

Nonlinear dose-response characteristics of alphaprodine sedation in preschool children*

L.A. Lambert, DDS M.M. Nazif, DDS, MDS
P.A. Moore, DMD, PhD T.G. Zullo, PhD

Abstract

Using double-blind conditions, 28 uncooperative and fearful preschool children received submucosal injections of either 0.0, 0.2, 0.4, or 0.6 mg/kg alphaprodine. Behavior was assessed during five specific treatment procedures. Results of a multivariate analysis of variance demonstrated greatest sensitivity to drug responses during local anesthesia administration and cavity preparation. Behavioral ratings indicated 0.4 mg/kg alphaprodine to be the optimal dose. Physiologic responses demonstrated large intersubject variations and apparently were not depressed for any dose. For pediatric sedation, increasing the dose of the narcotic from 0.4 to 0.6 mg/kg may not provide improved patient behavior.

Providing dental care for the fearful or uncooperative preschool dental patient can be 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 the management of these patients. In 1980, Aubuchon conducted a survey of the members of the American Society of Dentistry for Children and found that the most popular sedative agents were narcotics. The two narcotic agents that were used most frequently were alphaprodine and meperidine (Aubuchon 1982).

Alphaprodine is dl-1, 3-dimethyl-4-phenyl-4 piperidional proprionate hydrochloride. Its chemical structure and pharmacologic properties are very similar to meperidine with the notable exception of its more rapid onset and shorter duration of action (Caudill et al. 1982). As with meperidine, alphaprodine can produce analgesia, sedation, respiratory depression, nausea, and vomiting.

Alphaprodine has been used widely in obstetric medicine since the early 1950s. Lampshire (1959) described the advantages of using narcotics as part of a balanced sedation technique for pediatric dental patients. Because of its favorable pharmacokinetic properties and the desirable reversibility of the drug, alphaprodine became one of the more popular narcotic seda-

tives used in pediatric dentistry (Troutman and Renzi 1982).

However, there have been reports of a number of significant side effects involving high dosage of alphaprodine, and the safety of its uncontrolled use has come under close scrutiny (Goodson and Moore 1983).

Despite having been approved by the Food and Drug Administration, Roche Laboratory voluntarily withdrew the drug from the U.S. market in 1986. However, it is still available in other parts of the world. The research findings associated with alphaprodine may shed light on other narcotic techniques. The sedative efficacy and the optimal dose of alphaprodine and other narcotics have never been established in controlled clinical studies.

The objective of this controlled clinical trial was to evaluate the changes in the behavior of preschool dental patients who had received one of three submaximal doses of alphaprodine or a placebo in order to verify the efficacy, establish an optimum sedative dose, and evaluate the safety of this drug.

Materials and Methods

The patients for this study were selected from the general population of patients who presented for routine care at the Children's Hospital of Pittsburgh Dental Clinic. This clinic serves a racially heterogeneous population of predominantly urban, lower, and middle socioeconomic class people. The inclusion criteria for this study were:

1. Medically healthy (PS 1)
2. Between 24 and 60 months of age
3. Behavioral ratings of "negative" or "definitely negative" during the initial exam (Frankl scale)
4. Failure of nonpharmacologic management modalities
5. Restorative needs requiring administration of local anesthesia and utilization of rotary instruments.

Twenty-eight children were selected for this study. These children were then randomly assigned to one of the four study groups. Patients in the different groups received the following sedation regimens:

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- Group 1. 0.0 mg/kg placebo (sterile water)
- Group 2. 0.2 mg/kg alphaprodine
- Group 3. 0.4 mg/kg alphaprodine
- Group 4. 0.6 mg/kg alphaprodine.

The drugs for the lower doses were diluted to a standard volume, coded by a third party and administered in a double-blind fashion. Informed consent was obtained according to the guidelines approved by the hospital human experimentation committee. The patient was brought into the operatory and restrained, if necessary, while the monitors were placed. Each patient was monitored using a precordial stethoscope, a sphygmomanometer, and a pulse oximeter/recorder. During the course of treatment, oxygen saturation, pulse, and respiratory rate were monitored and recorded.

After the monitors were placed, alphaprodine was administered submucosally into the buccal region opposite the maxillary primary molars on the nontreatment side. Ten minutes later, local anesthesia was administered, using 2% lidocaine (maximum dose of 3.8 mg/kg) with 1:100,000 epinephrine. After adequate anesthesia was obtained, a rubber dam was placed and restorative treatment initiated.

The child's behavior was evaluated using three different scales. The first two (Scales A and B) were scored by a trained observer who rated the child's behavior during each of five specific treatment procedures:

1. Prior to sedation (baseline)
2. During local anesthesia administration
3. During rubber dam placement
4. During cavity preparation
5. During carving and polishing.

Scale A represented a more detailed instrument than Scale B. It originally was described by Nazif (1971) and Houpt (1985) and was modified for use in this study. This scale evaluates behavior using four separate determinants of behavior: crying, cooperation, apprehension, and sleep (Fig 1). For each behavior there is an objective four-point scale, where one is the worst possible behavior and four is the best possible behavior.

Scale B was modified from Moore's scale (Moore 1984). This is a 10-point scale, where one is the worst imaginable behavior and 10 is ideal behavior (Fig 2). The behavior of the child is rated by its relative degree of being "satisfactory" or "unsatisfactory" (Moore 1984).

Scale C is the only rating done by the operator; it is an overall clinical rating of the sedation that uses a five-point scale with one being the worst and five the ideal (Fig 3). Three scales were employed to permit validation of the measures and to ascertain if the more global instrument (Scale B) would produce results similar to the more detailed instrument (Scale A).

Results

The distribution of patients by age, gender, and

FIG 1. Scale A

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 movements/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

Assessment of behavioral responses using a four-point scale (Houpt 1985).

FIG 2. Scale B

Unsatisfactory					Satisfactory				
1	2	3	4	5	6	7	8	9	10

Assessment of behavioral response using a 10-point scale (1 = worst, 10 = best). Criteria for satisfactory and unsatisfactory behavior are event-specific. (See criteria described in Moore 1984.)

FIG 3. Scale C

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

This is an operator-rated five-point scale of overall success or failure of sedation.

weight is summarized in Table 1. The mean age for all patients combined was 36 months and the mean weight was 14.1 kg. There were no significant differences among any of the study groups for these parameters.

The physiologic parameters of oxygen saturation, respiratory rate, heart rate, and systolic and diastolic pressure were recorded and evaluated over time and in relation to the dose of alphaprodine. Data were evalu-

TABLE 1. Age, Gender, and Weight of Patients

Treatment Groups	Mean/Range Age (mo)	Mean/Range Weight (kg)	M:F Sex
0.0 mg/kg	37 (24-66)	14.7 (11.1-18.5)	3:4
0.2 mg/kg	29 (24-45)	13.5 (10.0-16.4)	6:1
0.4 mg/kg	39 (23-51)	14.0 (11.0-18.0)	6:1
0.6 mg/kg	41 (24-54)	14.2 (10.9-16.9)	4:3
Total average	36	14.1	19:9

TABLE 2. Behavioral Responses Versus Alphaprodine® Dosage for Sub-scales of Scale A

	0.0 mg	0.2 mg	0.4 mg	0.6 mg	P Value
Crying	2.03	2.26	3.29	2.67	< 0.01
Cooperation	2.31	2.31	3.26	3.09	< 0.01
Apprehension	2.17	2.37	3.46	3.00	< 0.01
Sleep	1.06	1.31	1.49	1.46	NS

ated as absolute values and maximum changes from baseline. Using a one-way multivariate ANOVA for respiratory rate and oxygen saturation, no significant differences were observed from baseline values.

The data from Scales A and B were analyzed by means of a 4 x 5R multivariate ANOVA (BMDP4V). Statistically significant differences for the main effects of drug dosage were found for the crying, cooperation, and apprehension subscales of Scale A. Scheffe's method of *post hoc* comparisons revealed that only the 0.4 mg/kg group had significantly better behavioral responses than the placebo group. Neither the 0.2 or 0.6 mg/kg dosage groups showed significant behavioral improvement when compared to the placebo group. There were no statistically significant differences on the sleep subscale at any dosage levels (Table 2, Fig 4).

Testing for the main effects of treatment procedures revealed statistically significant changes for the crying, cooperation, and apprehension subscales. No significant changes were observed for the sleep subscale. Examination of Figure 4 reveals similar response patterns for the crying and cooperation subscales with the worst behavior occurring during local anesthesia administration and cavity preparation. Because few children displayed sleep and/or drowsy behaviors, the sleep subscale demonstrated no procedure-dependent changes.

The results for Scale B were similar to those of Scale A. Statistically significant differences for the main effects of dosage level revealed that behavior for the 0.4 mg/kg group was better than that of the placebo (Fig 5). The 0.2 mg/kg and 0.6 mg/kg groups apparently were not as effective as the 0.4 mg/kg group. For the main effects of treatment procedures, the worst behavior was observed during local anesthesia administration and cavity preparation (Table 3, Fig 6). There were no statistically significant interactions between dose levels and treatment procedures for any of the subscales of Scale A or for Scale B.

One-way ANOVA for Scale C also revealed statistically significant differences. Similar to Scales A and B, behavior under the 0.4 mg/kg dosage of alphaprodine was the only dosage demonstrating significantly better values than the placebo (Table 3).

Discussion

The crying, cooperation, apprehension subscales of Scale A, Scale B, and Scale C all demonstrated the fact

BEHAVIORAL RESPONSE TO ALPHAPRODINE DURING DENTAL TREATMENT

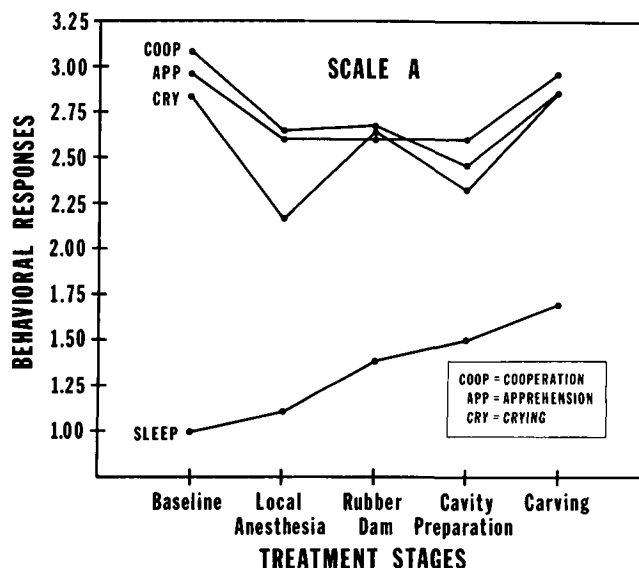


FIG 4. Behavioral response to alphaprodine during dental treatment (Scale A).

that the 0.4 mg/kg dosage level of alphaprodine produced significant improvement in the behavior of young unmanageable children irrespective of treatment procedure. Unexpected, however, was the common finding that the highest dose of alphaprodine (0.6 mg/kg) was not the most effective. It is quite possible that children who are deeply sedated are more likely to respond irrationally when exposed to noxious stimuli. It is also possible that synthetic narcotics, such as alphaprodine, have excitatory properties that are seen only with higher doses. It is obviously clinically significant that the higher dose of alphaprodine did not provide greater effectiveness. This finding also demonstrates the importance of performing dose-response studies to better understand drug efficacy and improve the clinical performance of premedicants used in sedation.

No significant measurable physiological changes were observed throughout the investigation. This finding was most likely due to the great variation in baseline and treatment measurements. Because pediatric patients are highly aroused during the beginning of an appointment, baseline measures rarely reflect "normal" cardiovascular and respiratory physiology. Changes from baseline measurements of respiratory rate, blood pressure, and pulse are therefore extremely variable and may not reflect significant drug-induced phenomena. Future data collection should include recording physiologic baseline data prior to the treatment appointment.

A significant decrease in oxygen saturation would be an absolute measure that might reflect narcotic-induced

respiratory depression. The mean maximum decrease in oxygen saturation in this study was 5.46% for all dosage groups. Only three patients (1 placebo, 1 alphaprodine 0.4 mg/kg, and 1 alphaprodine 0.6 mg/kg) had transient depressions greater than 10%.

The use of multiple scales by more than one rater provides valuable information regarding the validity of the behavioral findings. The agreement of the findings among the three scales indicates the reliability of the

TABLE 3. Mean Behavioral Responses for Scales B and C

Alphaprodine Dose (mg)	Scale B	Scale C
	Mean ± SE	Mean ± SE
0.0	3.49 ± 0.32	1.71 ± 0.18
0.2	4.29 ± 0.36	2.00 ± 0.53
0.4	7.11* ± 0.43	3.71* ± 0.52
0.6	5.11 ± 0.35	2.43 ± 0.53

* P < 0.05

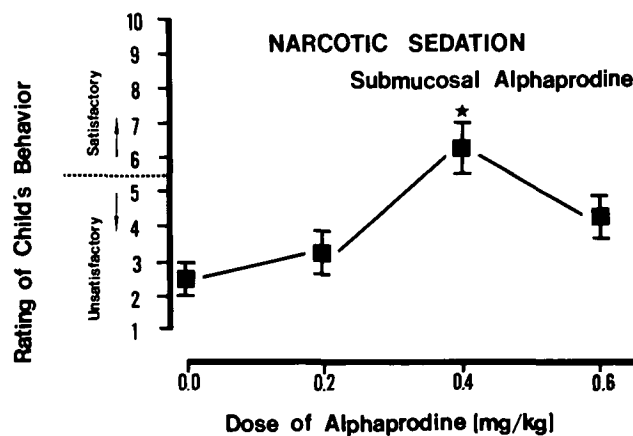


FIG 5. Narcotic sedation.

* = P < .05

BEHAVIORAL RESPONSE TO ALPHAPRODINE DURING DENTAL TREATMENT

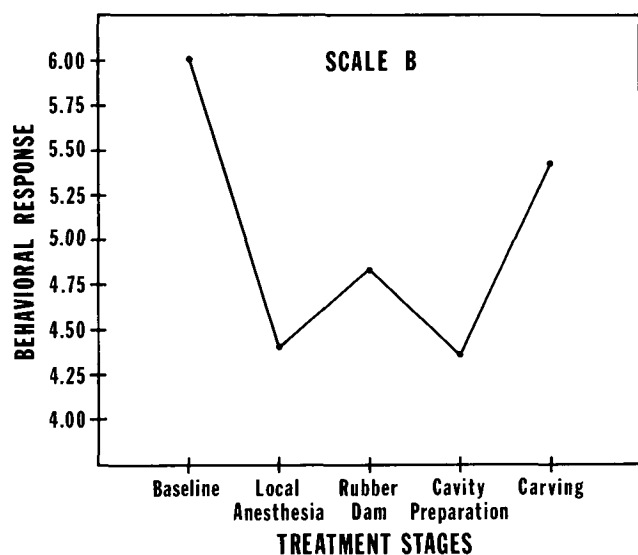


FIG 6. Behavioral response to alphaprodine during treatment (Scale B).

scales and confirms their clinical relevance.

It is interesting to note that data collected from Scale A indicate that the sleep subscale did not show alphaprodine-induced variations. When used for pediatric sedation, low doses of narcotics do not produce a significant degree of drowsiness or sleep. Other premedicants, such as chloral hydrate, may induce greater changes in this scale. Studies are underway to evaluate this possibility.

Conclusions

1. The effects of the alphaprodine sedation were most advantageous during periods of maximum stimulation; namely, local anesthesia and cavity preparation.
2. Alphaprodine exhibited a nonlinear dose response in the 0.0 to 0.6 mg/kg range. The most effective dose was 0.4 mg/kg.
3. No signs of drug-induced respiratory or cardiovascular depression were apparent for the alphaprodine doses studied.
4. Increasing the dose of alphaprodine from 0.4 to 0.6 mg/kg may not provide an improved behavioral response.

Dr. Nazif is chief of Dental Services and at the time of the study Dr. Lambert was a senior resident in pediatric dentistry, Children's Hospital of Pittsburgh; currently Dr. Lambert is an assistant professor, University of Illinois. Dr. Moore is an associate professor of pharmacology and Dr. Zullo is a professor, learning resources, both at the University of Pittsburgh. Reprint requests should be sent to: Dr. M.M. Nazif, Chief, Dental Services, Children's Hospital of Pittsburgh, One Children's Place, 3705 Fifth Ave. at DeSoto St., Pittsburgh, PA 15213-3417.

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