its structure which accounts for its stability in aqueous solution and rapid metabolism. Midazolam is 2-3 times as potent as diazepam. The short duration of midazolam (elimination half-life 1-4 hours) is the result of its lipid solubility, leading to rapid redistribution from the brain to inactive tissue, as well as its rapid hepatic clearance. Midazolam is almost totally metabolized by the hepatic microsomal enzymes, and very little is excreted unchanged in the kidneys.\(^8\)
Benzodiazepines exert their antianxiety effects by increasing the availability of glycine inhibitory neurotransmitter. Their sedative action reflects the ability of the benzodiazepines to facilitate the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The site of action for the production of amnesia has not been determined.

Midazolam also provides physiologic stability. It can decrease cerebral blood flow 39% and is an acceptable alternative to barbiturates for induction of anesthesia in patients with intracranial pathology. When considering the degree of depression of ventilation, midazolam 0.15 mg/kg is similar to diazepam 0.3 mg/kg. Cardiac output is not altered. The antegrade amnesia provided by midazolam is dose-related and parallels the degree of sedation.

The child in this case study had no recall of intraprocedural events and happily submitted to the initiation of sedation every day of his treatments. The combination of ketamine and midazolam appears to be an effective anesthetic for sedation of a 32-month-old undergoing radiotherapy for brain cancer. The child exhibited cardiovascular and respiratory stability and remained motionless in his body mold for the entire procedure.

To the advantage of the staff, a previously existing intravenous catheter was available for access. If it had been necessary to gain intravenous access by daily venopuncture, this technique may have been less desirable. Daily venopuncture might have led to the patient experiencing displeasure, but the child happily submitted to the daily routine of intravenous sedation. Sedation via other routes—oral, rectal, or intramuscular—may be inconsistent because of altered uptake and the bioavailability of active drug concentrations by these routes. It is believed that with appropriate monitoring and thorough planning, this technique can be repeated with equal success in other children.

REFERENCES

AUTHORS
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ACKNOWLEDGMENT
The authors would like to thank Col Henry Abbott, CRNA, for his editorial assistance on this article.

The opinions or assertions in this article are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Department of the Air Force or the U.S. Department of Defense.