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# *Comparison of the Safety and Efficacy of Intranasal Midazolam or Sufentanil for Preinduction of Anesthesia in Pediatric Patients*

*Helen W. Karl, M.D.,* Anne T. Keifer, M.D.,† James L. Rosenberger, Ph.D.,‡*
*Marilyn G. Larach, M.D.,† Joan M. Ruffle, M.D.†*

**Nasal administration of sufentanil or midazolam is effective for preinduction of pediatric patients, but there are no data on which to base a choice between them. This blinded randomized study compares behavioral and physiologic responses to sedation with one of these medications followed by inhalation or intravenous induction. Ninety-five patients aged 0.5–10 yr scheduled for elective surgery were stratified by age: 30 infants 0.5–2 yr, 38 preschoolers 2.1–5 yr, and 27 school-age children 5.1–10 yr. They were randomized to receive 0.04 ml/kg of midazolam (0.2 mg/kg) or sufentanil (2 μg/kg). Hemoglobin oxygen saturation by pulse oximetry ($Sp_{O_2}$) and sedation score were recorded prior to drug administration, at 2.5-min intervals for 10 min, at separation, and during induction with graded halothane in oxygen. Intubation was performed under deep halothane or 3 mg/kg of thiopental and 0.1 mg/kg of pancuronium. Chest wall compliance was assessed qualitatively in all patients prior to intubation. To assess the effects of a mild standardized stress on unpremedicated patients, 75 of the children with parents present were scored before and after oximeter probe placement: of these, in 63% the sedation score did not change; 33% appeared more anxious; and only 4% seemed reassured. Children of all ages reacted negatively to physicians, and 23% were crying prior to administration of drugs. Sufentanil appeared less unpleasant to receive than midazolam: children cried 46 ± 100 *versus* 76 ± 73 s ($P < 0.05$), respectively, but by 7.5 min, no child was crying. Median behavior scores at maximum anxiolysis were not different, but response to sufentanil was more variable. Only 24% of all patients cried at induction. Midazolam-treated patients remained well oxygenated (98% with $Sp_{O_2}$ > 95%), and their lungs were easy to ventilate (96%). In contrast, 55% of sufentanil patients had $Sp_{O_2}$ < 96%; the lungs of 37% were not easy to ventilate; and 3 required naloxone at the end of the procedure. These results support previous conclusions that intranasal midazolam and sufentanil are effective preinduction sedatives, and demonstrate that midazolam is preferable to sufentanil for most patients. (Key words: Analgesics, opioid: sufentanil. Anesthesia, pediatric: preinduction. Anesthetic techniques: transmucosal drug administration. Hypnotics, benzodiazepines: midazolam.)**

INDUCTION OF ANESTHESIA in pediatric patients is well known to be a challenge for anesthesiologists. A distressed child is at risk for potentially hazardous psychological[1–3],§ and physiologic[4,5] sequelae; in addition, medical personnel may be distracted by the child's unhappiness. The child's age, as well as characteristics of the family, illness, and hospital all contribute to the degree of distress.§ Traditional oral, intramuscular, and rectal premedicants have been helpful, but each has a number of disadvantages.[6,7] The bioavailability of both opioids and benzodiazepines administered *via* transmucosal routes has been shown to be at least equal to that of the same drugs administered orally or intramuscularly.[6] The rapid and reliable onset of action, avoidance of painful injections, ease of administration, and predictable effects have made intranasal administration of preinduction agents popular with anesthesiologists and parents.

While previous work by Henderson *et al.*[7] and Wilton *et al.*[8] has demonstrated the efficacy and safety of preinduction of anesthesia in children with nasally administered sufentanil or midazolam, no direct comparison of the two medications has been performed to clarify which drug is preferable in a particular clinical situation. We therefore performed a randomized, prospective, double-blind study to compare some psychological and physiologic effects of midazolam or sufentanil administered prior to inhalation or intravenous induction. The absence of a placebo control group reflects the conviction of the investigators, on the basis of published studies[1–5],§ and their experience in this institution, that withholding a preinduction agent for the sake of the study would not be justified.

## Materials and Methods

After approval from the Clinical Investigation Committee and informed parental consent, 95 patients aged 0.5–10 yr were studied. All ASA physical status 1 and 2 patients in this age group, both inpatients and outpatients, scheduled for elective surgery were eligible for the study. Patients were excluded if they had a recent upper respiratory tract infection, if tracheal intubation was not indicated, if an intravenous induction was required, or if they were judged to have very difficult venous access. Eligible patients were stratified by age and randomly assigned in blocks of 4 to one of the following treatment groups:

* Assistant Professor, Departments of Anesthesia and Pediatrics, The Milton S. Hershey Medical Center. Present affiliation: Department of Anesthesiology, Children's Hospital and Medical Center, University of Washington School of Medicine, Seattle, Washington.

† Assistant Professor, Department of Anesthesia, The Milton S. Hershey Medical Center.

‡ Associate Professor, Department of Statistics, The Pennsylvania State University.

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Address reprint requests to Dr. Karl: Department of Anesthesiology, Children's Hospital and Medical Center, University of Washington School of Medicine, 4800 Sand Point Way NE, P.O. Box C5371, Seattle, Washington 98105.

§ Meursing AEE: Psychological effects of anaesthesia in children. Current Opinion in Anesthesiology 2:335–338, 1989.

midazolam with inhalation induction (n = 24), midazolam with intravenous induction (n = 23), sufentanil with inhalation induction (n = 24), or sufentanil with intravenous induction (n = 24). Treatment groups were not different from each other with respect to age, weight, sex, ASA physical status, obesity,[9,10] or the number of previous operations (ANOVA and chi-square).

Each child received a commercially available preparation of either 2 μg/kg of sufentanil or 0.2 mg/kg of midazolam, the dose of each drug that was recommended by previous investigators.[7,8] Drug concentrations were such that the volume administered was the same (the above doses of sufentanil 50 μg/ml and midazolam 5 mg/ml result in a volume of 0.04 ml/kg). Undiluted medication was placed in a 1-ml (3-ml for those > 25 kg) syringe from which the needle had been removed, and was applied rapidly to the mucosa of one nostril of a patient in a supine or semirecumbent position. The duration of crying after drug application was recorded. Resuscitative equipment was immediately available at the bedside. During the 10-min interval between drug administration and separation, the anesthesiologists caring for the patient encouraged the parents to engage the child in a favorite activity. After a few minutes, the anesthesiologist joined the activity. At 10 min, the child was separated from the parents and taken to the operating room. Patients judged by the attending anesthesiologist responsible for the patient to be too agitated to be separated from the parents were given an additional dose of the same medication; if that was unsuccessful, an alternative drug was given at the discretion of the attending anesthesiologist.

Inhalation induction was accomplished with graded increments of halothane (0.5–4%) in oxygen. Ventilation was gently assisted as tolerated by the patient, and an intravenous catheter was inserted when an adequate level of anesthesia was achieved. Patients' tracheas were intubated under deep halothane anesthesia, and anesthesia was maintained with 70% nitrous oxide and halothane to maintain systolic blood pressure within 25% of the preoperative value. Muscle relaxants were administered as required by the surgical procedure. The patients randomized to receive intravenous inductions had a 22- or 24-G catheter placed through a 0.5% lidocaine skin wheal and then were given 0.01 mg/kg of pancuronium followed by 3 mg/kg thiopental and halothane in oxygen. Tracheal intubation was facilitated with 0.1 mg/kg (total dose) of pancuronium, and anesthesia was maintained with nitrous oxide and halothane as described above. Ventilation was controlled to maintain end-tidal carbon dioxide partial pressure between 35 and 40 mmHg. Respiratory gas concentrations were monitored with a mass spectrometer and recorded. Patients judged by the attending anesthesiologist responsible for their care to be too agitated to have an intravenous catheter inserted received an inhalation induction.

Local anesthetics were administered intraoperatively only when required by the surgical procedure. Near the end of the surgery, the effects of the muscle relaxant were antagonized as needed with atropine (0.02 mg/kg) and neostigmine (0.05 mg/kg), and ventilation was halved. Patients with respiratory rates more than 25% greater than their preoperative value received incremental doses of intravenous morphine sulfate as required to decrease respiratory rate to an age-appropriate level. Patients unable to maintain an end-tidal carbon dioxide partial pressure less than 65 mmHg received naloxone 1 μg/kg repeated at 1-min intervals. The trachea was extubated when the attending anesthesiologist judged the child to be awake and breathing well.

In the postanesthesia recovery room, the following data were collected: routine vital signs, peripheral oxygen saturation by pulse oximetry ($Sp_{O_2}$; model N-200, Nellcor, Inc., Hayward, CA), postanesthesia recovery score,[11] analgesic administration, and emesis. Each patient underwent a 5-min trial of breathing room air, every 15 min, to determine the length of time for which oxygen was required to maintain $Sp_{O_2} > 95\%$.

### Evaluation of Drug Efficacy

Wilton *et al.*'s sedation score[8] was modified and used to grade behavioral responses to preinduction medication (table 1). Three independent behavior assessments were performed by an attending anesthesiologist, anesthesia resident or nurse anesthetist, and by an anesthesia-trained observer not involved in care of the patient at the following nine times: prior to any intervention by anesthesia personnel, after an attempt to place a pulse oximeter probe, at 2.5-min intervals for 10 min after drug application, at separation from parents, upon arrival in the operating room, and during induction of anesthesia. All evaluators were blind to drug treatment group. The interval between intranasal drug application and the child's first smile was recorded. Questionnaires to elicit descriptions of the patients' responses to drug application and pharmacologic effects were administered just before dis-

Table 1. Behavior Scoring System

| Criterion | | Score |
|---|---|---|
| Agitated | Clinging to the parent and/or crying | 1 |
| Allert | Awake but not clinging to the parent, may whimper but not cry, anxious | 2 |
| Calm | Sitting or lying with eyes open, relaxed | 3 |
| Drowsy | Eyes closed but responds to minor stimulation | 4 |
| Asleep | Does not respond to minor stimulation | 5 |

Behavior scoring system modified from Wilton.[8] Scores were independently recorded by an attending anesthesiologist, a resident or a nurse-anesthetist, and an anesthesia-trained observer before (baseline) and after (predrug) oximeter probe placement, every 2.5 min for 10 min after nasal drug application, at separation from parents, arrival in operating room, and induction of anesthesia.

charge from the recovery room to patients believed to have appropriate verbal skills.

### Evaluation of Drug Safety

$Sp_{O_2}$ and heart rate were recorded continuously from the time of probe placement until discharge from the recovery room. Chest wall compliance during positive pressure ventilation was assessed by the resident or nurse anesthetist after loss of consciousness according to the following criterion[7]: easy, moderately difficult, very difficult, or requiring muscle relaxant. The independent observer watched the cardiac monitor for premature ventricular contractions and noted the presence of laryngospasm or movement during intubation.

### Summary Description

We combined safety and efficacy to formulate a summary description of the separation–induction period (separation from parents until completion of induction) of each patient in the study. Excellent conditions during separation and induction are defined as no display of anxiety (no median behavior score < 3), $Sp_{O_2}$ > 95%, and easy ventilation. Adequate conditions are defined as minimal crying (no median behavior score < 2), mild desaturation ($Sp_{O_2}$ 90–95%), or mild chest wall rigidity. Inadequate sedation was defined as the presence of any behavior score = 1 or a change in anesthetic plan due to inadequate sedation. Caution is required in the potentially unsafe situation of $Sp_{O_2}$ < 90% or severe chest wall rigidity.

### Data Analysis

The median of the three behavior scores at each time was considered to represent the child's behavior. Data

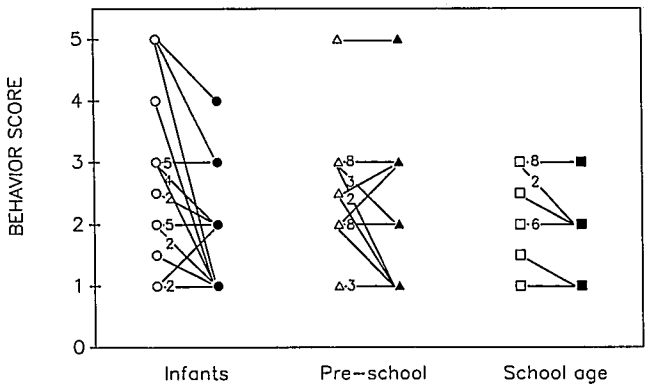


FIG. 1. Response to pulse oximeter placement. Behavior scores of individual patients are grouped according to age. Lines between symbols indicate the score from each individual before (open symbols) and after (closed symbols) pulse oximeter probe placement; where n > 1, the number of patients whose response is described by that line is noted. Within each age group, behavior scores after probe placement are lower than before ($P < 0.05$, one-sample one-tailed Wilcoxon).

TABLE 2. Response to Nasal Drug Application

| | Midazolam | Sufentanil |
|---|---|---|
| Infants | 91% (10/11) | 90% (9/10) |
| Preschool | 100% (16/16) | 50% (6/12)* |
| School age | 55% (6/11) | 55% (6/11) |

The incidence of crying at the time of administration of midazolam or sufentanil in patients who were not previously crying.
* $P < 0.01$ midazolam *versus* sufentanil (chi-square).

are reported as incidence (percentage) or mean ± standard deviation and were analyzed with analysis of variance, chi-square, and Wilcoxon tests. The $\kappa$-like statistic $\hat{S}_{av}$, with the constraint of marginal homogeneity and disagreement weights of the squares of the distances between scores, was used to estimate interobserver reliability.[12] Mean $\hat{S}_{av}$ (± standard deviation) over all time points is reported. A $P$ value < 0.05 was considered statistically significant.

## Results

### Presedation Behavior

In order to provide an index of the behavioral response of unmedicated children to a standard stress, 75 of the 95 infants and children were scored before and after oximeter probe placement (fig. 1). There were significant decreases in behavior score in each age group in response to this minimally unpleasant intervention. Overall, 47 patients (63%) did not change behavior score, but 6 of these patients were crying (score = 1) on the initial ratings. Twenty-five decreased their behavior score (appeared more anxious), and only 3 (4%) showed an increased score (seemed reassured). Twenty-three percent were crying prior to administration of drugs; there was no difference in the incidence of crying between age or drug groups ($P > 0.5$, chi-square).

### Response to Drug Administration

Of the 71 children who were not already crying, 75% cried in response to the administration of nose drops, 84% (32 of 38) after midazolam, and 64% (21 of 33) after sufentanil ($P = 0.09$, chi-square). Within age groups, only preschool children showed a significant difference in the incidence of crying between drug groups (table 2, chi-square). Patients who received midazolam cried significantly longer than those to whom sufentanil had been administered (76 ± 73 *vs.* 46 ± 100 s, $P = 0.002$, Wilcoxon).

### Sedation and Separation from Parents

Ninety-two percent of the patients (86% of infants, 93% of preschool children, and 100% of school-age children)

smiled within 10 min of administration of midazolam, whereas only 72% (42% of infants, 79% of preschool children, and 100% of school-age children) smiled after sufentanil ($P < 0.05$, chi-square). At the point of maximum anxiolysis (with parents still present, 10 min after the drug was administered), both drugs had produced significant effects (each individual's behavior score compared to that recorded just prior to drug administration; $P < 0.05$, one-sample Wilcoxon, all ages combined and within age groups). However, the behavioral response to midazolam was less variable than the response to sufentanil; the difference in variability is particularly apparent in infants and less marked in preschool and school-age children (fig. 2).

Overall variability in the behavior score at the time of separation from parents (approximately 11 min after drug administration) also was less after midazolam than after sufentanil. Each drug substantially blunted the children's' signs of stress at separation: only 9% of the 47 children treated with midazolam and 21% of the 48 who received sufentanil cried ($P = 0.24$, chi-square). Behavior scores after midazolam administration were not different compared with those recorded at 10 min (each individual's behavior score compared to that recorded just prior to separation, one-sample Wilcoxon, all ages together [$P = 0.06$] and within age groups [$P = 0.3$–$0.4$]). In contrast, children receiving sufentanil showed a significant increase in anxiety at separation ($P = 0.036$, one-sample Wilcoxon, all ages together). Three patients receiving sufentanil (6%) required a second dose of study medication for separation. One patient in each drug group required nonstudy medication in addition to a second dose; these two have been omitted from further analysis.

## Induction of Anesthesia

During inhalation (at 17 ± 3 min) or intravenous (at 22 ± 4 min) induction, children who had received either drug maintained or significantly improved the behavior scores observed prior to their administration (each indi-

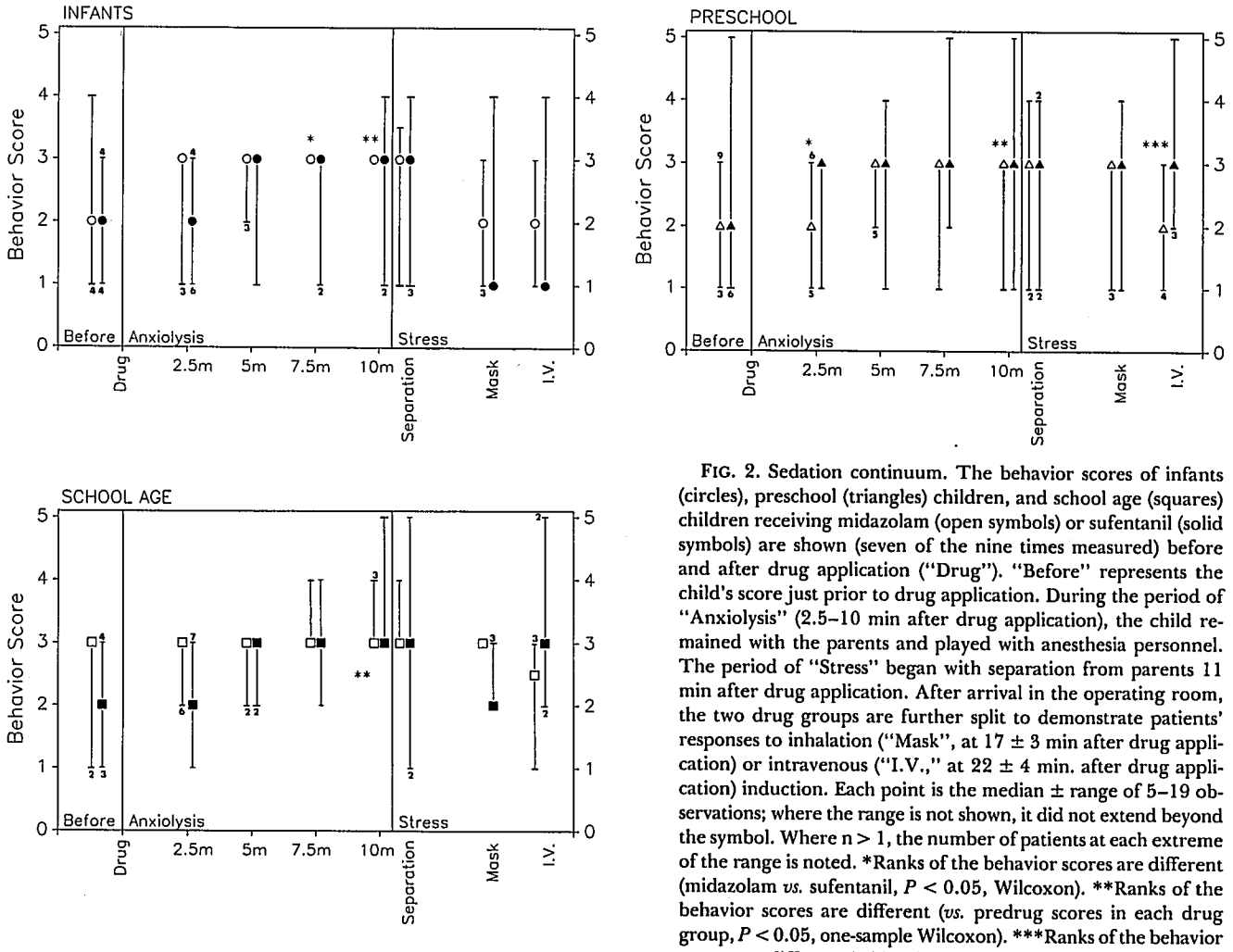


FIG. 2. Sedation continuum. The behavior scores of infants (circles), preschool (triangles) children, and school age (squares) children receiving midazolam (open symbols) or sufentanil (solid symbols) are shown (seven of the nine times measured) before and after drug application ("Drug"). "Before" represents the child's score just prior to drug application. During the period of "Anxiolysis" (2.5–10 min after drug application), the child remained with the parents and played with anesthesia personnel. The period of "Stress" began with separation from parents 11 min after drug application. After arrival in the operating room, the two drug groups are further split to demonstrate patients' responses to inhalation ("Mask", at 17 ± 3 min after drug application) or intravenous ("I.V.," at 22 ± 4 min. after drug application) induction. Each point is the median ± range of 5–19 observations; where the range is not shown, it did not extend beyond the symbol. Where n > 1, the number of patients at each extreme of the range is noted. *Ranks of the behavior scores are different (midazolam *vs.* sufentanil, $P < 0.05$, Wilcoxon). **Ranks of the behavior scores are different (*vs.* predrug scores in each drug group, $P < 0.05$, one-sample Wilcoxon). ***Ranks of the behavior scores are different (midazolam *vs.* sufentanil for this method of induction, $P = 0.006$, Wilcoxon).

vidual's behavior score compared to that recorded just prior to drug administration, one-sample Wilcoxon, all ages combined and within age groups). Of note was the continued increase in behavior score with time after the administration of sufentanil: this is particularly evident in the behavior of school-age children (fig. 2).

With inhalation induction, there was no difference in any age group between midazolam and sufentanil in the median behavior score (fig. 2, Wilcoxon). Seventy-seven percent of all children did not cry at the time of inhalation induction. Both drugs also prevented distress during intravenous induction (76% of all children had behavior scores > 2). There was a clear age-dependent difference between midazolam and sufentanil in facilitating intravenous catheter placement: no child older than 2 yr who had been sedated with sufentanil cried. The difference in behavior scores between the two drugs was significant only in the preschool group (fig. 2; $P < 0.05$, Wilcoxon with Bonferroni correction for six comparisons), since older children sedated with midazolam also rarely cried.

Only two of the midazolam–intravenous induction and one of the sufentanil–intravenous induction group were changed to an inhalation induction due to inadequate sedation during cannulation, for a 6% failure rate of intravenous catheter placement. When this is combined with the two children who required nonstudy medication for separation, 8% of all children studied required a change in the planned method of induction.

## Safety

Only one midazolam-treated patient, a 21-kg 6-yr-old child scheduled for tonsillectomy and adenoidectomy had $Sp_{O_2} < 96\%$ during the period between drug administration and induction of anesthesia (table 3). Nothing in this patient's history or physical examination, other than the procedure for which she was scheduled, provided any reason to suspect that she was at particular risk. The lungs of all but two (4%) of the patients receiving midazolam were easy to ventilate (table 4).

In contrast, 54% (26 of 48) of all sufentanil-treated patients had $Sp_{O_2} < 96\%$, and 23% (6 of 26) of these had $Sp_{O_2} < 90\%$ ($P < 0.0001$ *vs.* midazolam, chi-square; table 3). There was no association between obesity[9,10] and decreased $Sp_{O_2}$. The lungs of 37% were not easy to ventilate ($P < 0.005$, chi-square; table 4).

No patient in either group had premature ventricular contractions noted during induction or intubation. Sixteen percent of midazolam- and 7% of sufentanil-treated patients moved slightly during intubation. No patient in either group had laryngospasm, vomited, or had tonic–clonic activity prior to induction.

Figure 3 shows that for inhalation inductions, midazolam clearly provided excellent separation and induction conditions more frequently than did sufentanil ($P < 0.05$, chi-square).

TABLE 3. Lowest $Sp_{O_2}$

| | n | 90–95% | <90% | Total |
|---|---|---|---|---|
| Midazolam | 47 | 0 | 2% | 2% |
| Sufentanil | 48 | 42% | 13% | 54%* |

The relative number of patients with $Sp_{O_2}$ 90–95% or <90% during the sedation–induction period.
* $P < 0.0001$ midazolam *versus* sufentanil (chi-square).

TABLE 4. Incidence of Chest Wall Stiffness

| | n | Moderate (%) | Severe (%) | Total (%) |
|---|---|---|---|---|
| Midazolam | | | | |
| Inhalation | 24 | 0 | 0 | 0 |
| Intravenous | 22 | 9 | 0 | 9 |
| Sufentanil | | | | |
| Inhalation | 22 | 36 | 9 | 45* |
| Intravenous | 24 | 25 | 4 | 29 |

After loss of consciousness, positive pressure ventilation was assessed by the resident as easy, moderately difficult, or very difficult or requiring muscle relaxation. The percentage of patients with moderately or severely decreased compliance (very difficult or requiring muscle relaxation) is shown for each treatment group.
* $P < 0.001$ *versus* midazolam-inhalation (chi-square).

## Postoperative Course

There was no difference in the duration of anesthesia between the two drug groups. Not surprisingly, patients receiving midazolam were given more halothane and morphine ($P < 0.05$, Wilcoxon); three patients in the sufentanil group required (1–2.5 μg/kg) naloxone. There was no difference between the two drug groups in the length of recovery room stay, (94 ± 47 min, both groups), duration of oxygen administration required to keep $Sp_{O_2} > 95\%$ (19 ± 47 min, both groups), or the incidence of vomiting in the recovery room (10%, both groups).

## Questionnaires

Seventy-one percent of patients who received sufentanil reported that they felt "dizzy," whereas only 13% of those treated with midazolam used this word. All patients who received midazolam complained about its taste.

## Evaluation of Behavior Scoring System

With the exclusions described above (75 patients with nine time points, 20 without a preoximeter probe score, and 2 without arrival or induction scores), there were 831 times (sets) at which each of the three observers could record a score. Ninety-one percent of the data sets were complete with three observations per set; 9% contained two observations, 5 sets contained 1 observation, and 2 sets were empty. There was no difference in completeness of data sets between age groups. The estimated interobserver reliability ($\hat{S}_{av}$) was 0.54 ± 11 and 0.64 ± 12 for the midazolam- and sufentanil-treated patients respec-

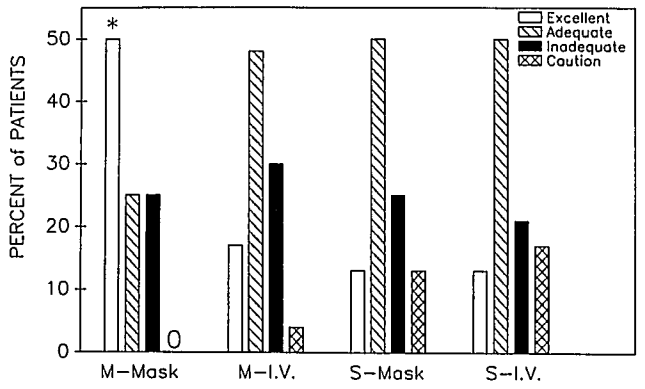


FIG. 3. Overall efficacy and safety. Behavior scores at separation from parents, arrival in the operating room, induction of anesthesia, and $Sp_{O_2}$ throughout this period; evaluation of chest wall compliance; and change in anesthetic plan due to inadequate sedation were grouped and rated without knowledge of drug treatment group. Each patient's record was rated as the least favorable of the following: 1) excellent (no median score < 3, $Sp_{O_2}$ > 95%, and no chest wall rigidity); 2) adequate (all median scores > 2, $Sp_{O_2}$ 90–95%, or mild chest wall rigidity); 3. inadequate (a median score <2 or change in anesthetic plan due to inadequate sedation); and 4. caution ($Sp_{O_2}$ < 90% or severe chest wall rigidity). *$P$ < 0.05 *versus* the other methods of sedation and induction, chi-square.

tively ($P$ = not significant); reliability was similar in each age group. If the mean of the three observers' scores is used as an index of behavior, overall reliability increases to 0.86.

## Discussion

The intranasal route for preinduction of anesthesia in pediatric patients has decreased the distress caused by separating unpremedicated youngsters from their parents and subjecting them to unpleasant procedures. Intranasal administration of sufentanil or midazolam has been shown previously to be an effective preinduction technique for pediatric patients. As a basis for choice between them when deciding on an anesthetic plan for any individual child, we designed a double-blind, randomized study to compare behavioral and physiologic responses to sedation with one or the other drug.

In the immediate premedication period, unmedicated children in the study showed signs of anxiety. Disruption of routine; hunger; removal of their clothes; and the presence of frightening sights, sounds, and smells contribute to this anxiety in children of all ages. Age-related specific fears regarding separation from parents and/or the procedure itself add to the stress.[2,13] Clearly, efforts need to be directed toward minimizing all of the anxiety-producing factors listed above; however, by the nature of perioperative care these cannot be entirely eliminated. As a previous investigator interested in pain management has demonstrated,[14] formal observation of behavior in a standardized situation is a useful assessment tool. In studies of preanesthetic medication, this kind of observation can provide an index of preoperative anxiety in children of different ages and may facilitate comparison of results of studies from different institutions.

Children of all ages responded with signs of increased anxiety to a standard stress: the approach of medical personnel for placement of a pulse oximeter probe. This change in behavior was measurable despite the presence of the children's' parents and despite the fact that this nonpainful procedure was compared to a character in a popular movie or to the child's game of shining a flashlight through their hand. As one would expect, infants reacted most negatively to this stimulus. If such a small stress provoked an increase in anxious behavior, it is likely that, despite the best efforts of the anesthesiologist, the far greater stresses of separation from parents and induction of anesthesia would result in a larger fraction of crying infants and children. The responses of patients receiving placebo in other studies to the stresses of separation and induction confirm this supposition: 20–53%[7,8] were judged crying or not calm at the time of separation from parents and 52–89%[7,8,15] rejected the face mask. Considering that more than one fourth of our patients cried in response to a minor stimulus in the presence of their parents, the expected frequency of crying in response to separation in unmedicated children in our hospital might be at the higher range of those reported.

The incidence and particularly the duration of crying can be taken as an index of the discomfort associated with intranasal drug application. Our overall incidence of crying in response to nose drop administration was higher than the 61% reported in response to sufentanil or placebo.[7] Particularly in preschool children, administration of sufentanil appeared to be less unpleasant than that of midazolam; this is probably due to the very unpleasant taste of midazolam. Crying as an index of discomfort is probably most useful in preschool children, who cry less in response to nonspecific stimuli than do infants and who suppress crying less effectively than do school-age children.

The larger number of children who smiled within 10 min of administration of midazolam and the lower variability in behavior score suggest that midazolam was associated more consistently than sufentanil with signs of anxiolysis. This finding is not surprising in consideration of the fact that benzodiazepines have been developed specifically to reduce anxiety, whereas opioids are primarily used for relief of pain.

With nasal drug administration, the overall incidence of crying at the time of separation from parents in our study (13%) was less than the 20–53% incidence reported by others in their saline-treated control groups.[7,8] Our results thus support previous experience[7,8] that both drugs effectively blunt the response to this stress: more than 80% of sufentanil-treated patients and more than 90% of those who had received midazolam were judged not to be agitated at the time of separation from parents.

Both drugs were effective sedatives for inhalation in-

duction. Our results show far greater face mask acceptance (77%) than observed in previous studies with sufentanil. Those investigators reported a 25–30% acceptance rate, one not different from that in the saline control group.[7] One possible reason for this difference is that administration of incremental increases in halothane concentration is less unpleasant than immediate application of 5%. An additional explanation is that for our patients, more time had elapsed between drug administration and separation (10 min) than in the previous study (4–10 min). Not unexpectedly, the analgesic drug sufentanil was more effective than midazolam in facilitating intravenous catheter placement in preschool children.

Experience with administration of opioids led us to consider that hypoxemia and decreased chest wall compliance would be the most common complications of preinduction of anesthesia with intranasal sufentanil.[7] The highly significant incidence of decreased $Sp_{O_2}$ in our patients is in contrast to the complete absence of $Sp_{O_2} < 95\%$ prior to induction reported by Henderson *et al.*[7] Of note in consideration of this discrepancy is the shorter period of time between drug administration and separation from parents in the latter study; 51% of patients were separated 4 min after drug administration. The progressive increase in sedation with sufentanil with time after administration and the association between desaturation and sedation make this explanation likely. Like Henderson *et al.*,[7] we avoided nitrous oxide during induction of anesthesia because of the well-described effects of this drug in potentiating the decrease in ventilatory compliance associated with opiates.[16]

Administration of midazolam has been associated with few complications in pediatric patients; however, depression of ventilation and circulation has been reported in adults.[17] The presence of a single child with an unexpected decrease in $Sp_{O_2}$, emphasizes the importance of continuous monitoring of children receiving either of these potent drugs by personnel trained in airway management and in a location suitably equipped for resuscitation. According to the overall criterion, the superior effect of sufentanil on the behavior of older children during placement of intravenous catheters is frequently counterbalanced by its impairment of oxygenation and/or ventilation. Both drugs, when used according to this protocol, usually provide good to excellent conditions for induction of anesthesia; however, in the doses studied, midazolam is clearly safer than sufentanil.

In summary, this direct comparison of the efficacy and safety of a single dose of these preinduction agents confirms that intranasal midazolam and sufentanil are effective preinduction sedatives[7,8] 10 min after their administration. Midazolam appears less pleasant initially; but it is a more reliable sedative and is associated with a lower incidence of decreased $Sp_{O_2}$ and chest wall compliance. Sufentanil facilitates insertion of intravenous catheters, particularly in preschool and older children, but requires close monitoring of oxygenation. If inhalation induction is planned, midazolam is clearly preferable to sufentanil. In any individual patient, the advantage of having an intravenous catheter prior to induction may outweigh the potential disadvantages of sufentanil. Further work is needed to develop formulations and routes of administration that are even less unpleasant than that described above, as well as to explore the safety and efficacy of combining a benzodiazepine and an opioid for painful procedures.

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