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A descriptive study of 201 uncombined alphaprodine HCl conscious sedations in pediatric dental patients (1982-1985)

Roger C. Lunt, DDS, MSD Harold E. Howard, DDS

Abstract

Alphaprodine HCl (Nisentil®) was a valued agent for pediatric dental sedation for more than 20 years. This study describes results from 201 pediatric dental sedations (mean age 4.6 years) using the pediatric dental dosage schedule specified in 1982 (0.3-0.6 mg/kg); no comedication (other than local anesthetic) was used with alphaprodine. The overall subjective success rate was 78%, at a mean dosage of 0.55 mg/kg. Objective success rates in terms of physical motion control, psychologic response, and accomplishment of dental procedures were generally 85% or better in the age range 3-6.5 years and the dosage range 0.3-0.6 mg/kg. Drug performance in managing children younger than 3 years was not acceptable. Minor side effects occurred in 9% of the sedations; risk factors were assessed to be low for this protocol in this sample. Clinical experience with alphaprodine played a part in the evolution of pediatric dental sedation to its current conservative plane. Sedation morbidity and mortality with alphaprodine (sometimes involving misuse), its route of administration, and liability trends contributed to a decline in its use.

Alphaprodine HCl (Nisentil®)[a] was for 20 years (1966-1986) a valued sedation agent in pediatric dentistry, where it earned a favored position among practitioners when they required an agent of rapid onset, short duration, and uncomplicated administration. Like other sedation agents, alphaprodine was employed to facilitate the accomplishment of dental operative or surgical procedures on children unable to cooperate due to fear, anxiety, immaturity, or handicapping conditions.

Alphaprodine HCl is a synthetic, rapid-acting narcotic analgesic with a short duration of action. Its pharmacologic properties are similar to both morphine and meperidine, although it is more potent than the latter. The recommended pediatric dental dosage, specifed in 1982, is 0.3-0.6 mg/kg, injected subcutaneously. Alphaprodine also has been used as a urologic and obstetric analgesic (Roche Laboratories 1986). The drug remains approved for clinical use (U.S. Food and Drug Administration, personal communication 1987).

The goals of this research were to: (1) study the clinical effectiveness of alphaprodine in pediatric dental sedation, using the drug under the 1982 dosage schedule and without comedication; (2) test behavior rating scales of physical and psychologic response during conscious sedation as objective measuring aids in evaluating drug performance; and (3) report on selected variables associated with alphaprodine sedation, including onset and operating time, side effects, and use of the narcotic reversal agent naloxone HCl (Narcan®).[b]

Although the use of alphaprodine in pediatric dentistry is virtually at an end concomitant with its unavailability, presentation of performance data for this agent was thought to be important for several reasons. First, there has been no report of the performance of alphaprodine used without comedication under the more conservative 1982 dosage schedule. Second, past evaluations of alphaprodine used performance criteria limited to general efficacy or based simply on whether or not dental procedures were completed.

Finally, alphaprodine left clinical practice under largely negative scrutiny; attention to its performance in a conservative regimen was viewed as important for a complete record. A television broadcast on dental anesthesia and sedation reviewed the history and experience with alphaprodine; risks and adverse reactions were emphasized at the expense of benefits (ABC News *20/20* 1983). Analyses of sedation accidents involving alphaprodine assigned primary responsibility to overdosage and misuse of multiple drug regimens (Goodson and Moore 1983; Moore and Goodson 1985). Concerns over morbidity and mortality reports involving alphaprodine and other sedation agents led to adoption of specific guidelines for pediatric dental sedation and anesthesia (American Academy of Pediatric Dentistry 1985).

Alphaprodine was introduced for pediatric dental

[a] Alphaprodine HCl (Nisentil®) is not presently manufactured.

[b] DuPont Pharmaceuticals Inc; Manati, Puerto Rico.

sedation by Corbett (1966). Published surveys of sedation use in pediatric dentistry revealed that alphaprodine was used by a range of 6-20% of respondents.[1] Success rates were reported in a range of 44-95%.[2] Chen (1982) reported an average of 2.8-2.9 efficacy (effectiveness) on a 3-point scale, where 1 was poorly effective and 3 was very effective. Both Tobias et al. (1975) and Troutman and Renzi (1982) used 3-point scales based on ability of the sedation to facilitate accomplishment of dental procedures.

Materials and Methods

The study was conceived as a prospective, descriptive report of the performance and characteristics of uncombined alphaprodine. Data were recorded and analyzed on alphaprodine conscious sedation of pediatric dental patients from 1982 to 1985 in the Department of Pediatric Dentistry, School of Dentistry, Oregon Health Sciences University. A standard sedation record was used; the 15 participating pediatric dental faculty and residents were oriented to the study goals and to use of the record.

The sample consisted of 98 children who were sedated based on a behavior assessment which determined that a pharmacologic agent would be needed to complete their dental care. Children were classified by the following reasons for sedation: (1) immaturity — children too young to pay attention and respond to behavior guidance; (2) failure of behavior management — children able to pay some attention and cooperate, but not sufficiently for comfortable completion of treatment; and (3) other — an undefined class with a blank space for explanation. With reference to the American Society of Anesthesiologists (ASA) physical status classification system (American Society of Anesthesiologists, Inc. 1963), 94 children were ASA 1 (normal, healthy patient) and 4 were ASA 2 (mild systemic disease). The choice of alphaprodine was based on a consideration of the individual child, the length and type of procedure, and the experience of the resident and/or faculty member with sedation in general and alphaprodine specifically; the selection was subjective in that prescribed criteria applied uniformly were not used.

Treatment of the 98 children resulted in generation of 201 valid sedation records. Data were analyzed by the number of sedations (N = 201). Group characteristics were determined for the 201 sedations. The mean age was 4.6 years with a range of 1-21 years; sexes were distributed at 52% girls and 48% boys.

Alphaprodine was administered submucosally intraorally with a 1-cc tuberculin syringe. The 1982 pediatric dental dosage schedule of 0.3-0.6 mg/kg was the guide for dosage selection. The selected dosage again was based on operator experience and consideration of the individual child; no standard criteria were in use. Additional drugs in the same syringe (such as promethazine HCl) were not used. Sedation records listing use of N_2O/O_2 or additional doses of alphaprodine at the same visit were excluded, limiting the data to cases managed with a single dose of alphaprodine and local anesthetic. Onset time was recorded as the period from drug administration to administration of local anesthesia.

The procedures planned included operative dentistry (192), oral surgery (7), and examination/preventive (2). Fifty patients (25%) were restrained with a Papoose Board.® [c] Twenty were 2.5 years and younger, comprising about half the 45 cases in that age group. Nineteen were 3-3.5 years of age, comprising about a third of the 67 in that age group. The remaining 11 were scattered from 4 to 7 years or older. Patients were considered recovered from sedation and ready for release when able to walk with assistance; if asleep they were required to be easily arousable and subsequently able to self-support their heads. Naloxone reversal of narcotic effects at the conclusion of apppointments was at the discretion of faculty and residents in cases deemed not recovered as described; there was no prescribed routine based on appointment duration. Any side effects of conscious sedation which were observed or reported later were required to be recorded.

Patient monitoring routines evolved during the study from general observation of vital signs (respiratory rate, pulse, color) to specific procedures using precordial stethoscopes and electronic blood pressure/pulse monitors. The changing routines reflected development of state and national rules and guidelines for management of sedated patients (State of Oregon 1983; American Academy of Pediatric Dentistry 1985).

Five-level rating scales for overall physical and psychologic response of the patient were adapted from Root (1962), pretested, and then used by treating dentists to rate patient responses during procedures after local anesthesia was given.

Ratings for physical response included: (1) relatively still; (2) slight motion; (3) moderate motion; (4) marked motion; and (5) violent motion. Those for psychologic response were: (1) quiet/asleep; (2) quiet/awake; (3) slight/infrequent cry; (4) frequent/intermittent cry; and (5) constant cry. Pretesting of the scales on a separate, prior sample revealed that they were clinically practical; their validity as measures of sedation success was part of the study. Two other scales were incorporated into the sedation record. One quantified the degree of accomplishment of planned procedures as: (1) all; (2) most; (3) few; or (4) none. The other was a 3-level

[1] Wright and McAulay 1973; Duncan et al.1980; Aubuchon 1982.
[2] Tobias et el. 1975; Mack 1982; Troutman and Renzi 1982; Dixon 1982; Doring 1985.

[c] Olympic Medical Corp; Seattle, WA.

scale to rate subjectively the overall appointment as successful, partially successful, or unsuccessful, no matter what was indicated elsewhere regarding physical or psychologic response, or procedures completed.

The Statistical Package for the Social Sciences (SPSS)[d] program was used for data analysis, using the Chi-square test to determine whether the results differed significantly from chance expectation. Summaries and data studies included the following:

1. Dosages of alphaprodine
2. Onset time
3. Operating time
4. Accomplishment of planned procedures
5. Naloxone HCl narcotic reversal
6. Side effects
7. Overall subjective success rate and comparison with success rates from the more objective physical and psychologic scales (A high association was anticipated because a motionless, quiet child is normally considered successfully sedated, and because operators might be influenced to standardize the results for all scales on the same sedation record.)
8. Relationships between dosage, successful physical and psychologic responses, and successful accomplishment of procedures (Study of initial data summaries suggested pooling behavioral and procedural rating responses into two levels of success and failure. With reference to the scales described above, success for data analysis purposes was defined as: physical ratings 1 or 2; psychologic ratings 1, 2, or 3; and, procedural accomplishment ratings 1 or 2. Operators were obviously unaware of these definitions, because they were selected at the time of data analysis, not at the outset. Resultant success rates for physical response, psychologic response, and procedural accomplishment were cross-tabulated with four alphaprodine dosage levels.
9. Success rates as in 8 (above) were cross-tabulated with 5 age groups
10. Separate analysis of success for the restrained group was done.

Results

The most frequent reasons given for employing sedation were failure of behavior management (99 sedations/49%) and immaturity (66 sedations/33%). The former was associated with ages 3-6 years and the latter with ages 2-3 years ($P < 0.001$). Thirty-six sedations (18%) were justified for other reasons, including mentally handicapped (9), non-English-speaking patient (3), length of appointment (10), request by parent (13), and extensiveness of treatment (1).

The mean dosage of alphaprodine was 0.55 mg/kg; the most frequently used dosage was 0.60 mg/kg. Figure 1 illustrates the distribution; no relation was found between age and selected dosage.

The mean onset time was 12 min; the most frequent values were 10, 15, or 20 min. The mean operating time was 72 min; the most frequent times were 90, 75, 60, and

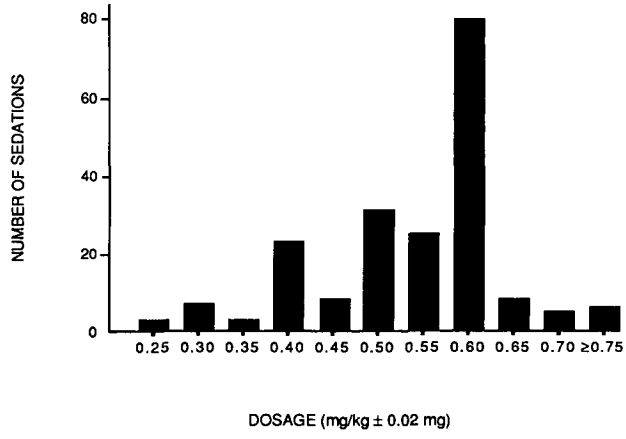

FIG 1. Alphaprodine dosage distribution.

45 min. The mean operating time for the 10 sedations justified by length of the appointment was 73 minutes. All planned procedures were accomplished in 82% of the sedations, and most procedures in another 9%.

Nineteen sedations (9.5%) were reversed with naloxone at the end of the appointments. The only factor distinguishing this group was a lower mean operating time, 51 as opposed to 72 min. Ten sedations were 45 min or less. Dosages in the 19 were skewed toward 0.5 or 0.6 mg/kg, just as in the main group; one was at 0.7 mg/kg.

Side effects were recorded for 18/201 sedations (9%). The occurrences included nausea (3), emesis during appointment (2), emesis postoperatively (4), local itching (3), swelling at alphaprodine injection site (2), skin rash (2), and conjunctival injection (bloodshot eyes) (2). The 18 occurrences involved 15 patients, including 13 who were affected once and 2 who experienced multiple events. One multiple-event patient had a 3-time nausea/emesis problem. The other was a 3-appointment series where local itching occurred twice. The 2 patients with transient skin rashes were sedated at least one other time without experiencing rashes. Dosages in 17 of the 18 sedations were between 0.3 and 0.6 mg/kg; one was at 0.7 mg/kg.

Results from the subjective overall assessment of sedation were 78% successful, 18% partially successful, and 4% unsuccessful. Those rated successful were strongly associated ($P < 0.001$) with success as defined on the objective behavior rating scales; that is, physical response levels 1 or 2 (still or slight motion), and psychologic response levels 1, 2, or 3 (quiet/asleep, quiet/awake, or slight/infrequent cry).

Figure 2 (next page) illustrates comparisons of dos-

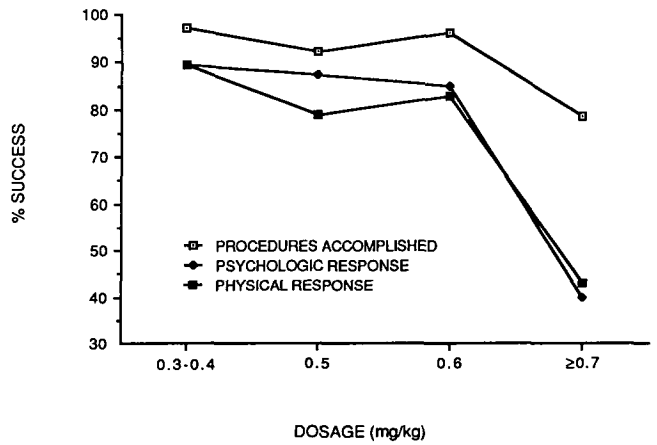

FIG 2. Success rates with alphaprodine as a function of dosage.

age with success rates for physical control (levels 1-2), favorable psychologic response (levels 1-3), and accomplishment of all or most dental procedures. The plots revealed the highest physical response success (90%) at 0.3-0.4 mg/kg, a marked similarity in success rates from 0.3 to 0.6 mg/kg, and a decline in success (to 40-45%) at 0.7 mg/kg and greater ($P < 0.01$). Nearly identical trends were observed for comparisons of successful psychologic response with dosage ($P < 0.001$). Success rates in accomplishing dental procedures were similarly high (92% or greater) at all dosage levels from 0.3 to 0.6 mg/kg, but declined (to 79%) at 0.7 mg/kg or more ($P < 0.10$).

Figure 3 illustrates comparisons of age with success rates for physical control (levels 1-2), favorable psychologic response (levels 1-3), and accomplishment of all or most dental procedures. The plots revealed the highest

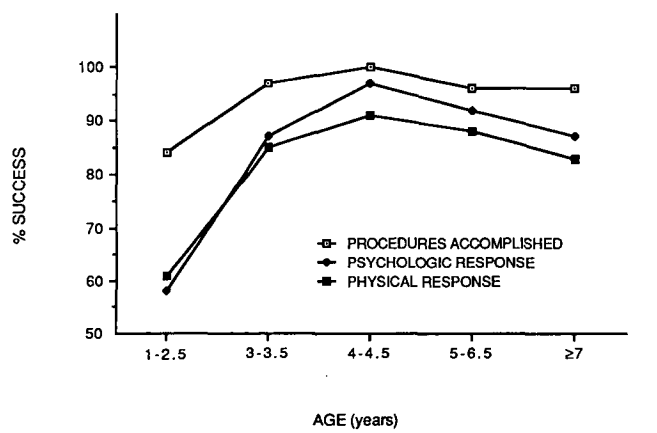

FIG 3. Success rates with alphaprodine as a function of age.

physical response success (91%) at 4-4.5 years, a marked similarity in success rates at all ages 3 years and older, and the lowest success rate (61%) at 2.5 years and younger ($P < 0.01$). Nearly identical findings characterized the comparisons of successful psychologic response with age ($P < 0.001$). Success rates in accomplishing dental procedures were similarly high (96% or better) at all ages 3 years and older, and declined slightly (to 84%) at ages 2.5 years and younger ($P < 0.05$).

For the restrained group alone (N = 50), results for the subjective overall assessment were 62% successful, 28% partially successful, and 10% unsuccessful. Exclusion of restrained cases from the main group and recomputing of this parameter gave results of 84% successful, 14% partially successful, and 2% unsuccessful.

A similar difference was seen in success rates for physical and psychologic responses between the restrained and unrestrained portions of the sample. The restrained physical response success rate was 63%, and that for psychologic response was 54%; figures for the main group minus restrained cases were 87 and 92%, respectively.

Discussion

Close correlation of subjective with objective success rates was not unexpected. The overall subjective success rate of 78% included all age and dosage groups. But data comprising Figures 2 and 3, in which objective success rates (physical, psychologic, and procedural) could be compared by age and dosage, was more informative in identifying patients who were the best candidates for alphaprodine sedation.

Alphaprodine performed well in potentially cooperative children 3 years and older, while more immature patients younger than 3 were likely to be physically resistant and upset within the recommended dosage range. This observation was not surprising because sleep was reported in only 33 of 201 sedations. Therapeutic doses of morphine-like drugs first produce analgesia, drowsiness, changes in mood, and mental clouding, without loss of consciousness (Gilman et al. 1985). In general, immature children do not seem very susceptible to these effects; increasing the dose to induce sleep could lead to overdosage.

Restraint was deemed necessary in 25% of sedations. In terms of success rates for physical response and psychologic response, it is noteworthy that results for most of the restrained group (1-3.5 years) were similar to those of the whole youngest group (1-2.5 years). Physical success rates were 63% (restrained group) and 61% (youngest group); psychologic success rates were 54% (restrained group) and 58% (youngest group). Thus, little more than half of patients in restraints could be expected to respond favorably to alphaprodine sedation.

The only data available for direct comparison with the 78% overall success rate in this sample of 201 was that of Troutman and Renzi (1982) who reported 73% effectiveness for the alphaprodine-only drug group. Also notable was Aubuchon's (1982) prediction that the more conservative dosage schedule of 1982 would decrease the success rate to 50-80%. As noted previously,

the exercise of considering only unrestrained patients elevated the success rate here to 84%.

There were biases and compromises in scientific method which should be acknowledged in the design of this study. First, two equal priorities were forced to coexist: recording of research data and completion of dental care in an educational setting for residents. With respect to the latter, involvement of resident and faculty in all details of sedation and its evaluation was necessary. But, using operators as evaluators introduces bias; also, these evaluators were both multiple and unstandardized. These factors affect the conclusions which are drawn from the data.

Another methodological question regards behavioral evaluation of candidates for sedation. A reported success rate is partly a function of patient difficulty. The classifications of immaturity and failure of behavior management successfully differentiated the toddlers from prechoolers (3 years) and older. Examination of other reasons for sedation revealed some subjectivity and inclusion of factors other than the child. The parental request cases involved anxious 8-year-old twin sisters appointed on 13 occasions for full coverage of teeth affected by dentinogenesis imperfecta. The 100% success rate for the 13 suggests that sedation would not have been elected by all operators. The 10 sedations justified for lengthy appointments were no longer than the mean operating time for the entire sample.

It was of interest that in children younger than 3 years or those given dosages of 0.7 mg/kg or greater, that the success rates in accomplishing all or most planned dental procedures did not decline parallel with physical and psychologic success rates. This reflected the tendency to complete the appointment if at all possible, even with unfavorable patient behavior. Similarly, a third of the physical response failures and a fourth of the psychologic response failures were rated subjectively as overall successful sedations. These incidental findings supported the view that evaluations based on procedural or general overview criteria reflect operator skill and attitude as well as drug performance.

The condensation of 5-level scales into 2 levels of success and failure better highlighted trends in data analysis and seemed to discriminate adequately whether the drug did or did not perform. Sedation evaluations in our clinic currently use 2-level success/failure evaluations of physical and psychologic responses as described in this study (physical response S/F: levels 1,2/3,4,5; psychologic response S/F: levels 1,2,3/4,5). Moore, et al (1984) found that a 2-response (satisfactory or unsatisfactory) system was reliable with multiple untrained observers and seemed to provide enough discrimination for practitioners, though perhaps not enough for researchers (Moore, 1986). Houpt (1986) has taken the direction of 4 to 6-level scales defined in terms of effect of behavior on the treatment.

The maximum recommended dosage was used most often, although lower dosages were just about as successful. The data gave the impression that case selection (primarily age) was more important than dosage. Of the 14 sedations where dosages of 0.7 mg/kg or more were given, 11 were for children younger than 3 years of age. This appeared to account for the distinct decline in successful physical and psychologic responses.

The mean operating time of 72 min and the low number of naloxone reversals confirmed previous experience that alphaprodine yields 1-1.5 hours working time, after which the child usually will be recovered sufficiently for release. Although the naloxone reversals were concentrated among sedations under 1 hr, the few reversals after 60 or 90 min indicated the need for case-by-case judgment.

Aubuchon (1982) felt that the more conservative dosage schedule of 0.3-0.6 mg/kg would greatly lower the incidence of adverse alphaprodine reactions; the absence of serious adverse reactions in this group of uncombined alphaprodine sedations confirmed his prediction. Three of the 18 reported side effects could not definitely be attributed to alphaprodine. One patient was known for vomiting in response to behavioral cues at home. Conjunctival injection seen in two patients was possibly the result of frequent crying in one and sleep in the other (due to dehydration if lids were partially open and uncovered); also, both patients received naloxone. Nine of the 18 events were nausea, and an interesting comparison can be made with Chen's (1982) breakdown of adverse reactions using uncombined alphaprodine. She found that most occurrences were nausea and that there were 3 times as many reports of nausea with alphaprodine alone than when combined with promethazine. The antiemetic effect of promethazine could have been the main factor in this regard. All of the side or adverse effects in the present group, though annoying and sometimes unexplainable, were minor when compared with the reports of major adverse reactions analyzed by Aubuchon (1982). He limited his discussion to serious respiratory depression, convulsion, or hospitalization experienced by a group who received a median dosage of 0.77 mg/kg. He emphasized that since one-half of these cases occurred by definition at dosages below the median, a low dosage did not preclude a serious adverse reaction. But, implicit in his description of protocols was that alphaprodine was commonly used in combination with other sedation agents.

Faculty at this institution would not discount risk factors with alphaprodine. Three adverse alphaprodine sedations (not part of the present sample) were managed without serious consequences. They included two respiratory depressions (one dose-related and one in-

volving airway problems) and one prolonged deep sedation. All 3 recovered without ill effects.

Moore and Goodson (1985), focusing on 19 sedation accidents involving narcotic combinations since 1972, concluded that 28 years' experience with narcotic sedation of children have seen an excessively high risk/benefit ratio. They felt that there was no evidence of narcotic superiority over other regimens and questioned narcotic use by clinicians untrained in managing anesthetic emergencies. These conclusions are not surprising from a review of cases characterized by doses in excess of recommended levels, and by combinations with a high aggregate dose.

In the present group of uncombined alphaprodine sedations, the analysis revealed little or no risk of serious adverse reaction under the 1982 dosage schedule, but found the efficacy limited to mood alteration and physical relaxation of potentially cooperative children 3 years or older. Used in this role, alphaprodine appeared to dovetail well with the category of conscious sedation under the 1985 American Academy of Pediatric Dentistry guidelines.

However, several constraints hastened the decline of alphaprodine use in practice and cast doubt on the future of parenteral sedation in pediatric dentistry. Increased professional liability consciousness has restricted this modality to dentists willing to enter a higher risk category. Sedation guidelines have elevated the standard of care for assessment of the patient, selection of drugs, informed consent, appropriate monitoring, and preparedness for emergencies. Three recent publications have included findings illustrating the occasionally fine line between conscious sedation and deep sedation.[3] The composite of these influences has increased the complexity and perceived risk of sedation practice. Some shrinkage in the availability of care for children requiring pharmacologic management might be expected in this environment.

Alphaprodine was a key participant in the evolution of pediatric dental sedation to a national standard. This report has attempted to add perspective to one portion of its history and performance.

[3] Moore et al. 1984; Doring 1985; Mueller 1985.

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Drs. Lunt and Howard are associate professors, pediatric dentistry, Oregon Health Sciences University. Reprint requests should be sent to: Dr. Roger C. Lunt, Dept. of Pediatric Dentistry, School of Dentistry, Oregon Health Sciences University, 611 SW Campus Dr., Portland, OR 97201.

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