# Effectiveness and safety of phentolamine mesylate in routine dental care

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Vasoconstrictors are used to compensate for vasodilatory effects, to reduce systemic plasma levels of local anesthetics, and to achieve local ischemia. The latter effect delays absorption of the local anesthetic, thus prolonging anesthesia. However, patients commonly feel disturbed by prolonged numbness, which is moreover associated with functional deficits, such as difficulties eating, drinking, or speaking, and with higher risk of experiencing self-inflicted injury by biting into the lips or tongue, particularly in young children.[1,2]

Phentolamine mesylate (PM) was first developed for the treatment of hypertension.[3] Because of its property as a nonselective inhibitor of $\alpha_1$- and $\alpha_2$-adrenergic receptors with the effect being a pronounced vasodilation,[4,5] PM was used in the treatment of patients with pheochromocytoma and dermal necrosis.[6] Further pharmacokinetic studies found that PM reverses local anesthesia by antagonizing the vasoconstricting property of epinephrine, resulting in systemic absorption of the local anesthetic.[4,7] The vasodilatory property of PM led to the development of a local dental anesthesia reversal agent (OraVerse, Septodont).[6] The US Food and Drug Administration approved it in 2008, and in Germany in 2011 for reversal of soft-tissue anesthesia in lip and tongue involving a catecholamine-containing vasoconstrictor in routine dental treatment.

To further increase knowledge on the effectiveness and safety of PM under routine dental practice conditions, observational research is needed. Studies should include a patient population with a broad range of medical backgrounds and use a range of concomitant medications.



## ABSTRACT

**Background.** Phentolamine mesylate (PM) is widely used to reverse local anesthesia after dental procedures. Limited knowledge is available regarding effectiveness and safety in routine dental practice.

**Methods.** The authors conducted 2 national, prospective, noninterventional, postauthorization effectiveness studies (OraVerse Post-Authorization Efficacy Study [ORAPAES] controlled, OraVerse Non-Interventional Study [ORANIS] uncontrolled) in patients receiving a local anesthetic as part of their dental treatment. They investigated time to recovery of normal sensation and function and the frequency of adverse events (AEs). The authors used Kaplan-Meier methods to analyze times to recovery; in ORAPAES, they used hazard ratios based on Cox models using the control group as a reference.

**Results.** In ORAPAES (n = 856), PM reduced the time to recovery of normal sensation and function with a difference in the median time of 70 and 79 minutes, respectively, with similar results observed in ORANIS (n = 445). In ORAPAES, patients in the PM group had, at any time point, a 2.77-fold higher chance of recovery to normal sensation (hazard ratio, 2.77; 95% confidence interval [CI], 2.35-3.26; $P < .001$) and for normal function 2.94-fold higher chance of recovery to normal sensation (95% CI, 2.49-3.47; $P < .001$) than in the control group. The observed incidence of AEs with PM treatment was 8.4% in ORAPAES (95% CI, 6.2-10.9) and 9.7% (95% CI, 7.1-12.7) in ORANIS. No serious AEs occurred.

**Conclusions.** PM substantially reduced the time to recovery of normal sensation and function after local anesthesia in routine dental treatment. The results confirm the effectiveness, safety, and tolerability of PM used in patients with routine dental conditions in Germany, and that PM augments the safety of dental treatments.

**Practical Implications.** The authors determined that PM is well suited to reverse local anesthesia after routine dental procedures.

**Key Words.** Phentolamine mesylate effectiveness; safety; noninterventional study; Germany.

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We initiated 2 noninterventional observational studies to gather further information on the effectiveness of PM, to gather data on the time to recovery of normal sensation in the lip and tongue, as well as the time to recovery of normal function (eating, drinking, and speaking). Moreover, the results of the study would provide clinicians with a better understanding of the incidence of adverse events (AEs) and patient response in the use of PM in routine dental practice.

## METHODS

**Study design.** We directed and performed 2 investigations in Germany. These were noninterventional, multicenter, prospective studies in patients undergoing routine dental treatment and receiving a local anesthetic containing epinephrine (adrenaline). The treatments were conducted in private practices and university medical centers across the country. We randomly selected sites by considering representiveness for geographic regions and according to the distribution of dental universities and private practices.

The OraVerse Post-Authorization Efficacy Study (ORAPAES) was a comparative study including patients undergoing dental treatment and either receiving PM or not (control group). The OraVerse Non-Interventional Study (ORANIS) was an uncontrolled study in which patients received a local anesthetic followed by PM because of their dental treatment. The study period for both studies was planned to last from the second quarter of 2013 (first patient documented) until 12 months after enrollment of the first patient. In both studies, data were collected on the day of the dental procedure and by phone thereafter. Safety data collection started at injection of PM (or with start of the routine procedure in the control group) and ended 48 hours later.

The ethics committee approved the observational plan. Patients provided written informed consent. In case of patients younger than 18 years in ORAPAES, written informed consent was provided by the legal representative.

**Patients.** ***ORAPAES.*** Patients eligible for ORAPAES were those

- who underwent local anesthesia by intraoral, submucosal injection of a local anesthetic containing a catecholamine vasoconstrictor, such as epinephrine (adrenaline) (dilution 1:100,000 or 1:200,000), after a routine dental procedure such as teeth cleaning, calculus removal, scaling and root planing, and restoration preparation including crown preparation;
- who were at least 6 years old and weighed at least 15 kilograms (33.1 pounds);
- for whom the dentist had made a decision to administer PM independent of the participation in the study;
- who had signed an informed consent form.

Patients allergic (hypersensitive) to PM or any other ingredient of the pharmaceutical preparation (for example, a history of a local reaction from injections) were not eligible. Eligible patients who accepted PM administration were included in the PM group and eligible patients to whom PM was proposed but who refused it were included in the control group.

***ORANIS.*** Patients eligible for ORANIS were patients

- who received local anesthesia by intraoral submucosal injection of a local anesthetic solution containing a catecholamine vasoconstrictor, such as epinephrine (dilution 1:100,000 or 1:200,000), after a routine dental procedure (teeth cleaning, scaling and root planing, restoration preparation, or preparation for crowns);
- who were at least 18 years old;
- those for whom the dentist had made a decision to administer PM independent of this documentation;
- who had signed an informed consent, and were included consecutively, if eligible.

We excluded patients if

- they were known to be allergic to the active component or any other ingredient of the local dental anesthesia reversal agent (OraVerse), or had a contraindication according to the summary of product characteristics (SmPC);
- they experienced an AE on application of the local anesthetic that prohibited the application of PM or made its application not appear reasonable;
- they did not fulfill the preconditions for the application of PM according to the dentist's general assessment on the basis of the recommendations provided in the SmPC.

**Objectives.** Our principal objective for both studies was to evaluate the time to recovery of normal sensation in the lip and tongue and the time to recovery of normal function (eating, drinking, and speaking). The secondary objective was to assess safety including AEs.

**Treatment.** The treating dentists performed all procedures according to package directions and the SmPC, and thus procedures were done under the sole responsibility of each dentist. No formal training was carried out before the onset of the study so as not to interfere with clinical practice. The SmPC stated that the amount of PM should match the amount of local anesthesia applied in adults. In children, the recommended maximum dose is 200 micrograms for children aged 6 to 11 years and a body weight of 15 to 30 kg (33.1 to 66.2 pounds) and 400 μg for those with a body weight of more than 30 kg (66.2 lbs). For children 12 years or older (body weight more than 30 kg [66.2 lbs]), the maximum recommended dose is 800 μg).

**ABBREVIATION KEY.** **ADRs:** Adverse drug reactions. **AEs:** Adverse events. **MedDRA SOC:** Medical Dictionary for Regulatory Activities System Organ Class. **NA:** Not applicable. **ORANIS:** OraVerse Non-Interventional Study. **ORAPAES:** OraVerse Post-Authorization Efficacy Study. **PM:** Phentolamine mesylate. **PT:** Preferred term. **SAE:** Serious adverse events. **SmPC:** Summary of product characteristics.

**Statistical analyses.** We calculated the ORAPAES sample size of 672 patients based on the primary objective of the effectiveness outcome. Under exponential assumption, to detect a reduction of the median time to recovery and of normal function by at least 20% (corresponding to a hazard ratio [HR] of 1.25 for the local dental anesthesia reversal agent group versus control group), a total of 631 events were required with a power of 80% and a 2-sided significance level of .05. As all patients were expected to recover within the study period, a number of 316 patients per treatment group was required. We took into account a 6% loss to follow-up; thus in total 672 patients, that is 336 in either treatment group, were needed. The distribution of patients over the treatment and the control group was not, however, 1:1 as expected, but 2:1 instead, causing a loss of statistical power. To keep the power at the 80% level, we increased the sample size per amendment by extending the study period until at least 750 patients (500 in the treatment group and 250 in the control group) were included.

**TABLE 1**

**Patient demographics and treatment variables.***

| CHARACTERISTICS | ORAPAES† | | | | ORANIS‡ |
|---|---|---|---|---|---|
| | Phentolamine Mesylate Group (n = 549) | Control Group (n = 307) | Total (N = 856) | *P* Value | Total (N = 445) |
| **Age, y** | 41.2 (16.8) | 39.2 (20.0) | 40.5 (18.0) | .12§ | 43.7 (14.7) |
| **Female Sex (%)** | 60.3 | 60.3 | 60.3 | .99¶ | 60.1 |
| **Anesthetic Injection Volume (Milliliters)** | 1.7 (0.8) | 1.6 (0.9) | 1.7 (0.8) | .09§ | 1.9 (1.1) |
| **Epinephrine Concentration (%)** | | | | | |
| **1:100,000** | 36.1 | 44.0 | 38.9 | .035# | 37.6 |
| **1:200,000** | 63.8 | 55.0 | 60.6 | | 59.7 |
| **1:400,000** | 0.2 | 1.0 | 0.5 | | 2.7 |
| **Anesthetic Injection Phentolamine Mesylate Application (min)** | 37.8 (23.1) | NA** | NA | NA | 39.5 (24.8) |
| **Phentolamine Mesylate Dose (%)** | | | | | |
| **200 micrograms** | 16.9 | NA | NA | NA | 7.8 |
| **400 μg** | 69.4 | NA | NA | | 81.7 |
| **600 μg** | 0.0 | NA | NA | | 2.3 |
| **800 μg** | 13.7 | NA | NA | | 8.2 |

* Percentages are based on patients with available information. Unless otherwise stated, means (standard deviations) are presented.
† ORAPAES: OraVerse Post-Authorization Efficacy Study.
‡ ORANIS: OraVerse Non-Interventional Study.
§ *t* test.
¶ Fisher exact test.
# Kruskal-Wallis test.
** NA: Not applicable.

For the ORANIS sample size, no formal hypothesis was stated and no sample size or power calculation was performed. With our planned ORANIS sample size of 2,660 patients, we expected the following statistical precision to be achieved for the estimation of the median time values to recovery of normal sensation in the lip and tongue, and of normal function: assuming a median time until recovery of 70 minutes, the 2-sided 95% confidence interval (CI) of the estimated median was 68.9-72.1 minutes. With a sample size of 2,660 patients, the probability of observing at least 1 rare AE with an occurrence of 0.001 (1 in 1,000) in this population is 93%. We performed the analyses based on less than 20% of the number of originally planned patients because we identified fewer patients willing to participate. With 445 evaluable patients there was a 95% probability to observe at least 1 AE with an incidence of .007 (7 in 1,000).

In each study, our analysis set encompassed all documented patients who fulfilled the criteria for documentation. We double-entered the data from case report forms into the study databases and checked them for plausibility in accordance with predefined criteria. Implausible data were corrected given the correct data were obvious but otherwise excluded from analysis. We excluded patients with missing time of anesthetic injection from analyses of primary variables, defined as time to recovery of normal sensation in the lips and tongue, and of normal function (eating, drinking, and speaking).

We calculated the estimated median time to recovery of normal sensation as well as the time to recovery of normal function, and corresponding 95% CIs with the Kaplan-Meier method. Recovery was expected to occur within the study period (24 hours) and was reported unless a patient was lost to follow-up. If the only follow-up information available was that recovery did not occur until the follow-up interview, we censored the time to recovery at the follow-up interview. If no follow-up information was available, we censored the time to recovery at the last documented visit in the case report form.

In ORAPAES, HRs for the investigation of the effects of age, oral region, and epinephrine concentration on treatment effects were calculated for the time to recovery based on Cox models using the control group as reference. AEs were the secondary variables and were coded using the Medical Dictionary for Regulatory Activities, Version 18.0.

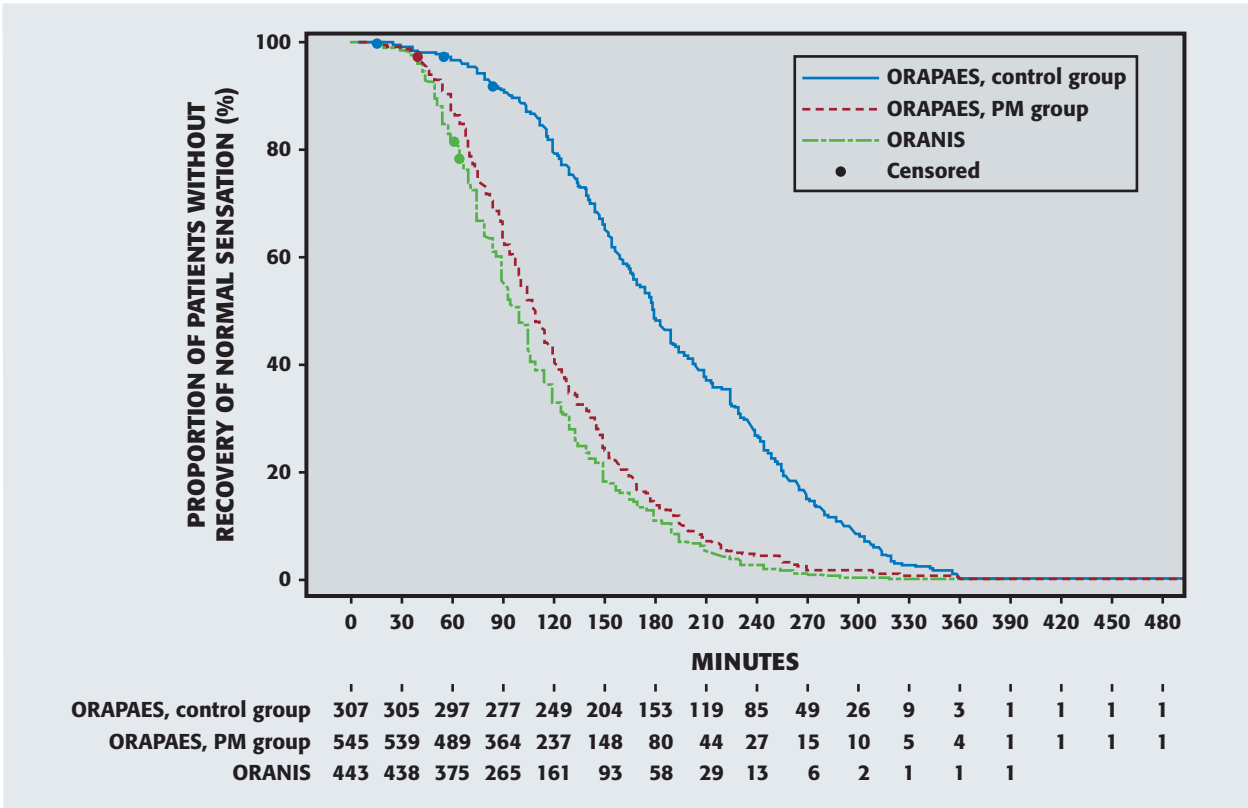


**Figure 1.** Time to recovery of normal sensation (Kaplan-Meier curve). The number of patients at risk is shown at the bottom. There were 4 patients from the phentolamine mesylate group (PM) in the OraVerse Post-Authorization Efficacy Study (ORAPAES) and 2 patients from the OraVerse Non-Interventional Study (ORANIS) who were excluded from the analysis owing to missing time of last anesthetic injection. Median time to recovery, minutes (95% confidence interval): ORAPAES, control group: 180 (170-190); ORAPAES, PM group: 110 (105-115); and ORANIS: 100 (92-105).

Data management and statistical analysis were performed using statistical software (SAS 9.2, SAS Institute).

## RESULTS

**Results of the controlled cohort study (ORAPAES).** ORAPAES included 856 patients at 13 study centers (11 private practices and 2 university medical centers) between June 2013 and December 2014. The PM group included 549 patients, and the control group encompassed 307 patients. Patients in the PM and control groups had a mean (standard deviation) age of 41.2 (16.8) years and 39.2 (20.0) years, respectively, with 60.3% in either group being female (Table 1).

Articaine (4%) was the only local anesthetic we used with epinephrine concentrations of 1:100,000 (36.1% of patients in the PM group, 44.0% of patients in the control group), 1:200,000 (63.8% PM group, 55.0% control group), and 1:400,000 (0.2% PM group, 1.0% control group), indicating a small difference between the groups ($P = .035$). The mean (standard deviation) injected volume was 1.7 (0.8) milliliters in the PM group and 1.6 (0.9) mL in the control group (range, 0.3-5.1 mL in both groups) (Table 1).

We assessed the anesthetic effect after the last injection of a local anesthetic per patient as "complete" by 92.0% (n = 505) of patients in the PM group and by 88.9% (n = 273) of patients in the control group. All other patients except for 1 control group patient (0.3%) assessed the anesthetic effect as being "sufficient." The mean (standard deviation) duration of the dental intervention was 31.8 (23.9) minutes in the total ORAPAES population (range, 5-217 minutes), and was nearly the same in both groups.

***Effectiveness of PM.*** The mean (standard deviation) duration between the last injection of the local anesthetic and injection of PM was 37.8 (23.1) minutes (range, 0-195 minutes) (Table 1). The median time to recovery of normal sensation in the lip and tongue after the last injection of the local anesthetic was 180 minutes in the control group (95% CI, 170-190) and 110 minutes in the PM group (95% CI, 105-115), representing a difference of 70 minutes (Figure 1). Patients in the PM group had, at any time point, a 2.77-fold higher chance of recovery to normal sensation than did patients in the control group, as revealed by an HR of 2.77 (95% CI, 2.35-3.26; $P < .001$) in a global Cox model analysis (Table 2). The

extent by which PM reduced the time to recovery of normal sensation was neither found to depend on the patient's age nor on the oral region (maxilla versus mandible) treated, but on the maximal adrenalin concentration used (Table 2). As there was also a small difference between both groups regarding maximal adrenalin concentrations, the results for the 1:100,000 and 1:200,000 subgroups were median time to recovery of normal sensation 172 minutes in the control group (95% CI, 155-190) and 105 minutes in the PM group (95% CI, 98-115), and median time to recovery of normal sensation 190 minutes in the control group (95% CI, 177-214) and 112 minutes in the PM group (95% CI, 105-120). The corresponding HRs for the 1:100,000 and 1:200,000 concentrations were HR, 2.25 (95% CI, 1.75-2.89); and HR, 3.19 (95% CI, 2.58-3.95).

The observed median time to recovery of normal function after the last injection of the local anesthetic in patients treated with PM was 111 minutes (95% CI, 105-116) compared with 190 minutes (95% CI, 179-203) in the control group (Figure 2) and similar to the time to recovery of normal sensation. The HR (95% CI, *P* value) for recovery to normal function was 2.94 (2.49-3.47; $P < .001$). For the 1:100,000 and 1:200,000 concentration subgroups, the results were, respectively, median times to recovery of normal function 184 minutes (95% CI, 164-201) in the control group and 107 minutes (95% CI, 99-115) in the PM group, and 196 minutes (95% CI, 180-225) in the control group and 114 minutes (95% CI, 105–120) in the PM group; HR, 2.46 (95% CI, 1.91-3.17) and HR, 3.34 (95% CI, 2.68-4.16).

***Incidence of AEs.*** A total of 8.4% (n = 46; 95% CI, 6.2-10.9) of patients in the PM group and 2.0% (n = 6; 95% CI, 0.9-4.0) of control group patients experienced AEs. All AEs in patients treated with PM were assessed to be causally related to PM; that is, adverse drug reactions (ADRs). No serious AEs (SAEs) occurred (Table 3). Based on the Medical Dictionary for Regulatory Activities terminology for Preferred Terms, the most frequent AE and ADRs were injection site pain (2.4% PM group versus 0.3% control group) and hypertension (1.6% PM group versus 0.3% control group). All of the latter AEs in the PM group were cases of bradycardia (0.9%, n = 5). Any AE in the control group except for the pain (0.7%) occurred in a single patient (Table 3).

**Results of the single-arm study (ORANIS).** ORANIS included a total of 445 analyzed patients treated at 170 centers in Germany and was conducted from November 2013 through December 2014. In total, 476 patients were included (those who provided informed consent). Of those, 466 patients (97.9%) had any documentation available.

The patients' mean (standard deviation) age was 43.7 (14.7) years and thus slightly higher than in the PM group of ORAPAES (41.2 [16.8]), with 60.1% being women (Table 1). Again, articaine (4%) was the only anesthetic used with a mean (standard deviation) volume of 1.9 (1.1) mL (range, 0.5-13.6 mL per patients). The most frequent maximum epinephrine concentration received over all injections per patient was 1:200,000 (59.7%).

***Effectiveness of PM.*** The most frequently injected dose of PM was 400 µg (81.7%) with a mean (standard deviation) time to the anesthetic injection of 39.5 (24.8) minutes. The median time to recovery of normal sensation in the lips and tongue after the last injection of the local anesthetic was 100 minutes (95% CI, 92-105) (Figure 1). Similar to ORAPAES, the extent by which PM reduced the amount of time to recovery of normal sensation was found to neither depend on a patient's age, sex, or the local anesthetic's maximum epinephrine concentration, nor the oral region (maxilla versus mandible) treated. The length of time to recovery of normal function (eating, drinking, and speaking) after the last injection of the local anesthetic in patients treated with PM yielded similar results (Figure 2).

***Incidence of AEs.*** In ORANIS, 9.7% (n = 43; 95% CI, 7.1-12.7) of patients experienced at least 1 AE which was

**TABLE 2**

**Hazard ratios for the time to recovery of normal sensation in OraVerse Post-Authorization Efficacy Study using Cox proportional hazard model analysis (event = recovery).**

| CHARACTERISTICS | NO. OF PATIENTS | PHENTOLAMINE MESYLATE VERSUS CONTROL HR* (95% CI†) | *P* VALUE | INTERACTION *P* VALUE |
|---|---|---|---|---|
| **Total** | 852 | 2.77 (2.35-3.26) | < .001 | |
| **Age Groups** | | | | |
| **6-11 y** | 68 | 4.10 (2.12-7.92) | < .001 | |
| **12-17 y** | 52 | 2.69 (1.31-5.53) | .007 | .370 |
| **18-64 y** | 659 | 2.61 (2.18-3.12) | < .001 | |
| **≥ 65 y** | 73 | 3.87 (2.10-7.13) | < .001 | |
| **Maxilla Versus Mandible** | | | | |
| **Maxilla** | 401 | 2.53 (2.03-3.16) | < .001 | .114 |
| **Mandible** | 367 | 2.79 (2.16-3.60) | < .001 | |
| **Epinephrine Concentration** | | | | |
| **1:100,000** | 332 | 2.25 (1.75-2.89) | < .001 | .030 |
| **1:200,000** | 516 | 3.19 (2.58-3.95) | < .001 | |

* Hazard ratio greater than 1 reflected a positive effect of phentolamine mesylate. The survival curves suggest that the assumption of proportional hazards are fulfilled (and so the hazard ratio was independent of the time).
† CI: Confidence interval.

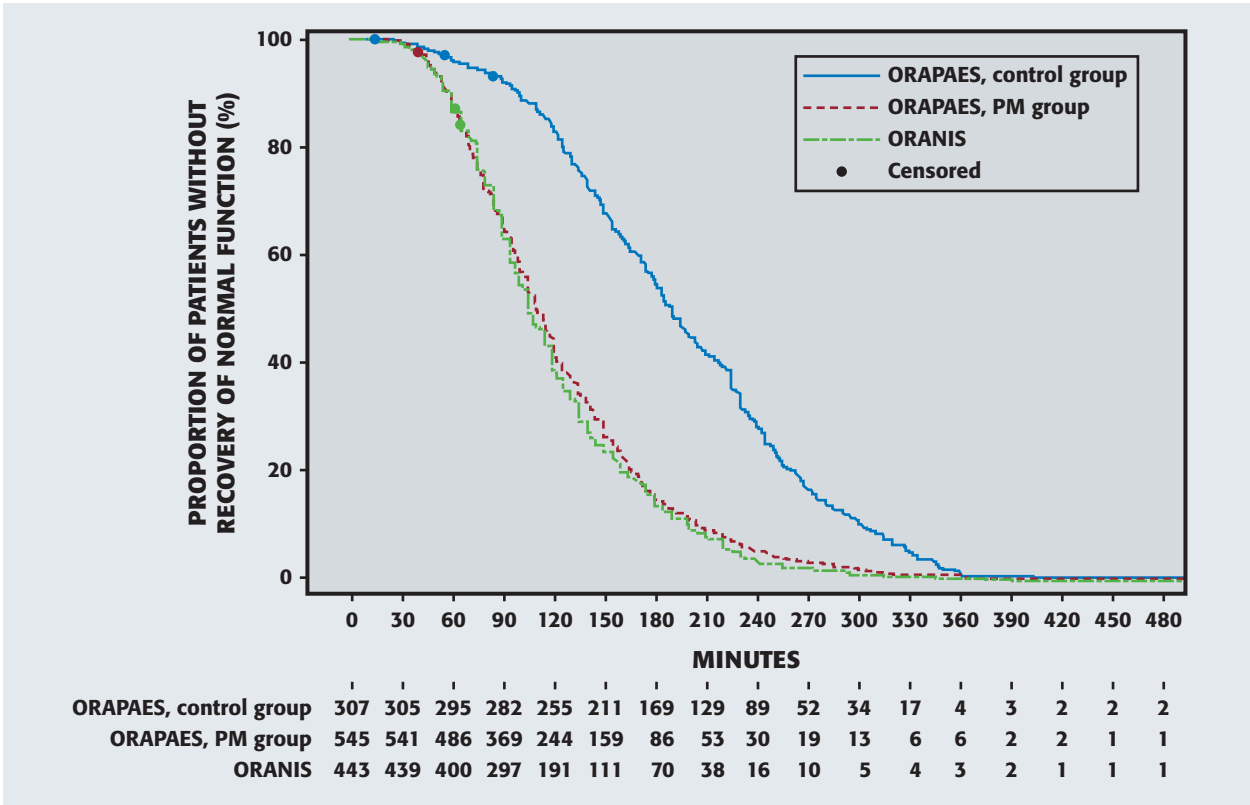


**Figure 2.** Time to recovery of normal function (Kaplan-Meier curve). The number of patients at risk is shown at the bottom. Four patients from the phentolamine mesylate (PM) group in the OraVerse Post-Authorization Efficacy Study (ORAPAES) were excluded from this analysis owing to missing time of last anesthetic injection. Median time to recovery, minutes (95% confidence interval): ORAPAES, control group: 190 (179-203); ORAPAES, PM group: 111 (105-116); and OraVerse Non-Interventional Study (ORANIS): 105 (100-115).

considered an ADR. No SAEs occurred (Table 3). As in ORAPAES, injection site pain (0.9%) was observed in 4 patients with no patient experiencing hypertension. Other than in ORAPAES, 4.0% of patients were reported in whom the drug seemed ineffective.

## DISCUSSION

The rationale of the 2 noninterventional studies reported was to evaluate the overall effectiveness of reversal of local anesthesia and the incidence of AEs of PM in routine dental treatment. With an average reduction for recovery of normal sensation of approximately 70 minutes as seen in ORAPAES and a low rate of transient AEs, the results support the effectiveness and safety of the drug.

**Scope and study populations.** Although ORANIS included adult patients only and ORAPAES included both adult and pediatric patients, the patient populations in both studies compared well. Specifically, the patients' mean age was 40.5 years and 43.7 years in ORAPAES and ORANIS, respectively, and approximately 60% in both studies were female. Moreover, the median dose of local anesthetic was similar and the most frequently used maximum adrenalin concentration was the same (1:200,000). The patient cohorts also compared well in terms of the length of time between the last anesthetic injection and injection of PM as well as its dose. A previous noninterventional study to investigate the clinical use of an articaine solution in routine dental treatments had similar patient characteristics: patients had a mean age of 42.6 years, 56% were women, and the mean volume of anesthetic solution was 1.3 mL.[8] The only local anesthetic chosen by dentists in both studies was articaine. This was in contrast to the pivotal studies, in which other local anesthetics, for example, prilocaine and mepivacaine, were used as well.[6]

**Effectiveness of PM.** As expected from the similar use of anesthetics and of PM in both studies, its effectiveness was also comparable in both studies. This was indicated by similar results regarding the time to recovery of normal sensation in lips and tongue, as well as regarding the time to recovery of normal function (eating, drinking, and speaking). These results are in line with previous findings from clinical studies. In a phase 2 study, PM reduced the median duration of the local anesthesia in the lips from 155 to 70 minutes[9] with a

pediatric phase 2 study including children aged between 6 to 11 years yielding similar results.[10] Similarly, in 2008, Hersh and colleagues[11] reported a reduced median time of local anesthesia in the lower lip by 85 minutes (55%) and in the upper lip by 83 minutes (62%) after injection of PM compared with a control (sham injection). The length of time to normalization of oral functions was reduced accordingly. As Nourbakhsh and colleagues[12] reported, PM moreover diminished the frequency of self-inflicted injuries in children.

Remarkably, the effect of PM on the time to recovery was not observed to depend much on the local anesthetic's epinephrine concentration. At least regarding the higher epinephrine concentrations used in the studies described here (1:100,000 and 1:200,000), the anesthetic efficacy and the mean duration of anesthesia induced with articaine (4%) have been shown to be similar in clinical studies.[13,14] Accordingly, one would speculate that the effect of PM on local anesthesia is essentially independent of whether the anesthetic's epinephrine concentration is 1:100,000 or 1:200,000.

**Safety of PM.** Another objective was to investigate the incidence of AEs in patients treated with PM in routine dental care. Overall, the incidence of AEs in patients treated with PM in ORAPAES was 4 times as high as in control group patients. This is not unexpected because intrinsic drug-related AEs, such as "drug ineffective" or cardiovascular side effects, can inherently occur only (or preferably) in patients treated with PM. This could possibly cause a general propensity of study investigators to focus on the active treatment group and thus underreport AEs in the control group.

No cases of death or other severe AE or ADR were reported. Overall, treatment with PM was safe and well tolerated, in line with the results found in clinical studies, in which also no SAEs were observed. For instance, Laviola and colleagues[9] reported a high tolerability of PM in a phase II study. A high tolerability was also found in a pediatric phase 2 study that included children aged 4 to 11 years. In this study, the frequency of AEs in the PM group was not higher than in the sham injection group. All reported AEs were nonserious and resolved within 48 hours.[10]

In addition, the AEs with the highest incidence in our study patients treated with PM compared well with findings from clinical studies. Specifically, "injection site pain," "hypertension," "bradycardia," and "oral pain" were also among the AEs with the highest incidences in clinical studies. Similarly, the AE with the second highest incidence in ORANIS, "headache," showed also an increased incidence in clinical studies.[6] Although "hypertension" had a higher incidence in the ORAPAES PM group than in the control group, use of PM was not associated with clinically relevant changes in blood pressure in clinical trials.[6]

Hypotension was rarely observed in our study and even less often than hypertension, reflecting the local efficacy of the pharmaceutical rather than a systemic antihypertensive effect as suggested. However, the low incidence of AEs observed particularly in the ORAPAES

**TABLE 3**

**Incidence of adverse events (including MedRA SOCs* and PTs†).**

| CHARACTERISTIC | ORAPAES‡ | | | ORANIS§ |
|---|---|---|---|---|
| | Phentolamine Mesylate Group (n = 549) | Control Group (n = 307) | Total (N = 856) | Total (N = 445) |
| **No. of Patients With Adverse Events (%)** | 46 (8.4) | 6 (2.0) | 52 (6.1) | 43 (9.7) |
| **No. of Patients With Serious Adverse Events (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **MedDRA SOC or PT** | | | | |
| **Cardiac disorders** | 5 (0.9) | 2 (0.7) | 7 (0.8) | 1 (0.2) |
| Bradycardia | 5 (0.9) | 1 (0.3) | 6 (0.7) | 0 (0) |
| **Gastrointestinal disorders** | 9 (1.6) | 0 (0) | 9 (1.1) | 4 (0.9) |
| Oral pain | 4 (0.7) | 0 (0) | 4 (0.5) | 1 (0.2) |
| Toothache | 4 (0.7) | 0 (0) | 4 (0.5) | 2 (0.4) |
| **General disorders and administration site conditions** | 27 (4.9) | 5 (1.6) | 32 (3.7) | 34 (7.6) |
| Application site hypoesthesia | 3 (0.5) | 0 (0) | 3 (0.4) | 2 (0.4) |
| Drug effect delayed | 0 (0) | 0 (0) | 0 (0) | 2 (0.4) |
| Drug ineffective | 6 (1.1) | 0 (0) | 6 (0.7) | 18 (4.0) |
| Fatigue | 2 (0.4) | 1 (0.3) | 3 (0.4) | 0 (0) |
| Injection site pain | 13 (2.4) | 1 (0.3) | 14 (1.6) | 4 (0.9) |
| Pain | 0 (0) | 2 (0.7) | 2 (0.2) | 0 (0) |
| Swelling | 3 (0.5) | 1 (0.3) | 4 (0.5) | 0 (0) |
| Therapeutic response decreased | 0 (0) | 0 (0) | 0 (0) | 5 (1.1) |
| Therapeutic response delayed | 0 (0) | 0 (0) | 0 (0) | 3 (0.7) |
| **Vascular disorders** | 11 (2.0) | 1 (0.3) | 12 (1.4) | 0 (0) |
| Hypertension | 9 (1.6) | 1 (0.3) | 10 (1.2) | 0 (0) |
| Hypotension | 2 (0.4) | 0 (0) | 2 (0.2) | 0 (0) |
| **Nervous system disorders** | 3 (0.5) | 2 (0.7) | 5 (0.6) | 11 (2.5) |
| Headache | 0 (0) | 1 (0.3) | 1 (0.1) | 4 (0.9) |
| Hypoesthesia | 2 (0.4) | 1 (0.3) | 3 (0.4) | 2 (0.4) |
| Paresthesia | 0 (0) | 0 (0) | 0 (0) | 3 (0.7) |
| **Investigations (heart rate increased)** | 3 (0.5) | 0 (0) | 3 (0.4) | 0 (0) |

* MedDRA SOC: Medical Dictionary for Regulatory Activities System Organ Class.
† PT: Preferred term. Only PTs with incidence greater than 1 in at least 1 study arm were tabulated; multiple answers per patient were possible.
‡ ORAPAES: OraVerse Post-Authorization Efficacy Study.
§ ORANIS: OraVerse Non-Interventional Study.

control group limits the expressiveness of comparisons among these data.

**Limitations of the studies.** It should be taken into consideration that, owing to the noninterventional study design, there was no randomization to equally distribute potential confounding factors across treatment groups. However, in an attempt to overcome this drawback, primarily patients who were proposed PM but refused it were allocated to the control group. In addition, adjustments of potential confounders were done to limit such drawbacks. ORANIS did not include a control group. However, the data above confirm the comparability of the ORAPAES PM group and the ORANIS population. Being a strength of both studies, the large number of patients with a variety of medical histories and age groups treated under a broad range of routine dental care conditions is likely to enhance the generalizability of the study outcomes.

## CONCLUSIONS

Overall, the results confirm the effectiveness and safety reported elsewhere[15] and support the applicability of clinical trial results with PM to contemporary routine dental treatment conditions in Germany. ■

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