Anesthesiology
76:28–33, 1992

Oral Ketamine Preanesthetic Medication in Children

Howard B. Gutstein, M.D., Kristen L. Johnson, M.D.,†‡ Maurine B. Heard, M.D.,† George A. Gregory, M.D.§*

The authors sought to define a dose of oral ketamine that would facilitate induction of anesthesia without causing significant side effects. Forty-five children (ASA Physical Status 1 and 2; aged 1–7 yr) were assigned randomly in a prospective, double-blind fashion to three separate groups that received either 3 mg/kg, 6 mg/kg, or no ketamine mixed in 0.2 ml/kg cola-flavored soft drink. They also were evaluated preoperatively and postoperatively for acceptance of oral ketamine as a premedicant, reaction to separation from parents, emotional state, and emergence phenomena. The authors detected no episodes of respiratory depression, tachycardia, or arterial hemoglobin desaturation before, during, or after surgery. The 6 mg/kg dose was well accepted; provided uniform, predictable sedation within 20–25 min; and allowed calm separation from parents and good induction conditions. The 3 mg/kg dose did not always cause sedation and calm separation from parents. Neither dose of ketamine increased the incidence of laryngospasm, prolonged recovery times, or caused emergence phenomena. The authors conclude that an oral dose of 6 mg/kg ketamine is easily administered and well accepted in young children and provides predictable, satisfactory premedication without significant side effects. (Key words: Anesthesia: pediatric. Anesthetic technique: oral. Premedication, pediatric: ketamine.)

UNDERGOING SURGERY can be a traumatic experience for a child. Fear of physicians, nightmares, and postoperative behavioral regression all have been reported.[1,2] Premedication may minimize these problems, but it can be difficult to administer atraumatically in the small child. In the current study, we attempt to define an oral dose of ketamine that provides adequate premedication in young children and to determine the side effects after oral administration of the drug. We also evaluate how well oral ketamine is accepted and its effect on the duration of recovery from relatively short operations.

Materials and Methods

With Human Research Committee approval and informed consent from parents, we studied 45 children (ASA Physical Status 1 and 2) undergoing peripheral surgery of approximately 1–2 h duration of anesthetic time (minimum duration, 30 min). Patients were 1–7 yr old, and their weights ranged from 9 to 25 kg. Using a randomized double-blind method, we prospectively assigned the children to one of three groups (15 children per group): no ketamine, 3 mg/kg ketamine, or 6 mg/kg ketamine in 0.2 ml/kg cola-flavored soft drink 20–30 min before induction of anesthesia. The drug was mixed by an anesthesiologist who was not observing the patient for the study or actually performing the anesthetic. This person drew a randomized card specifying the dose. After the appropriate solution was mixed, the patient's name and drug dose were placed in an envelope until the code was broken and the data were analyzed at the end of the study.

One of the authors (HBG) functioned as the observer throughout the study to avoid interobserver variation. All children were monitored with the use of a pulse oximeter and automatic blood pressure cuff at the time of administration; at 1, 2, and 5 min after administration; and every 5 min thereafter throughout the study. Heart and respiratory rates were monitored at the same intervals. Respiratory rate was counted at each time interval, and the children were observed for signs of upper airway obstruction. The times to onset of sedation and maximal sedation were recorded. Sedation was graded by evaluating the child's appearance with the sedation scale described in table 1. We observed each patient's level of consciousness, emotional state, and acceptance of the ketamine solution at the time of administration; then we observed the patient for loss of response to name or conversation, reaction to separation from parents (using the emotional state scale shown in table 1), and the presence of side effects.

As soon as a stable level of sedation was observed, children were transferred to the operating room and anesthesia was induced by an anesthesiologist not involved in observing the child for the study or mixing the premedication. If sedation did not occur within 30 min of administration of the premedication, the child was transferred to the operating room and anesthesia was induced with inhaled nitrous oxide and halothane. In sedated children, intravenous catheter insertion was attempted once before induction of anesthesia, and the child's response was recorded.

In all children, anesthesia was induced by face mask with 60% nitrous oxide in oxygen and incremental halothane administration from the start of induction. The child's acceptance of the mask was recorded, as was the

* Lecturer, Section of Pediatric Anesthesiology, University of Michigan.

† Staff Anesthesiologist, Children's Hospital, Oakland.

‡ Assistant Clinical Professor of Anesthesia, Stanford University.

§ Professor of Anesthesia and Pediatrics, University of California.

Received from the Section of Pediatric Anesthesiology, University of Michigan, Ann Arbor, Michigan; the Department of Anesthesia, Children's Hospital, Oakland, California; the Department of Anesthesia, Stanford University, Palo Alto, California; and the Departments of Anesthesia and Pediatrics, University of California, San Francisco, California. Accepted for publication August 13, 1991. Presented in part at the 1989 meeting of the American Society of Anesthesiologists, New Orleans, Louisiana.

Address reprint requests to Dr. Gutstein: Section of Pediatric Anesthesiology, C. S. Mott Children's Hospital, C-4139, Box 0800, Ann Arbor, Michigan 48109-0800.

TABLE 1. Evaluation Scales

Sedation Scale
1. Barely arousable: asleep; needs shaking or shouting to arouse
2. Asleep: eyes closed; arouses with soft voice or light touch
3. Sleepy: eyes open, but less active and responsive
4. Awake
5. Agitated

Emotional State Scale
1. Calm
2. Apprehensive: not smiling; tentative behavior, withdrawn
3. Crying
4. Thrashing: crying with movement of arms and legs, resistance

Secretion Scale
1. Decreased
2. Normal
3. Increased

time from mask application to loss of eyelash reflex. After intravenous catheter insertion, muscle relaxants were given to facilitate tracheal intubation. Secretions at the time of intubation were graded by the anesthesiologist as increased, normal, or none, and any occurrence of laryngospasm was recorded as a yes or no response. During the course of the anesthetic, the halothane concentration was maintained at the minimum level at which signs of light anesthesia could be avoided.

In the recovery room, patients were observed for emergence phenomena, time to responsiveness, incidence of nausea and vomiting, and need for airway support. We recorded blood pressure, heart and respiratory rates, hemoglobin oxygen saturation, and transcutaneous CO_2 levels at 15-min intervals, and the total amount of morphine required for analgesia. We also recorded the time to discharge and the patient's emotional state throughout recovery and at discharge.

The day after surgery, the patient's parents were contacted by telephone and asked whether the child experienced behavioral changes, nightmares, nausea or vomiting, or increased or decreased lethargy or appetite. Persistent side effects were followed-up with additional phone calls until they were resolved. Children older than 2.5 yr were asked to describe the last thing they could remember before surgery. Parents and children then were asked whether they were satisfied with oral ketamine premedication and whether they would choose it again.

Data were analyzed with one-factor analysis of variance for continuous variables (age, weight, onset of sedation, time to maximum sedation, maximum halothane concentration, operative time, awakening time, time and dose of morphine, time to discharge, duration of lethargy); chi-squared analysis for nominal variables (memory of induction of anesthesia, lethargy at home, crying, requirement of morphine); and the Kruskal-Wallis test and Mann-Whitney U test for ordinal variables (level of sedation, emotional state). The Bonferroni correction was applied to all multiple pair-wise comparisons. Mean values were reported as mean ± standard deviation. A value of $P < 0.05$ indicated significant differences.

Results

The three study groups were similar in average age, weight, and baseline emotional state. The two ketamine-treated groups had a similar level of sedation and accepted the ketamine premedication with a pattern of emotional responses that did not differ significantly (tables 2–4). Four children in the group treated with 3 mg/kg and one child in the group treated with 6 mg/kg ketamine complained about the taste of the premedication, but no one spit it out. Values for hemoglobin oxygen saturation, blood pressure, and heart and respiratory rates were within normal limits, with no significant differences between groups. Seventy-three percent of patients given 3 mg/kg ketamine obtained some level of sedation, with onset occurring in 12.5 ± 1.3 min and maximal sedation in 19.6 ± 3.6 min. One hundred percent of children given the 6 mg/kg dose were sedated, with onset occurring in 11.2 ± 2.4 min and maximal sedation in 19.6 ± 4.6 min (table 2).

Children receiving ketamine were significantly more sedate and had a considerably better reaction to separation from parents than patients in the control group (tables 3 and 4). The data in tables 3 and 4 were analyzed by converting the sedation and emotional state scales to numeric scales and then performing the Kruskal-Wallis test and the Mann-Whitney U test for pair-wise comparisons. Nystagmus was reported in 33% of patients who received 3 mg/kg and 60% of those given 6 mg/kg ketamine. Random limb movements were apparent in 7% of patients given the 3 mg/kg dose and 13% of those receiving the 6 mg/kg dose (not significant). Tongue fasciculations occurred in 20% of patients given 6 mg/kg ketamine.

On entering the operating room, 67% of patients given 6 mg/kg ketamine were judged sedate enough to attempt insertion of the intravenous catheter before induction of anesthesia ($P < 0.005$). No child on whom cannulation was attempted offered significant resistance (*i.e.*, purposeful withdrawal of the limb). Induction time was shortened significantly by ketamine administration (table 2). The amount of oral secretions present at intubation did not differ significantly between the groups receiving 3 mg/kg, 6 mg/kg, or no ketamine. The incidence of laryngospasm and the duration of anesthesia and surgery did not differ between groups.

In the recovery room, the time to awakening; incidence of increased secretions, nausea, vomiting, and crying; and the need for airway support did not differ among groups (table 2). The number of children in each group needing

TABLE 2. Preinduction, Induction, and Recovery Variables

	Dose of Ketamine (mg/kg)		
	0	3	6
Preinduction			
Age (yr)	3.3 ± 1.2	3.5 ± 1.7	3.0 ± 1.3
Weight (kg)	16.4 ± 3.1	16.2 ± 4.7	14.7 ± 3.9
Onset of sedation (min)	NA	12.5 ± 1.3[a]	11.2 ± 2.4
Time to maximum sedation (min)	NA	19.6 ± 3.6	19.6 ± 4.6
Increases secretions (%)	0	13	13
Nystagmus (%)	0	33*	60*
Random limb movement (%)	0	7	13
Anesthesia			
Intravenous cannulation (%)[b]	0	13	67†
Induction time (s)	108 ± 31	83 ± 33*	51 ± 19*
Increased secretions (%)	7	13	33
Laryngospasm (%)	7	0	7
Operative time (min)	44 ± 25	53 ± 46	53 ± 36
Anesthesia time (min)	74 ± 33	82 ± 52	84 ± 34
Recovery			
Awakening time (min)	9 ± 8	12 ± 10	11 ± 10
Jaw thrust required (%)	20	13	13
Increased secretions (%)	20	7	20
Nystagmus (%)	0	7	20
Vomiting (%)	20	13	20
Crying (%)	87	87	87
Morphine required (%)	60	67	73
Time to morphine dose (min)	3.3 ± 4.1	18.8 ± 17.6*	17.7 ± 13.3*
Average dose (mg/kg)	0.08 ± 0.022	0.08 ± 0.038	0.16 ± 0.28
Postanesthetic			
Time to discharge (min)	68 ± 19	73 ± 30	77 ± 29
Memory of induction (% of responding)	75	17‡	9‡
Vomiting at home (%)	33	33	20
Lethargy at home (%)	47	53	67
Duration of lethargy (h)	11 ± 9	7 ± 8	4 ± 3*

Means ± standard deviation.
NA = not applicable.
[a] Sedation observed in 12 patients.
[b] Percent of patients in which intravenous cannulation was possible before the induction of anesthesia.

* $P < 0.05$ compared with control.
† $P < 0.005$ compared with control and <0.05 compared with 3-mg/kg group.
‡ $P < 0.005$ compared with control.

morphine for postoperative analgesia and the amount of morphine required also did not differ significantly. The overall emotional state of the children on arrival in the recovery room was significantly better in the group treated with 6 mg/kg ketamine compared with controls (table 4). Nystagmus was apparent in 6% of children who received 3 mg/kg and in 20% given 6 mg/kg ketamine. No hemoglobin desaturation or hemodynamic instability was recorded in the recovery room. Also, emergence delirium did not occur in any of the children.

Time to discharge was not delayed in patients receiving ketamine. Postoperative evaluation showed no apparent differences among groups in the incidence of lethargy, vomiting, or unusual behavioral reactions at home. Children older than 2.5 yr were asked whether they remembered application of the face mask at the start of surgery. Seventy-five percent of children responding in the control group (9 of 12) remembered the mask being applied during the induction of anesthesia, compared with only 17% of those given 3 mg/kg ketamine (2 of 12) and 9% of those receiving 6 mg/kg (1 of 11) ($P < 0.05$). The only two children who had nightmares were members of the control group, which did not receive ketamine. Parents uniformly were satisfied with the use of oral ketamine before surgery.

Discussion

There is still no entirely satisfactory way to ensure smooth induction of anesthesia for children. The ideal premedication would be easily administered, well accepted, act rapidly, not prolong emergence from anesthesia, and have few side effects. To our knowledge, ours is the first study to concurrently examine these attributes and level of sedation, separation reaction, preoperative and postoperative emotional state, amnesia, acceptance of technique, and evidence of side effects after the oral administration of ketamine to young children. Almost all of the drugs currently available for preanesthetic medication require either an injection, administering a pill, or

TABLE 3. Level of Sedation

	Dose of Ketamine (mg/kg)		
	0	3	6
Baseline			
Barely arousable	0	0	0
Asleep	0	0	0
Sleepy	0	0	0
Awake	93	87	93
Agitated	7	13	7
Premedicated		*	†
Barely arousable	0	0	13
Asleep	0	13	13
Sleepy	27	60	74
Awake	66	20	0
Agitated	7	7	0
Upon PAR arrival			
Barely arousable	20	20	13
Asleep	7	20	33
Sleepy	27	40	40
Awake	0	0	7
Agitated	46	20	7
Upon discharge to second-stage recovery			
Barely arousable	0	13	0
Asleep	0	7	7
Sleepy	40	40	33
Awake	53	40	60
Agitated	7	0	0

Values are percent of group.
PAR = postanesthesia recovery.
* $P < 0.05$ for distribution of sedation scores of 3-mg/kg group compared with control (0-mg/kg) group.
† $P < 0.05$ for distribution of sedation scores of 6-mg/kg group compared with control (0-mg/kg) group.

nasal or rectal administration of the drug. Any of these methods could be difficult or traumatic for 1–7-yr-old children. In addition, many of the currently used drugs cause respiratory depression, and none provides a uniform balance of sedation, amnesia, and analgesia before surgery.[3,4]

In adults, intravenous and intramuscular administration of subdissociative doses of ketamine provide balanced sedation without causing respiratory depression, emergence phenomena, or significant changes in blood pressure or heart rate.[5–7] In children, side effects of excess salivation, purposeless movements unrelated to surgical stimuli, emergence reactions, and, rarely, prolonged behavioral changes have been reported after intravenous and intramuscular administration of ketamine.[8–11] The incidence of emergence phenomena in children may be less (in the range of 0–5%) than in adults (as great as 30%).[9]

In a previous uncontrolled study, children given an oral dose of 8–10 mg/kg ketamine as the sole anesthetic for minor procedures had excellent preoperative sedation without significant perioperative complications.[12] They exhibited no changes in blood pressure or heart and respiratory rates, and no emergence phenomena. In our study, we found oral ketamine to be predictable, reliable, and well accepted. The side effects observed were of short duration and minor significance. Nystagmus was reported in many children who received ketamine; however, none of the children seemed distressed by this while it was occurring or when questioned postoperatively. We did not use ketamine as a premedication for patients undergoing extraocular muscle surgery because of our concern that it might alter extraocular muscle tone and interfere with surgical correction. Sedation occurred in 15–20 min, which is comparable to the time in which it occurs with other oral premedication regimens, and probably represents a delay secondary to intestinal absorption and hepatic metabolism.[13,¶]

Only 16% of ketamine is bioavailable orally, as opposed to 93% intramuscularly or intravenously.[14] It also has been shown that oral ketamine doses equivalent to intramuscular doses produce peak plasma ketamine concentrations only one fifth as high as intramuscularly delivered concentrations and the time to reach peak plasma concentration is longer.[14] However, the plasma concentration of norketamine, an active metabolite with one third the potency of ketamine, is twice as high after oral administration of ketamine.[14,15] This increased amount of norketamine relative to ketamine with oral administration may account for part of the sedative effect observed and possibly the reduced incidence of unwanted side effects with oral administration.

Oral administration of premedicant drugs has been studied by several other investigators. Brzustowicz *et al.* administered a solution of meperidine, diazepam, and atropine to children older than 6 months.[13] The only statistically significant differences observed between control and premedicated patients were that premedicated patients had fewer oral secretions and cried less on arrival in the operating room. Oral administration of midazolam has been shown to provide sedation and improved induction conditions.¶ However, even with the maximum midazolam dose used (0.75 mg/kg, by mouth), there were some children (28%) that were either anxious or combative when separating from parents. Postoperative amnesia was not evaluated in this study. Oral transmucosal administration of fentanyl has resulted in significant side effects, including hemoglobin desaturation, itching, and increased nausea and vomiting.**

Nasal administration of drugs also has been used for pediatric premedication.[16,17] Nitrous oxide (commonly used to speed the induction of anesthesia) was not used

¶ Feld LH, Negus JB, White PF: Oral Midazolam: Optimal dose for pediatric premedication (abstract). ANESTHESIOLOGY 71:A1054, 1989.

** Ashburn MA, Streisand JB, Stanley TH, Elwyn R, Tarves S, Mears S, Wilms Floet A: Clinical evaluation of oral transmucosal fentanyl citrate, OTFC, for use as a premedication in pediatric outpatient surgery (abstract). ANESTHESIOLOGY 71:A1172, 1989.

TABLE 4. Emotional State

	Dose of Ketamine (mg/kg)		
	0	3	6
Baseline			
Calm	60	67	60
Apprehensive	27	20	27
Crying	13	13	13
Thrashing	0	0	0
Premedicant acceptance			
Calm	87	87	66
Apprehensive	13	13	20
Crying	0	0	7
Thrashing	0	0	7
Premedicated			*
Calm	67	80	100
Apprehensive	20	13	0
Crying	13	0	0
Thrashing	0	7	0
Separation reaction			*
Calm	47	73	93
Apprehensive	13	0	7
Crying	33	27	0
Thrashing	7	0	0
Upon PAR arrival			*
Calm	33	66	66
Apprehensive	0	7	20
Crying	7	7	7
Thrashing	60	20	7
Upon discharge to second-stage recovery		†	
Calm	53	100	73
Apprehensive	27	0	20
Crying	13	0	7
Thrashing	7	0	0

Values are percent of group.
PAR = postanesthesia recovery.
* $P < 0.05$ for distribution of emotional state scores of 6-mg/kg group compared with control (0-mg/kg) group.
† $P < 0.02$ for distribution of emotional state scores of 3-mg/kg group compared with control (0-mg/kg) group.

after nasal sufentanil because of frequent increases in muscle tone reported in pilot studies.[16] Other investigators have found that the incidence of apnea and laryngospasm increases with nasal administration of sufentanil.†† Nasal administration of midazolam provided satisfactory preoperative sedation, but the issues of amnesia and satisfaction with the technique were not addressed.[17] In addition, nasal premedications often burn and leave a bitter taste in the pharynx after administration. Intramuscular injection of premedicant drugs generally is effective and provides a relatively quick onset of action; however, it is not well accepted by children and is displeasing to many parents.[18] Rectal premedicants, although effective, can be awkward to administer in some children.

We decided to use a cola-flavored soft drink as the vehicle for ketamine administration after pilot studies indicated that it was better accepted by children than other liquids. The *p*H of the solution was 3.0, greater than the most conservative *p*H limit of 2.5 thought to promote lung damage after aspiration of gastric contents.[19–21] The volume of solution, 0.2 ml/kg, also was chosen to remain below the most conservative residual gastric volume limit of 0.4 ml/kg.[20,22–24] Although the *p*H of apple juice was 4.0 and the *p*H of a sweet, clear syrup from the pharmacy was 4.5, neither of these solutions was accepted as well as the cola-flavored drink. However, some children in the treatment groups did notice the ketamine taste. Use of cola syrup instead of the soft drink might minimize this taste. We decided not to administer oral atropine to reduce secretions because it also imparts a bitter taste and the time to peak decrease in salivation is 2 h,[25] significantly slower than the time to peak ketamine effect (15–20 min after administration). Oral atropine also delays gastric emptying.[26] Our results indicate that atropine pretreatment is unnecessary.

In summary, we found that oral administration of 6 mg/kg ketamine for pediatric premedication provides rapid onset of satisfactory sedation with appropriate amnesia and few minor side effects. The 3 mg/kg dose did not provide uniform sedation in all patients and did not provide a statistically significant improvement in premedicated emotional state and separation reaction when compared with controls. Children accepted the technique well, and parents were satisfied with the outcome. We were able to use this technique effectively in a busy private practice setting with the cooperation of our nurses in the preoperative area. Although we observed no serious side effects, we believe that all premedicated children should be observed in an area in which resuscitation equipment is immediately available.

The authors thank Dr. Dennis Fisher, Dr. John Severinghaus, and Jerry Okikawa for loaning equipment used during the study. They also thank Drs. Julien Hoffman and Anthony Schork for assistance with study design and for biostatistical advice.

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