Preinduction of Anesthesia in Children with Rectally Administered Midazolam

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The authors evaluated the efficacy of rectally administered midazolam for preinduction (i.e., premedication/induction) of anesthesia in 67 pediatric patients, ASA physical status 1 or 2, undergoing a variety of elective surgical procedures. In phase 1, 41 children weighing 12 ± 3 kg (range 7–20 kg) and 31 ± 16 months (range 8–67 months) of age (mean ± SD) received midazolam, 0.4–5.0 mg·kg⁻¹, in an attempt to produce unconsciousness. Only one child lost consciousness (4.5 mg·kg⁻¹). However, at all doses, inhalational induction of anesthesia was facilitated because children were tranquil and calmly separated from their parent(s). There were no clinically significant changes in arterial blood pressure, heart rate, oxyhemoglobin saturation, and end-tidal carbon dioxide concentration, 10 min after drug administration. In phase 2, 26 children weighing 17 ± 4 kg (range 10–26 kg) and 44 ± 19 months (range 17–84 months) months of age undergoing tonsil and/or adenoid surgery were studied to determine the optimal sedative dose of rectally administered midazolam. Patients received 0.3, 1.0, 2.0, or 3.0 mg·kg⁻¹ of midazolam in a randomized, double-blind fashion. One third (3 of 9) of patients receiving 0.3 mg·kg⁻¹ struggled during mask induction. All patients receiving ≥1.0 mg·kg⁻¹ were adequately sedated ($P < 0.008$). Discharge from the postanesthesia care unit (PACU), however, was delayed (>60 min) in children receiving ≥2.0 mg·kg⁻¹ ($P < 0.03$). Therefore, the authors conclude that rectally administered midazolam in a dose of 1.0 mg·kg⁻¹ is effective for preinduction of anesthesia and does not delay discharge from the PACU. (Key words: Anesthesia: pediatric. Anesthetic techniques: rectal. Anesthetics, rectal: midazolam. Induction: anesthesia. Premedication: midazolam.)

FEAR OF PAINFUL and unpleasant procedures, separation from parents, and an unwillingness to breathe through an anesthesia face mask may produce stormy anesthetic inductions in unpremedicated children.[1,2] Because of this, preanesthetic sedation has become an integral part of pediatric anesthetic practice. A variety of medications ad-

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ministered at various times and by various routes (oral,[3,4] nasal,[5,6] intramuscular,[7] transmucosal,[8] and rectal[9,10]) have been used for this purpose. Unfortunately, each drug and administration technique has some disadvantage. A drug and method of delivery that enhance the anesthesiologist's ability to induce anesthesia effectively and atraumatically remain elusive.

Henderson et al. have recently introduced the concept of "preinduction of anesthesia" with nasally administered sufentanil.[5] "Preinduction of anesthesia induces a state of consciousness different from that produced by premedicants administered orally or intramuscularly. In this technique, children become relaxed, occasionally euphoric, and usually calm and cooperative. It differs from premedicants such as rectally administered methohexital in that it does not produce drowsiness or sleep."[5]

The rectal route of drug administration is our preferred approach for children less than 6 yr of age. It is reliable, rapid, and virtually painless, and it allows anesthesia to be induced in children in the presence of their parents. Additionally, rectal administration allows a drug to be given in the operating room when it is needed, immediately prior to the induction of anesthesia, rather than "on call."

Midazolam is well absorbed after rectal administration.[11,12] A potential benefit of midazolam is that its hypnotic and respiratory depressant effects may be antagonized by the investigational agent flumazenil.[13,14] The purpose of this study was to determine if rectally administered midazolam could produce unconsciousness in young children. In addition, we sought to determine if an optimal dose for preinduction of anesthesia existed that would still allow rapid recovery from general anesthesia and timely discharge from the postanesthesia care unit (PACU).

Materials and Methods

We studied 67 children, ASA physical status 1 or 2, undergoing a variety of elective surgical procedures. Approval was obtained from the Institutions' Joint Committee on Clinical Investigation, and informed parental consent was obtained.

The study was conducted in two phases. In phase 1 we sought to determine the dose of rectally administered midazolam that would produce unconsciousness within 10 min of drug administration. We also sought to study

the hemodynamic and respiratory consequences of midazolam when administered in this fashion. In phase 2 we sought to determine an optimal dose of rectally administered midazolam for preinduction of anesthesia that would also allow rapid recovery from general anesthesia and timely discharge from the PACU.

In phase 1, midazolam was diluted with saline and given rectally through the lubricated tip of a 14-Fr suction catheter. It was administered as a 2 mg/ml solution unless the volume exceeded 10 ml, in which case it was not diluted (5 mg/ml). The drug was administered in the presence of the child's parent(s), 10 min prior to the start of anesthesia, in a preinduction area, immediately adjacent to the operating rooms. An escalating dose schedule was used, starting at 0.4 mg·kg^{-1}. Five children were to be studied at each dose. If loss of consciousness, defined as unresponsiveness to verbal stimulation and/or absence of voluntary and purposeful movements when unstimulated, did not occur within 10 min of drug administration in 2 patients at any given dose, that dose was abandoned, and the next higher dose was begun in subsequent patients. The study was designed to be terminated if apnea or prolonged postanesthetic recovery (>60 min) occurred at any dose. Two children were studied at all but the highest of the following doses: 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.5, 4.0, 4.5, and 5.0 mg·kg^{-1}. Noninvasive systolic arterial blood pressure (model 1846SX, Dinamap), heart rate, and oxyhemoglobin saturation (Sp$_{O_2}$) (N-100 pulse oximeter, Nellcor) were measured before and 10 min after drug administration. End-tidal carbon dioxide concentration was measured 10 min after midazolam administration in 16 children by an infrared capnometer (model 47210A, Hewlett-Packard) attached to the anesthesia face mask.

Anesthesia was induced in all patients with halothane (2–4%), nitrous oxide, and oxygen (30%), administered by a resident physician. Anesthesia was maintained with a variety of anesthetic agents and techniques according to the preference of the attending anesthesiologist. All patients were responsive prior to transfer from the operating room to the recovery room. A standardized scoring system based on consciousness, airway control, and movement was used to assess awakening at 0, 15, 30, 45, and 60 min after arrival in the PACU.[15]

In phase 2, midazolam 0.3, 1.0, 2.0, 3.0 mg·kg^{-1} was administered rectally in a randomized fashion by an attending anesthesiologist unaware of the dosage of drug being administered. The anesthetic technique was standardized. Anesthesia was induced, by a resident physician, with halothane (2–4%), nitrous oxide, and oxygen (30%), 10 min after midazolam administration. With loss of consciousness, an intravenous infusion was started, and atracurium 0.5 mg·kg^{-1} was administered. Halothane was

discontinued after oral tracheal intubation, and anesthesia was maintained with nitrous oxide (70%), oxygen (30%), and fentanyl (2.0 μg·kg^{-1}). At the conclusion of surgery, nitrous oxide was discontinued and muscle paralysis antagonized with edrophonium (1 mg·kg^{-1}) and atropine (0.01 mg·kg^{-1}). The trachea was extubated when regular spontaneous ventilation occurred and when a nerve stimulator demonstrated sustained tetanus.

The attending anesthesiologist assessed the child's mood (calm or agitated) and attempted to separate the child from his or her parent(s) immediately before and 10 min after midazolam administration. The attending anesthesiologist also determined the child's cooperation (acceptance of an anesthesia face mask and absence of physical and verbal resistance at the induction of anesthesia) as well as airway complications at the induction and emergence from anesthesia (e.g., laryngospasm, coughing, or vomiting). Finally, using the same standardized postanesthesia recovery scoring system used in phase 1, the attending anesthesiologist determined the time of emergency and recovery from anesthesia.[15] If three or more patients experienced prolonged recovery (>60 min) after a study dose of midazolam, that dose was eliminated from further study.

In phase 1, the effects of increasing the midazolam dose on arterial blood pressure, heart rate, Sp$_{O_2}$, and end-tidal carbon dioxide concentration were analyzed using linear regression analysis. P values less than 0.05 were considered significant. In phase 2, differences among midazolam dosage groups in the proportion of patients accepting face mask, resisting gas induction, and requiring prolonged PACU stays were compared using the chi-squared test with 3 degrees of freedom. Patients receiving 1.0 mg·kg^{-1} or more of midazolam were combined into a single group for comparison to those receiving 0.3 mg·kg^{-1} by means of Fisher's exact test. Data are presented as the mean ± standard deviation (SD).

Results

In phase 1, we studied 41 children, ASA physical status 1 or 2, weighing 12 ± 3 kg (range 7–20 kg) and 31 ± 16 months of age (range 8–67 months), who underwent a variety of elective surgical procedures. Rectally administered midazolam did not reliably produce unconsciousness at any administered dose (0.4–5.0 mg·kg^{-1}). In fact, only 1 child lost consciousness, and that occurred at a dose of 4.5 mg·kg^{-1}. The highest dose (5.0 mg·kg^{-1}) resulted in delayed discharge (>60 min) from the PACU. The duration of anesthesia and surgery averaged 163 ± 133 (range 30–630) min.

There was no clinically significant effect of midazolam dose (0.4–5.0 mg·kg^{-1}) on arterial blood pressure, heart

rate, and Sp_{O_2}, 10 min after drug administration. Indeed, regardless of dose, the effects of midazolam on heart rate and blood pressure were inconsistent. Ten minutes after administration, heart rate ranged between 88 and 147 beats per min, and arterial blood pressure ranged between 75 and 111 mmHg. In addition, Sp_{O_2} did not decrease below 96%, and end-tidal carbon dioxide concentration did not exceed 42 mmHg after any dose of midazolam.

In phase 2, we studied 26 children, weighing 17 ± 4 kg (range 10–26 kg) and 44 ± 18 months of age (range 17–84 months), who underwent elective adenoid and/or tonsil surgery. Every child enrolled in this phase of the study was sedated, as determined by a willingness to separate from parent(s), within 10 min of receiving midazolam rectally (fig. 1). This occurred regardless of the administered midazolam dose (0.3, 1.0, 2.0, or 3.0 $mg \cdot kg^{-1}$). The pattern of sedation was similar in all patients receiving ≥ 1.0 $mg \cdot kg^{-1}$ of midazolam. Before sedation, many (10 of 17) of these children were terrified or crying or were clinging to their parent(s). Within 5–7 min of midazolam administration, their behavior changed dramatically. Children stared dreamily into their parent's eyes, became tranquil, and often started to laugh and act giddy. Indeed, they appeared intoxicated. Approximately 10 min after drug administration, patients appeared to be even more heavily sedated, although none was asleep (fig. 1).

At the lowest dose (0.3 $mg \cdot kg^{-1}$), one third (3 of 9) of the children struggled when the anesthesia face mask was initially applied and during the inhalational induction of

anesthesia, even though they appeared calm when placed on the operating room table (fig. 1). Physical resistance to the induction of anesthesia did not occur in the 17 children receiving doses ≥ 1.0 $mg \cdot kg^{-1}$ ($P < 0.04$, Fisher's exact test). Mask acceptance differed significantly between those receiving different doses of midazolam, and resistance occurred most commonly at the lowest dose ($X^2 = 8.68, P < 0.04$). There were no airway complications, such as coughing, laryngospasm, or vomiting, at induction or emergency from anesthesia in this study, even in the children not adequately sedated and who struggled during anesthetic induction. Furthermore, there was no need for postoperative airway support or opioid antagonism in any patient in the study, even among patients who experienced delayed (>60 min) awakening. No child complained of rectal pain or burning after administration of the midazolam solution in this study, and only 3% (2 of 67) defecated intraoperatively.

Finally, in phase 2 of the study, 1.0 $mg \cdot kg^{-1}$ of rectally administered midazolam did not significantly delay discharge from the PACU (fig. 1). In this phase of the study, anesthesia and surgery averaged 52 ± 11 min (range 35–77 min). Patients receiving 1.0 $mg \cdot kg^{-1}$ of midazolam met discharge criteria from the PACU within 32 ± 14 min (range 20–60 min) of arrival, approximately 90 min after the drug was administered. At the higher doses (2.0, 3.0 $mg \cdot kg^{-1}$), recovery was prolonged and averaged 105 ± 44 min (range 70–150 min) after arrival in the PACU (fig. 1). The proportion of patients requiring prolonged PACU stays differed significantly among groups ($X^2 = 15.38, P < 0.0015$).

Discussion

Rectal administration of midazolam, at a dose of 1.0 $mg \cdot kg^{-1}$, is a clinically useful tool in the anesthetic management of children. As a preinduction agent, this dose of midazolam reliably eases separation of a child from his or her parent(s) and facilitates a smooth, struggle-free inhalational induction of anesthesia. Additionally, this dose of midazolam neither delayed emergence from general anesthesia nor prolonged the discharge time from the recovery room. Rectally administered midazolam did not reliably result in the loss of consciousness over a wide dose range (0.4–5.0 $mg \cdot kg^{-1}$). It also had no clinically significant effect on heart rate, arterial blood pressure, and Sp_{O_2}. Finally, in this small study, airway complications, such as coughing, laryngospasm, or vomiting, were uncommon at both induction and emergence from anesthesia.

Rectal (or nasal) preinduction of anesthesia is unlike classic premedication using either the oral or intramuscular route of drug administration.[2-11] With the latter
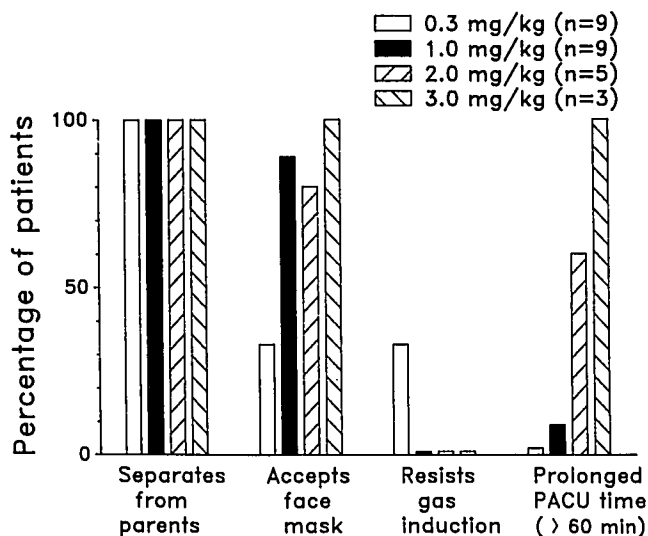

FIG. 1. The percentage of patients (phase 2) who separated from their parent(s), accepted an anesthesia face mask calmly, and did not physically struggle during the mask inhalational induction of anesthesia. Prolonged or delayed (>60 min) discharge from the postanesthesia care unit is also shown.

approaches, timing is crucial if the sedation achieved is to be useful to the anesthesiologist. In our experience, the administered drug must be given at least 30–45 min, and no longer than 90 min, prior to induction of anesthesia. Unfortunately, this is becoming extremely problematic in current anesthetic practice. Unanticipated changes in the operating room schedule and the occasional hindrances in patient transport to the operating room, particularly in an active outpatient practice, commonly result in children either entering the operating room before sedation has taken effect or after the effect has abated.

On the other hand, preinduction of anesthesia is very rapid (usually 10 min), allowing the anesthesiologist to administer sedative drugs when they are needed, immediately prior to the induction of anesthesia, rather than "on call" to the operating room. Furthermore, because the anesthesiologist is personally administering the drug, it allows for constant observation of the patient from the time the drug is given. Thus, sedation can be achieved more safely because a trained observer with readily available resuscitation equipment is always present.

Rectally administered midazolam must also be differentiated from rectally administered methohexital.[9,10] Rectally administered methohexital produces unconsciousness, which greatly facilitates the mask (or intravenous) induction of general anesthesia but potentially increases the risk of apnea and airway obstruction. On the other hand, children receiving midazolam rectally are awake but cooperative and are calmly willing to separate from their parent(s). Additionally, they offer minimal resistance either to the mask inhalational induction of anesthesia or to the placement of monitoring devices.

Midazolam has several characteristics that potentially make it a useful drug for preinduction sedation in children.[5,6,11,12] It is water-soluble and nonirritating; it is rapidly absorbed and metabolized; and it has anxiolytic and amnestic properties. Additionally, it may be antagonized by the investigational agent flumazenil.[13,14] On the other hand, it is an expensive drug (approximately $1.00 per milligram).

There were no clinically significant changes in arterial blood pressure, heart rate, and Sp_{O_2} over a wide dosage range (0.4–5.0 mg·kg^{-1}). In addition, Sp_{O_2} did not decrease to less than 96%, nor did end-tidal carbon dioxide concentration increase to more than 42 mmHg in any patient in this study. In comparison, a recent report of Sp_{O_2} after rectal methohexital (24–34 mg·kg^{-1}) administration in children showed desaturation (oxygen saturation 89% or less) in 17% of patients receiving the drug.[16] Our measurements of end-tidal carbon dioxide concentration were obtained via an anesthesia face mask and must be interpreted cautiously. In this method, the increased dead space of the anesthesia face mask, as well as

entrainment of room air, may dilute the carbon dioxide measured. However, this technique has been used by others, and we believe that it provides a reasonable approximation of the true carbon dioxide tension.[17] Nevertheless, midazolam is known to depress both the chemoreceptor response to hypoxia and the ventilatory response to carbon dioxide, and close patient monitoring is mandatory whenever this drug is given to any patient, regardless of the route of administration.[18–20]

No child complained of either rectal pain or itching after the administration of midazolam in this study, and only 3% of patients (2 of 67) defecated intraoperatively. This incidence of defecation compares favorably to rectally administered methohexital. In the latter technique, defecation occurs in 2–20% of patients.[21]

At our recommended dose of midazolam, 1.0 mg·kg^{-1}, recovery from general anesthesia is rapid and discharge from the PACU is not delayed. At this dose, children were awake and cooperative approximately 90 min after drug administration. This also compares favorably to rectally administered methohexital, with which full recovery from the affects of sedation usually occur within 60–90 min of drug administration.

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