Reversal of soft-tissue local anesthesia with phentolamine mesylate in pediatric patients

Mary Tavares, DMD, MPH; J. Max Goodson, DDS, PhD; Deborah Studen-Pavlovich, DMD; John A. Yagiela, DDS, PhD; Laura A. Navalta, BA; Siegfried Rogy, PhD; Bruce Rutherford, DDS, PhD; Sharon Gordon, DDS, MPH, PhD; Athena S. Papas, DMD, PhD; and Soft Tissue Anesthesia Reversal Group

Vasoconstrictors in local anesthetics increase the frequency of complete nerve conduction blocks at low anesthetic concentrations, and their use is more appropriate than increasing the anesthetic concentration to prolong the duration of pain control.[1] However, associated soft-tissue anesthesia (STA) of the lips and tongue typically lasts three to five hours, which is longer than is required for pain control after routine restorative and periodontal prophylactic procedures.[2] Prolonged STA can lead to inadvertent biting of the lips, tongue and cheeks, particularly in children. The results of a prospective study of 320 children showed that 16 percent of 4- to 7-year-olds and 13 percent of 8- to 11-year-olds reported having postoperative soft-tissue trauma after mandibular anesthetic blocks.[3] Accelerated recovery from STA could reduce the unwanted side effects of STA. To accelerate recovery, an injectable form of phen-

ABSTRACT

Background. The authors evaluated the safety and efficacy of a formulation of phentolamine mesylate (PM) as a local anesthesia reversal agent for pediatric patients.

Methods. A total of 152 pediatric subjects received injections of local anesthetic with 2 percent lidocaine and 1:100,000 epinephrine before undergoing dental procedures. The authors then randomized subjects to receive a PM injection or a control injection (sham injection in which a needle does not penetrate the tissue) in the same sites as the local anesthetic was administered in a 1:1 cartridge ratio after the procedure was completed. Over a two- to-four-hour period, they measured the duration of soft-tissue anesthesia and evaluated vital signs, pain and adverse events.

Results. The median recovery time to normal lip sensation was 60 minutes for the subjects in the PM group versus 135 minutes for subjects in the control group. The authors noted no differences in adverse events, pain, analgesic use or vital signs, and no subjects failed to complete the study.

Conclusions. PM was well-tolerated and safe in children 4 to 11 years of age, and it accelerated the reversal of soft-tissue local anesthesia after a dental procedure in children 6 to 11 years of age.

Clinical Implications. PM can help dental clinicians shorten the posttreatment duration of soft-tissue anesthesia and can reduce the number of posttreatment lip and tongue injuries in children.

Key Words. Local anesthetics; dental care for children; drugs; injections; pain measurement; pediatric dentistry; randomized controlled clinical trials.

JADA 2008;139(8):1095-1104.

Dr. Tavares is a senior clinical investigator, Clinical Research Collaborative, The Forsyth Institute, 140 The Fenway, Boston, Mass. 02115-3799, e-mail "mtavares@forsyth.org". Address reprint requests to Dr. Tavares.
Dr. Goodson is a senior member of the staff, and the director of Clinical Research, Clinical Research Collaborative, The Forsyth Institute, Boston.
Dr. Studen-Pavlovich, a professor and the chair, Department of Pediatric Dentistry, School of Dental Medicine, University of Pittsburgh.
Dr. Yagiela is a professor and the chair, Diagnostic and Surgical Sciences, University of California Los Angeles, School of Dentistry, and a professor of anesthesiology, David Geffen School of Medicine at UCLA, Los Angeles.
Ms. Navalta is senior vice president, Clinical and Regulatory Affairs, Novalar Pharmaceuticals, San Diego.
Dr. Rogy is senior director, Clinical Operations and Clinical Development, Novalar Pharmaceuticals, San Diego.
Dr. Rutherford is vice president, Clinical Development, Novalar Pharmaceuticals, San Diego.
Dr. Gordon is an associate professor, Biomedical Sciences, Department of Biomedical Sciences, University of Maryland Dental School, Baltimore.
Dr. Papas is a professor, general dentistry and nutrition, and the research director, Department of Oral Medicine, Tufts University School of Dental Medicine, Boston.

tolamine mesylate (PM) has been developed.

PM is a nonselective, competitive, α-adrenergic antagonist that has been used for more than 50 years in both animals and humans to reverse the effects of extravasation of adrenergic agonists such as epinephrine.[4,5] PM also is a vasodilator and has blocked the effects of endogenous vasoconstrictors in the oral tissues of cats, including the dental pulp and oral mucosa.[6] It also is used to block extravasated epinephrine or norepinephrine and to diagnose and treat pheochromocytoma.[7] It is proposed that a submucosal injection of PM after an injection of local anesthetic with vasoconstrictor could enhance the clearance of the local anesthetic and accelerate recovery from STA.

In two U.S. Food and Drug Administration (FDA) Phase III controlled clinical trials of PM in adolescent and adult dental subjects who received local anesthetic with vasoconstrictor, PM accelerated recovery of normal sensation in the lower lip by 54.8 percent and in the upper lip by 62.3 percent compared with a sham control.[8]

In this article, we report on the safety and efficacy of the injectable formulation of PM in accelerating the return of normal sensation in pediatric patients who had received injections of lidocaine with epinephrine before receiving dental restorations or undergoing scaling.

SUBJECTS, MATERIALS AND METHODS

Clinical trial design. This randomized, double-blind, controlled, Phase II clinical trial comprised 152 pediatric subjects who were 4 to 11 years of age and enrolled at 11 sites in the United States (eight within universities and three private practices). Each site obtained approval from its own institutional review board (IRB) or from an IRB of an affiliated institution. The subjects' parents or guardians provided informed consent for the study, and the subjects gave written or, in the case of younger children, oral assent.

Our primary objective in conducting this study was to evaluate the safety and tolerability of a formulation of PM (OraVerse, Novalar Pharmaceuticals, San Diego) that was approved by the FDA in May 2008. We did this by recording the incidence and severity of adverse events (AEs) and of intraoral pain as measured by the Wong-Baker FACES Pain Rating Scale (W-B PRS), in which zero is equal to no hurt and 5 is equal to "hurts worst."[9] Additional measures included vital signs, oral cavity assessments (OCAs) and the need for posttreatment analgesics. Our secondary objective was to determine if PM accelerated the return of normal soft-tissue sensation by means of standardized lip palpation for mandibular and maxillary procedures and of tongue sensation by means of standardized tongue palpation for mandibular procedures. The secondary objective measurements were performed with subjects in the 6- to 11-year-old group who learned the standardized palpation procedures before the start of dental treatment.

Eligible patients were from 4 to 11 years old at the time of the study and met the following additional inclusion criteria:

- sufficiently healthy to receive routine dental care and no allergies or intolerance to anesthetics, epinephrine, sulfites or PM;
- need for a routine dental procedure (restorative or periodontal maintenance) requiring local anesthesia with 2 percent lidocaine with 1:100,000 epinephrine;
- completion of the dental procedure within 60 minutes of the anesthetic injection;
- could be taught to complete the W-B PRS;
- weight greater than or equal to 15 kilograms.

For 6- to 11-year-olds, we had three additional requirements:

- normal lip sensations before local anesthetic;
- persistent lip numbness after completion of dental procedure;
- negative urine pregnancy test for subjects who were postmenarche.

Patients who required a different local anesthetic, sedation and more lidocaine than the amount required by the protocol or who had taken an opioid or opioidlike analgesic within 24 hours were ineligible for study inclusion.

Clinical procedures. Before we administered the local anesthetic injections and performed the dental procedures, we taught the 6- to 11-year-old subjects how to assess numbness of their lips and, when applicable, their tongues, by using finger palpation—a soft tapping of the soft tissues with the index or middle finger. We asked them to tap the injected sides of their mouths and to rate it as normal, tingling or numb, using the side of their

ABBREVIATION KEY. AEs: Adverse events. **FDA:** U.S. Food and Drug Administration. **IM:** Intramuscularly. **IRB:** Institutional review board. **IV:** Intravenously. **OCA:** Oral cavity assessment. **PI:** Principal investigator. **PM:** Phentolamine mesylate. **STA:** Soft-tissue anesthesia. **W-B PRS:** Wong-Baker FACES Pain Rating Scale. **WHO:** World Health Organization.

mouths that did not receive an injection as a reference. We assessed the onset of anesthesia and posttreatment STA in this manner. We assigned any child who could not learn to do the palpation procedure to the same protocol as the 4- and 5-year-old subjects.

We trained all study clinicians and clinical researchers in the study procedures during a two-day program before the study began. Independent clinical monitors' visits to the study sites maintained the integrity of the training effect.

At baseline, we assessed each subject's soft-tissue sensation, vital signs, temperature, respiration and oral cavity status before administering the injection of 2 percent lidocaine with 1:100,000 epinephrine. Subjects who weighed 15 kg or more and less than 30 kg received one-half cartridge of anesthetic. Those weighing 30 kg or more received one-half or whole cartridge, per the clinician's clinical discretion.

After completion of the procedure, if the time since the anesthetic was administered was 60 minutes or less and if the subjects had residual STA of the lip, we randomized them to receive a PM or a sham injection (control). The allocation ratio was 2:1 (PM: sham), stratified according to site and whether the dental procedure was performed on the mandible or the maxilla. We placed a visual barrier over the subject's eyes and administered the PM or the sham injection. For subjects who received one-half cartridge, the PM dose was 0.2 milligrams; for subjects who received a full cartridge, the dose was 0.4 mg. For the sham injection, we placed a shielded needle attached to a syringe against the site that had received the local anesthetic mimicking an injection. We removed the visual barrier from the subject's eyes, and blinded study investigators carried out the subsequent treatment assessments.

The observation period for safety assessments was two hours for the 4- and 5-year-olds and any older subjects who could not learn the lip and tongue palpation procedure (Table 1). For the majority of 6- to 11-year-olds, the observation period for safety and efficacy assessments was four hours. We recorded AEs and categorized them as to severity (mild, moderate or severe) and possible relationship to the study drug (the PM and the sham injections).

The study personnel telephoned subjects and parents who went home less than four hours after the study drug was administered on that same day to ask about AEs, analgesic use for intraoral pain and other concomitant medications. They contacted all subjects within 48 hours for this follow-up, which concluded participation in the study.

Statistical methods. We used descriptive statistics to characterize the safety and tolerability of the PM injection compared with the sham injection. We assessed the incidence, severity and duration of intraoral pain; we considered anything rated greater than mild (2 on the W-B PRS) clinically significant. We summarized vital signs (blood pressure, pulse, respiration and temperature) descriptively, as well as according to the frequencies of the following: decreases in supine systolic and diastolic blood pressure of greater than 20 millimeters of mercury and increase in pulse of greater than 20 beats per minute on two consecutive measurements as compared with the baseline reading.

We used the Medical Dictionary for Regulatory Activities, Version 8.2, (MedDRA Maintenance and Support Services Organization, Chantilly, Va.) to categorize AEs, the World Health Organization (WHO) Toxicity Criteria to determine severity of AEs and the WHO Drug Dictionary to record analgesics and concomitant medications. We determined the frequency of clinically significant findings in the oral cavity by means of the OCAs.

We analyzed the efficacy endpoints—time to return of normal lip and tongue sensation—in accordance with the modified intent-to-treat principle.[10] We used time-to-event methodologies comparing the median times to recovery and their corresponding 95 percent confidence intervals between treatment groups to analyze all efficacy data. We used the stratified log-rank test to test the null hypothesis that the distributions for the time to recovery of normal soft-tissue sensation were equal between the two treatment groups. All tests were two-sided with a significance level set at .05. The sample size of our Phase II study was based on the probability of detecting potential AEs that might occur in the PM treatment group. With 100 subjects in the PM arm of the study, there would be a 95 percent confidence level of observing at least one occurrence of a specific AE if the true proportion of subjects who would develop this AE in the population was 3 percent.[11] Our study was not prospectively powered to detect treatment differences in the efficacy endpoints.

RESULTS

We screened 160 patients for the study; 152 subjects were enrolled and completed all study assessments at 11 sites in the United States. There were

TABLE 1

Timetable for safety and efficacy assessments.

SAFETY AND EFFICACY MEASUREMENTS	BEFORE ANESTHETIC ADMINISTRATION	AFTER ANESTHETIC ADMINISTRATION	BEFORE RANDOMIZATION	AFTER STUDY DRUG ADMINISTRATION	FIRST HOUR (MINUTES)			
					15	30	45	60
Lip and Tongue Palpation	✓*		✓	✓	✓	✓	✓	✓
W-B PRS† at Injection Site		✓		✓				
W-B PRS at Procedure Site			✓			✓		✓
Vital Signs, Blood Pressure and Pulse	✓		✓		✓	✓	✓	✓
Vital Signs, Temperature and Respiration	✓				✓			
General Oral Cavity Assessment	✓		✓					
Specific Oral Cavity Assessment: Procedure and Injection Sites		✓		✓	✓	✓	✓	✓

* ✓: The procedure was performed or the measurement was made at the time specified.
† W-B PRS: Wong-Baker FACES Pain Rating Scale.[9]
‡ There was a two-hour observation period for safety assessments in subjects who were 4 to 5 years of age and in any subjects who were 6 to 11 years of age who could not learn the standardized palpation procedures. Vital signs and general oral cavity assessments were performed at the end of the two hours for this group

(continued on next page)

96 subjects in the PM group and 56 subjects in the sham group. The dental procedure sites were divided nearly evenly for both groups. In the PM group, 49 subjects received mandibular injections and 47 received maxillary injections. In the sham group, 26 subjects received mandibular injections and 30 subjects received maxillary injections. Table 2 (page 1100) summarizes the demographic and height and weight characteristics of subjects by treatment group and procedure site.

Approximately one-half of the subjects (53.9 percent) weighed between 15 and less than 30 kg and, therefore, received one-half cartridge of anesthetic and of the study drug. Of the subjects who were 30 kg or greater, 50 percent received one-half cartridge and 50 percent received a whole cartridge. Most subjects (94.7 percent) underwent tooth preparation and restoration. Six subjects (three in each treatment group) received crowns and two (one in each group) underwent periodontal maintenance. Approximately one-half of the subjects (49.3 percent) had procedures performed in their mandibles and approximately one-half had procedures performed in their maxillas (50.7 percent); similar numbers of procedures were performed in the right and left sides of the mouth. Eighty-three of the 152 subjects (54.6) received supraperiosteal injections of local anesthetic, 44 (28.9 percent) subjects received inferior alveolar nerve blocks and 20 (13.2 percent) received Gow-Gates nerve blocks, allowing for injection of PM by using the standard methods of anesthetic administration encountered in pediatric practice. Most subjects in the PM and sham groups (76.1 percent and 83.9 percent, respectively) received the study drug between 20 and 49 minutes after the injection of local anesthetic. Both the mean and median elapsed times from injection of the local anesthetic to injection of the study drug were similar in the PM group and the sham group.

The majority of subjects (73.7 percent) reported having no prior or current medical conditions. Medical conditions were reported by 24 percent of subjects in the PM group and 30.4 percent of subjects in the sham group. The most common condition was asthma (17.7 percent for subjects in the PM group and 21.4 percent for subjects in the sham group).

Safety and tolerability results. Thirty-five of the 152 subjects (23.0 percent) reported 37

SECOND HOUR (MINUTES)				THIRD HOUR (MINUTES)				FOURTH HOUR (MINUTES)			
15	30	45	60	15	30	45	60	15	30	45	60
✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	✓		✓				✓				✓
✓				✓				✓			✓
			✓‡								✓
			✓‡								✓
			✓				✓				✓

treatment-emergent AEs (all reported AEs that were related and unrelated to the study drug administration). Table 3 (page 1101) shows the study drug administration–related AEs in 21 subjects, with similar frequencies of events in both treatment groups (14 [14.6] in the PM group and 7 [12.5 percent] in the sham group). There were no deaths or other serious AEs, and all subjects completed the study. All but one treatment-related AE were mild or moderate in severity. There was one severe AE (injection site pain) in one subject in the sham group. All AEs were transient and resolved within 48 hours. The most frequently reported treatment-related AEs were injection site pain, increased blood pressure and postprocedural pain.

We found no evidence in this study for an effect of PM treatment on vital signs; there were only small deviations from the baseline values. The reference for normal blood pressure by age for children was sourced at eMedicineHealth.com.[12] During the observation period, 42.7 percent of the subjects in the PM group and 37.5 percent of the subjects in the sham group recorded systolic blood pressure readings of 120 mm Hg or higher. By the time of discharge, four subjects in the PM group (9.7 percent) and five subjects in the sham group (23.8 percent) had systolic blood pressure readings of 120 mm Hg or higher with a mean of 123 and 134 mm Hg, respectively (normal age-dependent range = 99 to 112 ± 20). Twenty-three subjects in the PM group (23.9 percent) and 13 subjects in the sham group (23.2 percent) had diastolic blood pressure readings of 85 mm Hg or higher during the entire observation period. At discharge, one subject in the PM group (4.3 percent) had a diastolic blood pressure reading of 88 mm Hg, while two subjects in the sham group (15.4 percent) had diastolic blood pressure readings of 85 mm Hg or higher, with a mean of 93 mm Hg (normal age-dependent range = 65 to 68 ± 15 to 20). Since PM is a vasodilator, possible drug side effects of PM related to vital signs are a decrease in blood pressure and an increase in pulse. Few subjects in both groups had clinically significant changes from baseline (> 20 mm Hg decreases in systolic or diastolic blood pressure or > 20 beats per minute increases in pulse rate on two consecutive measurements). These changes occurred with blood pressure, and we coded them as "mild" AEs (Table 3). The mean values for respiration and temperature taken within 15 minutes after we administered the study drug and before we discharged the subjects also showed little change from baseline.

The incidence of subjects who experienced no intraoral pain was similar in both groups (Figure 1, page 1102). The subjects reported the highest mean W-B PRS scores just after we administered the local anesthetic and then their scores declined steadily over time. The distribution of the most severe intraoral pain scores was similar in subjects in both treatment groups. The frequency of subjects who reported analgesic use for intraoral pain was low for both groups within the four-hour observation period (two subjects in the PM group and one subject in the sham group) and within 24 hours after discharge (three subjects in the PM group and one subject in the sham group). These data show that the PM injection was not associated with more intraoral pain than was the sham injection.

General OCAs and specific OCAs at the injection site and dental procedure site revealed minor abnormalities in both subjects groups. Only one subject in the PM group had a clinically significant OCA—hyperemia at the injection site—that resolved three hours after we administered the study drug. The subject did not report using any

TABLE 2

Subject demographics, by treatment group and procedure site.

DEMOGRAPHIC VARIABLE	PHENTOLAMINE MESYLATE			SHAM		
	Mandible (N = 49) (N [%])	Maxilla (N = 47) (N [%])	Total (N = 96) (N [%])	Mandible (N = 26) (N [%])	Maxilla (N = 30) (N [%])	Total (N = 56) (N [%])
Sex						
Male	24 (49.0)	19 (40.4)	43 (44.8)	14 (53.8)	18 (60.0)	32 (57.1)
Female	25 (51.0)	28 (59.6)	53 (55.2)	12 (46.2)	12 (40.0)	24 (42.9)
Race						
White	25 (51.0)	25 (53.2)	50 (52.1)	16 (61.5)	14 (46.7)	30 (53.6)
Black	14 (28.6)	15 (31.9)	29 (30.2)	5 (19.2)	10 (33.3)	15 (26.8)
Asian	3 (6.1)	2 (4.3)	5 (5.2)	0 (0.0)	3 (10.0)	3 (5.4)
Native American	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (1.8)
Other	7 (14.3)	5 (10.6)	12 (12.5)	4 (15.4)	3 (10.0)	7 (12.5)
Ethnicity						
Hispanic	9 (18.4)	9 (19.1)	18 (18.8)	5 (19.2)	2 (6.7)	7 (12.5)
Age (Years)						
Mean (SD*)	7.9 (2.1)	7.7 (2.0)	7.8 (2.0)	7.7 (2.2)	7.7 (1.8)	7.7 (2.0)
Median	8.0	8.0	8.0	8.0	8.0	8.0
Range	4.0-11.0	4.0-11.0	4.0-11.0	4.0-11.0	4.0-11.0	4.0-11.0
Height (Centimeters)						
Mean (SD)	128.6 (16.0)	125.9 (12.9)	127.3 (14.6)	131.8 (12.8)	130.4 (15.1)	131.1 (14.0)
Median	130.0	127.0	127.0	131.5	127.5	129.5
Range	71.0-152.0	97.0-152.0	71.0-152.0	101.0-152.0	96.0-157.0	96.0-157.0
Weight (Kilograms)						
Mean (SD)	31.8 (9.7)	30.0 (10.8)	30.9 (10.2)	30.3 (9.3)	31.0 (10.4)	30.7 (9.8)
Median	30.0	27.0	29.0	27.5	29.0	29.0
Range	15.0-53.0	16.0-57.0	15.0-57.0	20.0-56.0	18.0-56.0	18.0-56.0

* SD: Standard deviation.

analgesic for this abnormal OCA finding.

Efficacy results. We did not include the 4- and 5-year-olds or any older children who could not learn the lip and tongue palpation procedure in the efficacy analyses, as they could not reliably provide the necessary data. We analyzed 72 subjects in the PM group and 43 subjects in the sham group for STA recovery. The reduction in median time to normal lip sensation for subjects in the PM group (60 minutes) compared with that of subjects in the sham group (135 minutes) was 75 minutes (55.6 percent) (Figure 2, page 1102). There was a statistically significant difference ($P < .0001$) in time to return of normal lip sensation between the PM and sham groups as analyzed by the stratified log-rank test; the mandibular or maxillary location was the stratification factor.

We performed analyses on subgroups that could be evaluated for efficacy for mandibular or maxillary procedures (38 and 34, respectively). For the 38 subjects in the PM group who underwent mandibular procedures, the reduction in median time to normal sensation was 120 minutes (66.7 percent, $P < .0001$). For the 34 subjects in the PM group who underwent maxillary procedures, the reduction in median time to normal lip sensation was 52.5 minutes (46.7 percent, $P = .0002$).

For the 32 subjects in the PM group who could measure their tongue sensations, we found a statistically significant difference ($P = .0003$) in tongue recovery time, with a 60 percent reduction in median time (67.5 minutes) (Figure 3, page 1103).

DISCUSSION

The proposed mechanism of action of PM, which is a vasodilator, with respect to local anesthesia reversal is that increased local blood flow accelerates the clearance of local anesthetic from the

submucosal tissue to the bloodstream.[4] This idea is supported by findings from nonclinical studies (Bruce Rutherford, DDS, PhD, vice president clinical development, Novalar Pharmaceuticals, unpublished data, July 2008) that show that PM at more than 100-fold concentration does not interact with sodium channels and that administering equivalent doses submucosally in the oral cavity of dogs stimulated only ipsilateral increases in mucosal blood flow without altering blood pressure. Other data have demonstrated that when PM injections are administered in adults after lidocaine injections are administered, the maximum plasma concentration of lidocaine increases—a finding consistent with the proposed mechanism.[13]

TABLE 3

Incidence and type of all study drug-related adverse events, by treatment group and severity.

ADVERSE EVENTS	PHENTOLAMINE MESYLATE			SHAM		
	Mandible (N = 49) (N [%])	Maxilla (N = 47) (N [%])	Total (N = 96) (N [%])	Mandible (N = 26) (N [%])	Maxilla (N = 30) (N [%])	Total (N = 56) (N [%])
Subjects With Adverse Events	10 (20.4)	4 (8.5)	14 (14.6)	3 (11.5)	4 (13.3)	7 (12.5)
Adverse Event Types						
Abdominal pain upper, mild	0 (0.0)	1 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea, mild	0 (0.0)	1 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Facial pain, mild	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site pain, mild	1 (2.0)	1 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site pain, moderate	3 (6.1)	0 (0.0)	3 (3.1)	0 (0.0)	2 (6.7)	2 (3.6)
Injection site pain, severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.8)
Injection site reaction, mild	0 (0.0)	1 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oral pain, mild	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Postprocedure pain, mild	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Postprocedure pain, moderate	0 (0.0)	1 (2.1)	1 (1.0)	1 (3.8)	0 (0.0)	1 (1.8)
Blood pressure diastolic, mild*	2 (4.1)	0 (0.0)	2 (2.1)	1 (3.8)	0 (0.0)	1 (1.8)
Blood pressure,† mild	2 (4.1)	0 (0.0)	2 (2.1)	0 (0.0)	1 (3.3)	1 (1.8)
Headache, mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (1.8)
TOTAL NUMBER OF ADVERSE EVENTS	**11**	**5**	**16**	**3**	**4**	**7**

* With respect to blood pressure, "mild" designates that a more than 20 millimeters of mercury decrease in blood pressure was clinically significant but of minimal magnitude.
† Data from one site did not delineate systolic or diastolic and could not be clarified retrospectively.

Due to the vasodilatation caused by PM, the predicted potential side effects primarily are hypotension and a reflex tachycardia, neither of which occurred in the children in our study. For other indications in children such as to diagnose or treat pheochromocytoma, PM is administered as 1 mg intravenously (IV) or 1 to 3 mg intramuscularly (IM).[7] In our study, children received one-15th to one-fifth of current approved IV or IM doses of PM, and we think that these low levels may have contributed to the favorable safety profile. All 152 subjects enrolled in our study completed all phases of the trial. We recorded no serious AEs and the few nonserious AEs that did occur were divided almost equally between the PM and the sham groups. During the clinical development program of OraVerse and in discussion with the FDA, we agreed that a sham injection would be used as the control group in our study. The validity of this sham control was supported by the occurrence of treatment-related AEs in the control group, including a "severe" injection site pain rating recorded after we administered the sham injection.

Local anesthetics with vasoconstrictors are used widely to deliver routine dental treatment in children.[1] Epinephrine, the most commonly used vasoconstrictor, prolongs the duration and depth of anesthesia without using larger amounts of local anesthetic, which can be toxic.[14] However, STA beyond the point that is useful for the dental procedure can result in children's inadvertently biting their lips, tongues or cheeks.[3] The safety and efficacy data revealed in our study, which were similar to those reported for patients aged 12 to 92 years,[8] establish an excellent benefit-to-risk profile for PM as a means of accelerating recovery from STA in 6- to 11-year-old patients after routine dental procedures.

The results of our study suggest that administration of PM to pediatric patients who are under local anesthesia after routine dental procedures may have a clinical benefit. Faster recovery of normal lip and tongue sensation is highly desirable. The potential for PM to return patients' soft tissues to normal sensation with minimal risk in approximately one-half the time likely would be

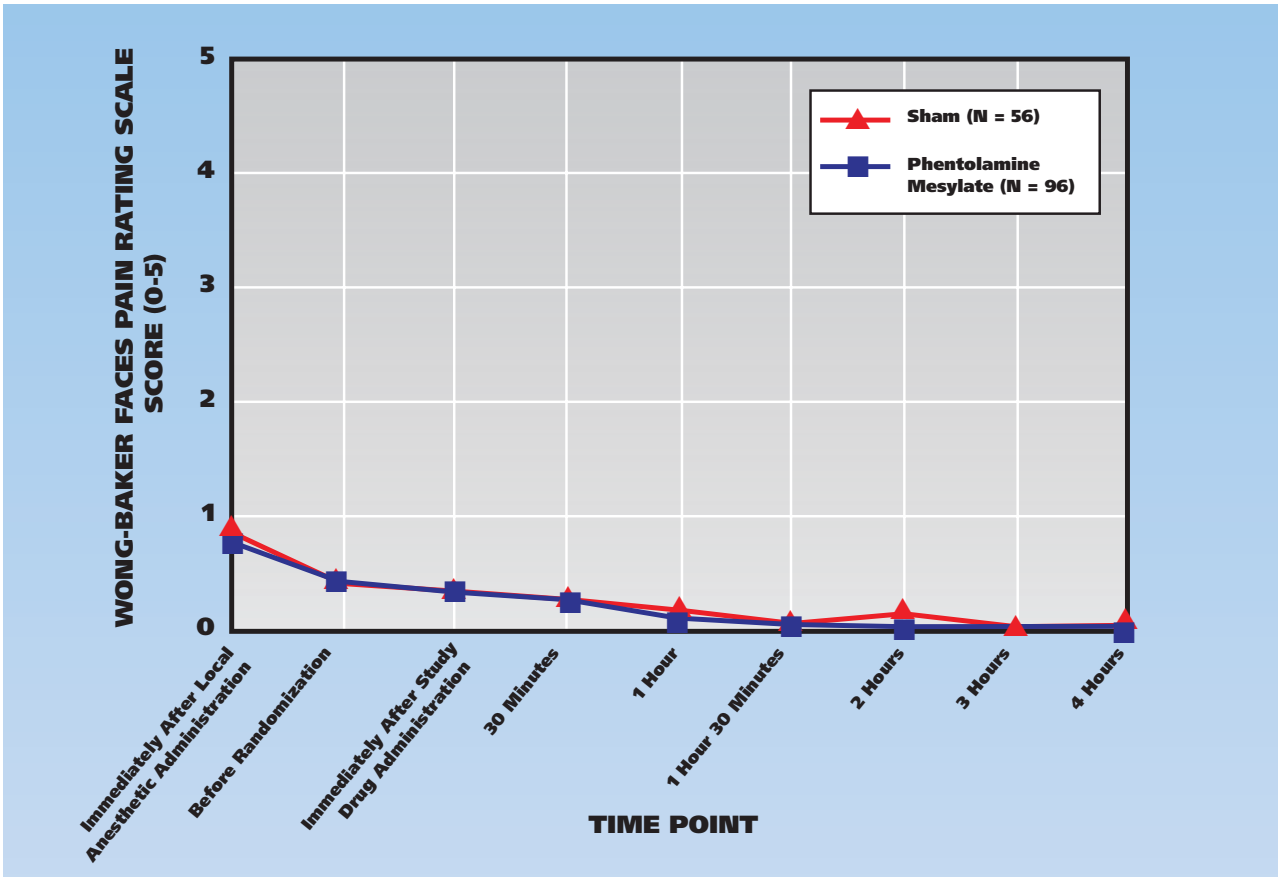

Figure 1. Mean Wong-Baker FACES Pain Rating Scale scores over study period.

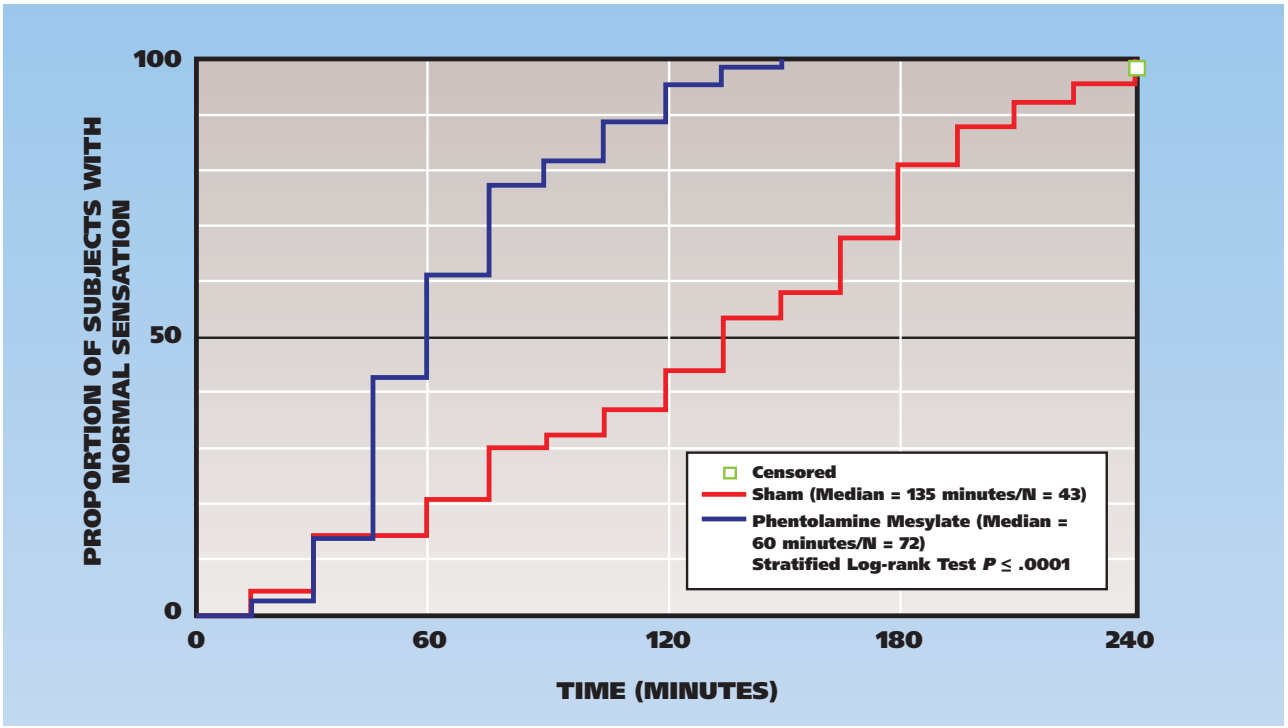

Figure 2. Time to recovery of normal lip sensation.

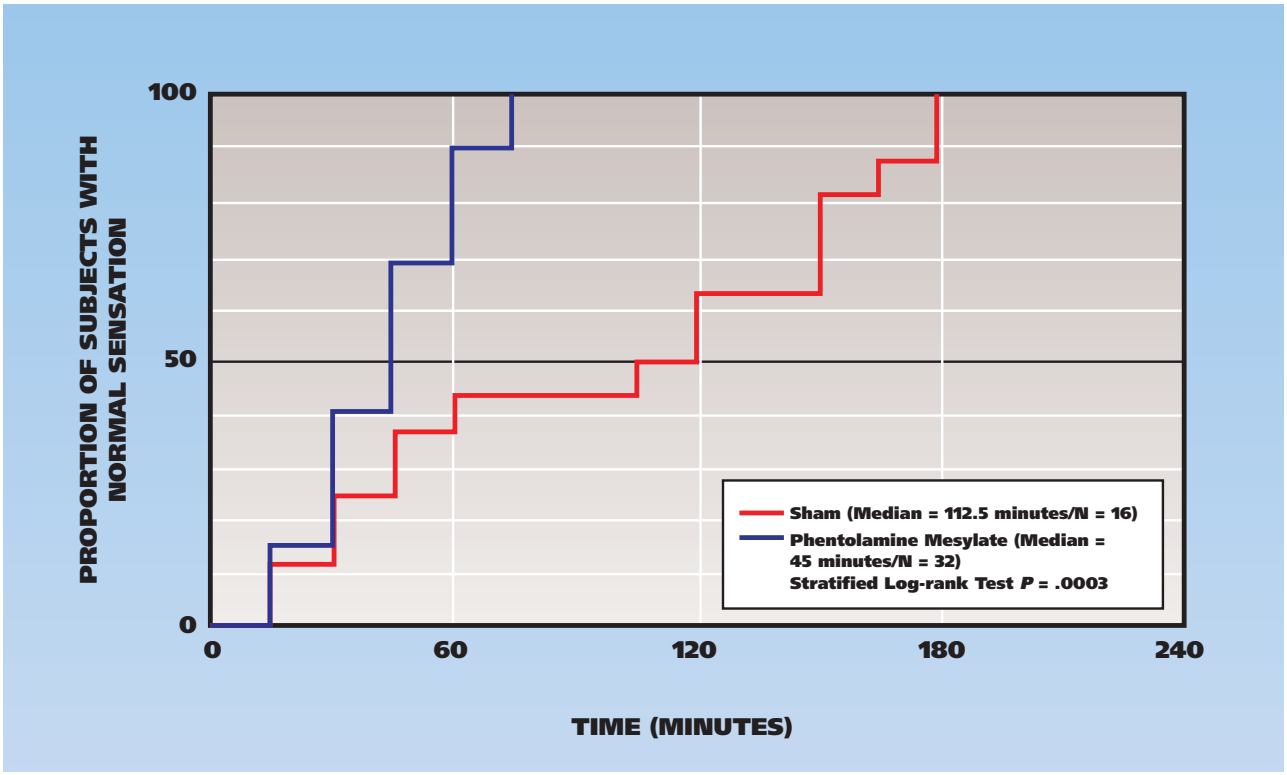

Figure 3. Time to recovery of normal tongue sensation.

perceived as desirable and beneficial by many pediatric patients and their parents or guardians.

There were limitations to our study that were imposed by the study design. The study's findings cannot be generalized to include children younger than 4 years for safety and younger than 6 years for efficacy assessments, children who have preoperative pain or children requiring additional sedation or to the administration of anesthetics without a vasoconstrictor.

CONCLUSIONS

Based on the results of this Phase II clinical trial, PM administered as one-half (0.2 mg) or full cartridges (0.4 mg) (as determined by subjects' body weight) was well-tolerated and safe for the 4- to 11-year-old children in this study. There were no serious AEs. PM had no measurable effect on the frequencies of AEs, vital signs, intraoral pain and soft tissue changes.

The findings from our study demonstrate that when PM is injected in the same volume and at the same site as a local anesthetic with vasoconstrictor injection was administered, it significantly reduced the duration of STA in children after routine dental procedures in the maxilla and mandible. We observed a 55.6 percent reduction in median time to return of normal lip sensation and a 60 percent reduction in median time to return of normal tongue sensation. ■

This study was sponsored by Novalar Pharmaceuticals, San Diego.

Disclosures. *Authors.* Drs. Rutherford and Rogy and Ms. Navalta are employees of Novalar Pharmaceuticals. Dr. Yagiela is a paid consultant for Novalar Pharmaceuticals. Drs. Papas and Goodson are members of the Clinical Advisory Board for Novalar Pharmaceuticals. Drs. Tavares, Gordon and Studen-Pavlovich reported no disclosures. *Study group members.* In the past five years, Dr. Moore has served as medical director, research coordinator or both to pharmaceutical companies marketing local anesthetic products including Dentsply Pharmaceuticals Division (York, Pa.), Kodak Dental Systems (Rochester, N.Y.), Septodont USA (New Castle, Del.) and Novocol Pharmaceutical of Canada (Cambridge, Ontario, Canada) a division of the Septodont Group (New Castle, Del.) regarding the developments of new anesthetics for dentistry. He also has served as a principal investigator or subinvestigator for FDA-required Phase II and Phase III clinical research contracts awarded to the University of Pittsburgh by Wyeth Consumer Healthcare (Philadelphia), Novocol Pharmaceutical of Canada and Novalar Pharmaceuticals. Within the past five years, Dr. Boynes has served as a consultant to pharmaceutical companies marketing local anesthetic products including Novocol Pharmaceutical of Canada and Novalar Pharmaceuticals.

The results of the study described in this article were presented at the International Association for Dental Research/Canadian Association for Dental Research/American Association for Dental Research 85th General Session and Exhibition, March 22, 2007, New Orleans.

The authors acknowledge the valuable contributions of the principal investigators (PI), clinical dentists and coordinators at all the sites in this study: Jennifer Soncini, DMD, The Forsyth Institute, Boston; Judith R. Chin (PI), DDS, MS, Indiana University School of Dentistry,

Indianapolis; Jeffrey Dean, DDS, Indiana University School of Dentistry; Jodie L. Jarrett, RDH, Indiana University School of Dentistry; Melissa S. Mau, BS, Indiana University School of Dentistry; Paul A. Moore, DMD, PhD, MPH, University of Pittsburgh; Sean G. Boynes, DMD, MS, University of Pittsburgh; Anne L. Lemak, DMD, University of Pittsburgh; Mohammad Abdulwahab, DMD, University of Pittsburgh; Margaret Elliott, DDS, MPH, University of Pittsburgh; Jayme G. Zovko, BS, University of Pittsburgh; Morton Rosenberg, DMD, Tufts University School of Dental Medicine, Boston; Mabi Singh, DMD, MS, Tufts University School of Dental Medicine; Nooruddin Sadruddin Pradhan, DMD, MS, Tufts University School of Dental Medicine; Ted P. Raybould (PI), DMD, University of Kentucky College of Dentistry, Lexington; Jason M. Mailhot (PI), DMD, MS, School of Dentistry, Marquette University, Milwaukee; Roy A. Rockman, DDS, Medical College of Georgia, Augusta; H. Thom Akins, DMD, Medical College of Georgia; Jennifer Balcum Turner, DMD, Medical College of Georgia; John L. Pfail (PI), DDS, Mount Sinai Medical Center, New York City; David V. Vaulari, DDS, Mount Sinai Medical Center; Yordanka K. Ivanova, DMD, Mount Sinai Medical Center; Jacqueline Kleven (PI), DDS, private practice, Bedford, Texas; Olga Pulgar-Vidal, DDS, MS, University of Maryland Dental School, Department of Health Promotion and Policy, Baltimore; Jean Chan (PI), DDS, private practice, El Cason, Calif.; Donna L. Minnick, RDA, private practice, El Cason, Calif.; Gloria Martinez, RDA, private practice, El Cason, Calif.; Anthony Henegar (PI), DDS, private practice, Irving, Texas.

1. Malamed SF. Pharmacology of vasoconstrictors. In: Malamed SF, ed. Handbook of Local Anesthesia. St. Louis: Mosby; 2004:41-54.

2. Hersh EV, Hermann DG, Lamp CJ, Johnson PD, MacAfee KA. Assessing the duration of mandibular soft tissue anesthesia. JADA 1995;126(11):1531-1536.

3. College C, Feigal R, Wandera A, Strange M. Bilateral versus unilateral mandibular block anesthesia in a pediatric population. Pediatr Dent 2000;22(6):453-457.

4. Yagiela JA, Dowd FJ, Neidle EA. Pharmacology and Therapeutics for Dentistry. St. Louis: Mosby; 2004:251-270.

5. McGovern SJ. Treatment of accidental digital injection of adrenaline from an auto-injector device. J Accid Emerg Med 1997;14(6): 379-380.

6. Koss MC. Differential neural activation of vascular alpha-adrenoceptors in oral tissues of cats. Eur J Pharmacol 2002;440(1):53-59.

7. Approval letter for phentolamine mesylate, 1998. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. "www.fda.gov/cder/foi/anda/98/40235ap.pdf". Accessed Nov. 26, 2007.

8. Hersh EV, Moore PA, Papas AS, et al.; the Soft Tissue Anesthesia Recovery Group. Reversal of soft-tissue local anesthesia with phentolamine mesylate in adolescents and adults. JADA 2008;139(8):1080-1093.

9. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs 1988;14(1):9-17.

10. Ivanov A, Van Glabbeke M. Design, management and handling of a randomized trial [in French]. Bull Cancer 1995;82(suppl 5): 553s-557s.

11. Louis TA. Confidence intervals for a binomial parameter after observing no success. J Am Statist 1981;35:154.

12. Pediatric Vital Signs. "www.emedicinehealth.com/pediatric_vital_signs/article_em.htm". Accessed Nov. 26, 2007.

13. Moore PA, Hersh EV, Papas AS, et al. Pharmacokinetics of lidocaine with epinephrine following local anesthesia reversal with phentolamine mesylate. Anesth Prog 2008;55:40-48.

14. Hilgers KK, Douglass J, Mathieu GP. Adolescent pregnancy: a review of dental treatment guidelines. Pediatr Dent 2003;25(5): 459-467.