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Dose-responsive characteristics of meperidine sedation in preschool children

Kraig C. McKee, DDS Mamoun M. Nazif, DDS, MDS Douglass L. Jackson, DMD, MS
Douglas C. Barnhart, BS John Close, MS Paul A. Moore, DMD, PhD

Abstract

Using double-blind conditions, 60 uncooperative and fearful preschool children (24–66 months) received intramuscular injections of meperidine 0.25, 0.50, 1.00 mg/lb or placebo prior to restorative dental treatment. Behavior was assessed by the dentist and an independent observer during five specific treatment procedures. Behavioral ratings found meperidine to be an effective sedative, with 0.50 mg/lb and 1.00 mg/lb being significantly more effective than placebo ($P < 0.05$, Kruskal-Wallis). Children receiving 1.0 mg/lb of meperidine had significantly more nausea and vomiting than patients receiving lower doses of the drug ($P < 0.05$, Chi-square). Physiologic monitoring demonstrated that the highest dose of meperidine was associated with transient drops in arterial oxygen saturation. Meperidine sedation was found to be more effective for older children (37–66 months) and for children initially rated as being only moderately uncooperative and fearful.

Introduction

Providing dental care for fearful and uncooperative preschool dental patients is a challenge for the pediatric dentist. When acceptable behavior cannot be achieved using traditional behavior modification techniques, pharmacologic sedation frequently is employed as an adjunct in management. Aubuchon (1982) surveyed the members of the American Society of Dentistry for Children and found that the most popular sedative agents were narcotics, with alphaprodine and meperidine being most frequently used. With the withdrawal of alphaprodine from the United States market in 1986, the use of meperidine by pediatric dentists probably has increased.

Meperidine (ethyl, 1-methyl-4-phenyl-4-piperidine-carboxylate hydrochloride) is a synthetic opioid and was first synthesized in 1939. Its chemical structure and pharmacologic properties are similar to those of alphaprodine. As with alphaprodine, meperidine can produce profound analgesia and sedation (Lampshire 1959; Moore and Goodson 1985). Meperidine appears to have a longer period of onset and duration of action than alphaprodine (Caudill et al. 1982). Meperidine's efficacy when used in combination with promethazine or hydroxyzine for pediatric dental sedation also has been demonstrated (Album 1961).

The ability to reverse the effects of meperidine with a narcotic antagonist is among the advantages of this agent (Aubuchon 1982). Despite these advantages, there still have been reports of significant side effects, including nausea, vomiting, and even death when high doses of meperidine, alone and in combination with other CNS depressants, are used for pediatric sedation (Mitchell et al. 1982; Goodson and Moore 1983). These reports support the need for clinical studies evaluating the therapeutic efficacy and safety of narcotics used for sedation.

The objective of this controlled clinical trial was to evaluate the efficacy and safety of three doses of meperidine in uncooperative preschool-age dental patients.

Materials and Methods

Subject Selection and Research Design

Subjects were selected from the population of patients presenting for routine care at Children's Hospital of Pittsburgh Dental Clinic. This clinic serves a racially heterogenous population of predominantly urban, lower and middle socioeconomic class people. Inclusion criteria for this study were:

1. Medically healthy children (PS I)
2. Children 24 to 60 months of age
3. Frankl Scale behavioral ratings of "negative" or "definitely negative" during the initial exam (Frankl et al. 1962)
4. Failure of nonpharmacologic management modalities

5. Need for restorative dentistry requiring administration of local anesthesia and use of rotary instruments.

Informed consent was obtained according to the guidelines approved by the hospital's and school's human experimentation committees. The procedures, possible discomforts or risks, as well as possible benefits were explained fully to the parent and child involved, and their informed consent was obtained prior to the investigation.

The 60 children participating in this clinical trial were randomly assigned to one of the following four treatment groups:

Group 1—placebo (sterile water)
Group 2—0.25 mg/lb meperidine hydrochloride (Elkins-Sinn Inc, Cherry Hill NJ)
Group 3—0.50 mg/lb meperidine hydrochloride
Group 4—1.00 mg/lb meperidine hydrochloride.

The placebo and lower doses of meperidine were diluted to a standard volume, coded by a third party, and administered using blinded conditions. The dentist, patient, and research observer were unaware of treatment allocation.

Following the placement of physiologic monitors, one of the coded solutions was injected intramuscularly into the upper, outer quadrant of the patient's right anterior thigh. Thirty minutes later, 2% lidocaine, 1:100,000 epinephrine was administered, not exceeding 3.8 mg/kg of lidocaine. After adequate anesthesia was obtained, a rubber dam was placed and restorative treatment initiated.

If at any time the sedation was considered inadequate, dental treatment was discontinued, and the patient's participation in the study was concluded. At this point, the study code was broken, and the child was either sedated with appropriate agents to complete the dental procedure or reappointed.

Physiological Monitoring

Each patient was monitored with a precordial stethoscope, an automatic sphygmomanometer (Dynamap Model 18465X — Critikon Inc., Tampa, FL 33630), and a pulse oximeter/recorder (Model N100 — Nellcor Inc., Hayward, CA 94545). At five-min intervals during treatment, pulse, respiratory rate, and blood pressure were monitored and recorded. Oxygen saturations were monitored continuously and recorded on a strip recorder. To determine the depth of sedation, airway patency was assessed by repositioning the child's head using a method described previously (Moore et al. 1984).

Behavioral Assessments

The child's behavior was evaluated five times during the appointment:

1. Immediately prior to sedation
2. During local anesthesia administration
3. During rubber dam placement
4. During cavity preparation
5. During carving and polishing of the restoration.

Previous studies have shown that sedative drug effects are best distinguished during these periods of stimulation (Moore et al. 1984; Lambert et al. 1988).

Four assessment scales were employed to permit validation of the measures and to ascertain if the more simplified assessments would produce results similar to the more detailed evaluation instruments. Three of the four scales were rated by a trained research observer. These included a *categorical behavior rating scale,* a *dichotomous behavior scale,* and a *10-point rating scale.*

The *categorical behavior rating scale* was used to evaluate four components of behavior: crying, cooperation, apprehension, and sleep (Table 1). This scale has been described by Nazif (1971) and Houpt et al. (1985) and was modified for recent studies in our clinic. This scale has utility in evaluating quantitative as well as qualitative aspects of pharmacosedation.

Table 1. Categorical Rating Scale

Crying	
	1 = Screaming
	2 = Continuous crying
	3 = Mild, intermittent crying
	4 = No crying
Cooperation	
	1 = Violently resists/disrupts treatment
	2 = Movements which make treatment difficult
	3 = Minor movement/intermittent
	4 = No movement
Apprehension	
	1 = Hysterical/disobeys all instructions
	2 = Extremely anxious/disobeys some/delays treatment
	3 = Mildly anxious/complies with support
	4 = Calm/relaxed/follows instructions
Sleep	
	1 = Fully awake
	2 = Drowsy
	3 = Asleep/intermittent
	4 = Sound asleep

The *dichotomous behavioral scale* was used to rate the acceptability of the child's response to specific events of treatment as either satisfactory or unsatisfactory (Table 2, next page). This scale provides a simple and clinically relevant assessment of a child's behavior at specific periods during the appointment. The scale has a high interrater reliability and is sensitive for assessing pharmacologic sedation in children (Moore et al. 1984).

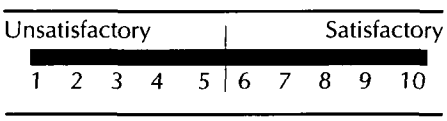
The third scale, a *10-point rating* of behavior (Figure 1) was developed to increase the sensitivity of the di-

Table 2. Dichotomous Behavioral Scale

I. Response to operative procedures (drilling, carving/polishing)	
Satisfactory:	drowsy, asleep, cooperative, accepting instructions.
Unsatisfactory:	drying, fussing, resistant to directions, postures other than supine
II. Response to injection	
Satisfactory:	No resistance, no gross motor or verbal responses, wincing or slight vocalization
Unsatisfactory:	Crying, struggling, kicking, fighting, grabbing the dentist's hand or arm

chotomous scale. This scale assigns relative levels of unsatisfactory behavior with values of 1 (the worst) through 5 and levels of satisfactory behavior as 6 through 10 (the best). This rating procedure was valuable in evaluating a previous study of narcotic sedation (Lambert et al. 1988).

Figure 1. Ten-Point Rating



The fourth scale was a *global rating of overall behavior* that was scored by the child's dentist (Table 3). The same dentist (KCM) performed all services for this study and rated the clinical adequacy of sedation at the conclusion of the dental appointment. This global rating is a valid and reliable indicator of overall sedation efficacy in previous studies at our clinic (Lambert et al. 1988). Children not completing the treatment because of inadequate sedation were arbitrarily rated "poor".

Table 3. Global Rating Scale

5 = Excellent
4 = Very Good
3 = Good
2 = Fair
1 = Poor/aborted

Side Effects

The parents of all participants were contacted by telephone the evening following the appointment and asked if the child had experienced any side effects. Side effects which occurred during the procedure and immediately postoperatively were recorded by the research assistant.

Statistical Analyses

Parametric and nonparametric procedures were used in the analysis of drug effects. The Kruskal-Wallis analysis was used to assess the categorical global scales. The Mann-Whitney U test was used for *post hoc* pairwise comparisons. Because presedation behavior was found to be correlated with behavioral responses, a multivariant analysis of covariance (MANCOVA for repeated measures) was used for the three other behavioral ratings. *Post hoc* tests included ANCOVAs and Tukey pairwise analyses. Frequency data such as side effects and the incidence of O_2 desaturation, were assessed with Chi-square analyses.

Results

Demographics

The age, weight, and presedation behavior of the children in each of the four treatment groups are shown in Table 4. One child was found to be six months older than the maximum inclusion criteria but was included in the analyses. The mean ages and weights were not significantly different between groups. All groups had an even distribution of presedation behaviors as described by Frankl (1962).

Table 4. Demographics of Pediatric Sedation Population

Dose	*0.0 mg/lb*	*0.25 mg/lb*	*0.50 mg/lb*	*1.00 mg/lb*
Age (months)				
Range	24-66	25-60	24-56	32-60
Mean ± SE	36.5± 2.7	41.7± 3.0	35.9± 2.7	43.0± 2.7
Weight (lb)				
Mean ± SE	33.0± 1.5	35.2± 1.7	31.9± 1.3	36.1± 1.1
Range	27.3–48.2	25.5–53.5	26.2–42.5	30.4–44.0
Presedation Behavior				
Negative	7	8	8	7
Def. Negative	8	7	7	8
Total Subjects	15	15	15	15

Physiologic Responses

Changes in cardiovascular and respiratory conditions were analyzed at each of the five treatment events. Wide variations from baseline measures were noted in respiratory rate, blood pressure, and pulse rate. No significant differences were noted between treatment groups for these changes in vital signs. In addition, the maximum decrease in oxygen saturation was determined. Oxygen saturations of 90% or less were reported for 18 children (Table 5, next page). The greatest incidence of desaturations occurred in the group treated with the highest dose of meperidine ($P < .05$, Chi-square).

Behavioral Responses

Dental treatment was completed for 58 of the subjects. Two subjects (one receiving 0.25 mg/lb and one receiving 0.50 mg/lb) were unmanageable, and treat-

Table 5. Incidence of Desaturation* vs. Dose

Dose	*0.0 mg/lb*	*0.24 mg/lb*	*0.50 mg/lb*	*1.00 mg/lb*
Incidence	1/15	4/15	5/15	8/15

* Desaturation defined as O_2 saturation < 90% at any time during the procedure.

ment was aborted and rescheduled.

As shown in Table 6, the global rating of behavior indicated that all of the doses of meperidine were more effective than the placebo (Kruskal-Wallis analysis, Mann-Whitney U *post hoc* tests). Meperidine 1.0 mg/lb was more effective than 0.25 mg/lb ($P = .0186$) but was not significantly better than 0.50 mg/lb ($P = .4157$).

Table 6. Global Rating vs. Dose of Meperidine

Dose	*0.0 mg/lb*	*0.25[a] mg/lb*	*0.50[bc] mg/lb*	*1.00[bc] mg/lb*
Global Rating				
Excellent	0	1	5	9
Very good	0	3	3	1
Good	2	5	4	1
Fair	3	5	1	2
Poor/aborted	10	5	1	2

[a] = $P < 0.05$ compared to placebo
[b] = $P < 0.01$ compared to placebo
[c] = $P < 0.05$ compared to 0.25 mg/lb

Global ratings were found to be correlated to the age (Eta coefficient = .69) and to the presedation behavior (Frankl scale) of the child (Spearman correlation = .224) such that sedation responses were less effective with younger children (24–36 months) and with children who initially were most uncooperative and fearful.

Because meperidine-induced sedation behavior, as judged by the global scale, was related significantly to presedation behavior, the three observer-rated scales were analyzed using a MANCOVA, with presedation behavior as a covariant. The results of the categorical, dichotomous, and extended 10- point behavioral scales substantiate the results of the dentist's global ratings (MANCOVA and Tukey *post hoc* analyses). The overall main drug effects and overall main observation period effects were significant ($T^2 = 26.2619$, $P = .0074$; and $T^2 = 27.2478$, $P = .0022$, respectively). *Post hoc* univariate ANCOVA showed that all three scales significantly contribute to the overall MANCOVA. No significant interaction effects were noted. The lowest behavior ratings were observed during local anesthesia injection and rubber dam placement. The two higher doses of meperidine consistently were found to be better than placebo for all observer-rated behavior. Table 7 (see below) provides the breakdown of behavior by categorical subscales of crying, cooperation, apprehension, and sleep. The overall drug response is noted in all subcategories of behavior.

Side Effects

Side effects were classified and recorded during and immediately following the dental procedures (Table 8, see below). Four patients receiving the highest dose of meperidine reported nausea or vomiting ($P < .05$, Chi-square). No airway obstruction was noted for any child at any dose. None of the side effects required medical management.

Discussion

This clinical trial provides a basis for dosage selection of meperidine for pediatric sedation. While all doses of meperidine were found to be more effective than placebo, no statistically significant difference could be shown between the two highest doses of the drug. When used as the sole sedative agent, IM meperidine at doses of 0.5 mg/lb and 1.0 mg/lb appears equally effective. Twelve of 15 children in the 0.5 mg/lb group (80%) and 11 of 15 children in the 1.0 mg/lb group (73%) were rated as having good to excellent sedations on the global rating scale.

The finding that higher doses of a narcotic are not necessarily more effective already has been noted in a previous study in our clinic (Lambert et al. 1988). When doses of sedatives are limited to assure consciousness, pediatric sedation techniques never have been shown to be 100% effective. Although this may represent an inherent inadequacy of conscious sedation for children, it also may reflect a dysphoria associated with the nausea and vomiting that was noted with the highest dose of

Table 7. Mean Categorical Ratings of Meperidine Sedation

Dose	*0.0 mg/lb* Mean	SD	*0.25 mg/lb* Mean	SD	*0.5 mg/lb* Mean	SD	*1.0 mg/lb* Mean	SD
Crying	2.2	± .8	2.8	± 1.0	3.1	± 1.0	3.2	± .9
Cooperation	2.0	.8	2.2	.9	3.0	.9	3.2	.9
Apprehension	2.2	.9	2.7	1.0	3.1	1.0	3.3	.9
Sleep	1.4	± .5	1.7	± .6	2.01	± .5	2.2	± .5

Table 8. Side Effects vs. Dose of Meperidine

Dose	*0.0 mg/lb*	*0.25 mg/lb*	*0.50 mg/lb*	*1.00 mg/lb*
Sleepy/drowsy	3	0	1	0
Aroused/hyperexcited	0	0	1	0
Nausea/vomiting	0	0	1	4*
Other (dizzy)	0	0	1	0

* $P < .05$ Chi-square

meperidine (1.0 mg/lb).

The four children experiencing nausea and vomiting in our study received the highest dose of meperidine. These patients also were found to have sedations that were rated as ineffective by the operator. If these children are removed from the global rating analysis, the highest dose, 1.0 mg/lb of meperidine, would provide sedation ratings that are significantly higher than the 0.5 mg/lb group (Fig 2). This may justify the combined use of an antiemetic such as promethazine or hydroxyzine with meperidine.

The highest dose of meperidine also produced a significant increase in the incidence of transient drops in arterial oxygen saturation. Similar drops in oxygen saturation have been reported for alphaprodine pediatric dental sedations (Mueller et al. 1985). A desaturation threshold of 90% was selected because no supplemental O_2 was administered, and O_2 saturations below this level represent a significant lowering of oxygen partial pressure. In our clinic, drops in O_2 saturation below 90% are addressed immediately by patient stimulation, and/or airway management. If O_2 supplementation is provided, a desaturation threshold of 96% may be more appropriate (Anderson and Vann 1988). Whether the respiratory depression that was noted with 1.0 mg/lb of meperidine is enhanced with the addition of an antiemetic is a topic of an ongoing trial at our clinic.

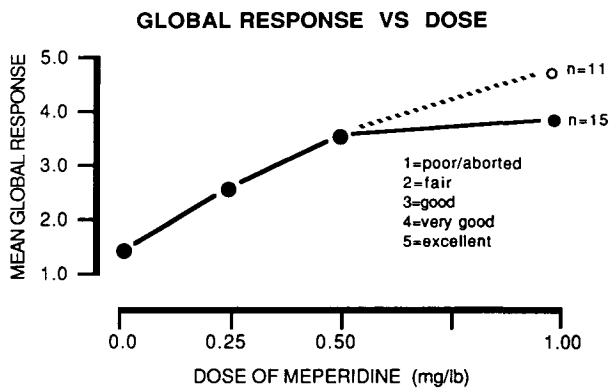


Fig 2. Improvement in global assessments with increasing doses of meperidine. Solid line represents all subjects. Dashed line indicates children (4) who reported nausea and/or vomiting.

The four behavior rating scales used in the present study provided remarkably similar results. It is particularly useful to find that the global rating provided by the dentist was as sensitive as the other measures for determining drug-induced changes in behavior. If the same operator dentist is used throughout the study, the global rating scale should be both a reliable and simple measure. The categorical scale that evaluated crying, apprehension, cooperation, and sleep may be useful in studies comparing different drugs where qualitative as well as quantitative drug effects may be significant. In the present study, where different doses of the same drug were evaluated, the qualitative differences in treatment groups would not be as likely to occur.

It is not surprising that the meperidine sedations were least effective in younger children (ages 2 to 3 years) and in children who demonstrated definitely negative presedation behavior. Younger children have not yet developed advanced communication skills, and are less receptive to routine behavioral management strategies. Very young, extremely uncooperative children may not be good candidates for narcotic sedation, and many are better managed utilizing a general anesthetic technique.

Conclusions

1. IM meperidine was shown to be an effective sedative premedicant for preschool dental patients, with 0.50 mg/lb and 1.00 mg/lb being significantly more effective than placebo.

2. Meperidine administered at 1.0 mg/lb was associated with an increased incidence of transient drops in oxygen saturation (< 90%) when compared with lower doses of the drug.

3. Meperidine administered at 1.0 mg/lb was associated with a significant increase in nausea and vomiting when compared to lower doses of the drug.

4. Meperidine sedation was significantly more effective for older preschoolers and children who demonstrate better presedation behavior.

Dr. McKee is an assistant professor, and Dr. Nazif is director of the dental department of Children's Hospital of Pittsburgh, Pittsburgh, PA. Dr. Jackson is a research associate; Mr. Barnhart is a research assistant; and Dr. Moore is a professor; all are in the department of pharmocology/physiology at the University of Pittsburgh School of Dental Medicine, Pittsburgh, PA. Mr. Close is a research associate/biostatistician in the Learning Resource Center of the University of Pittsburg School of Dental Medicine Center of the University of Pittsburg School of Dental Medicine. Reprint requests should be sent to: Dr. Kraig C. McKee, Children's Hospital of Pittsburgh, Dental Department, 3705 5th Avenue at DeSoto Street, Pitsburgh, PA 15213.

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Suicide rates don't rise right after HIV testing: study

On average, thoughts of suicide do not increase immediately after a positive human immunodeficiency virus (HIV) test, according to an article in the February 2, 1990 issue of the *Journal of the American Medical Association.*

During the week following test results, self-reported suicidal thoughts decreased significantly among those who tested negatively and did not increase significantly among those who were seropositive, wrote Samuel Perry, MD, of the Cornell University Medical College, New York, NY, and his colleagues.

But there is reason for concern, according the the authors, who focused on the immediate and intermediate effects of HIV antibody testing, not on the longer-term effects of living with an incurable and stigmatizing infection or on the development of physical symptoms. Both effects have been associated with increase psychological morbidity.

Two earlier studies, conducted in 1985 and 1986, concluded the suicide rate among men with AIDS who were 20 to 59 years old ranged from 21 to 36 times higher than the rate of men without AIDS.

Since this *JAMA* study focused on people before the debilitating effects of AIDS set in, the authors noted that their findings do not contradict those previous studies' conclusions.

Test subjects were recruited through newspaper advertisements, public service announcements and study information sent to medical clinics and drug rehabilitation centers throughout New York City. Free HIV testing and confidential counseling were offered to those recruited. Before blood samples were drawn, a psychiatric nurse monitored a self-reporting depression survey (Beck Depression Inventory) along with counseling the subject about various aspects of HIV testing.

Of the 301 study participants, 36 had a history of intravenous drug use, 75 had heterosexual risk factors and 199 were homosexuals (22 subjects reported multiple risks). The median income of the participants ranged from $15,000 to $30,000 and educationally, 162 had college degrees, 100 had some college credits, 23 had high school diplomas and 16 did not finish high school.

Among all those surveyed, the rate of suicidal thoughts dropped from 30.2% at the start of the study to 18.8% after the first week. After the first week, those who tested negatively had a 15.5% suicidal thought rate and those who tested positive had a 25% rate. Both groups reported even lower rates two months after the testing began.

But too much optimism should not be attached to these findings. Less reassuring to the authors was their finding that even in the context of confidential HIV testing with extensive pretest and post-test counseling of self-selected volunteers, suicidal ideation persisted after notification in more than 15% of both the seropositive and seronegative groups.

"Since as many as 15% of patients with affective disorders are known to commit suicide and estimates suggest that 10 to 20 times as many make suicide attempts, physicians must be alert to the possibility that a small but clinically meaningful subpopulation seeking the HIV antibody tests may require psychiatric treatment, " the authors cautioned.