Review Article

Reversal of Residual Soft-Tissue Anesthesia: A Review

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Abstract

Phentolamine mesylate, a nonselective α-adrenergic blocking drug, is the first therapeutic agent marketed for the reversal of soft-tissue anesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anaesthetic containing a vasoconstrictor. In clinical trials, phentolamine injected in doses of 0.2 to 0.8 mg (0.5 to 2 cartridges), as determined by patients' age and volume of local anaesthetic administered, significantly hastened the return of normal soft-tissue sensation in adults and children 6 years of age and above, median lip recovery time reduced by 75 to 85 minutes, functional deficits, such as drooling and difficulty in drinking, smiling, or talking — and subjects' perception of altered function or appearance consistently resolved by the time sensation to touch returned to normal.

Keywords: Phentolamine mesylate, Reverse, Residual anesthesia

INTRODUCTION

Phentolamine is an old drug. It was first approved by the United States Food and Drug Administration (FDA) in 1952 under the trade name of Regitine and is currently indicated for the diagnosis and treatment of severe hypertension in patients with pheochromocytoma, a rare tumour of the adrenal medulla that secretes excessive epinephrine and/or norepinephrine, and the prevention or treatment of dermal necrosis following the intravenous administration or extravasation of norepinephrine. Phentolamine is a nonselective α-adrenergic receptor antagonist that competitively inhibits the ability of sympathomimetic amines like norepinephrine and epinephrine to cause vascular contraction. An injectable form of phentolamine mesylate has been developed to terminate the numbing action of local anesthesia when it is no longer desirable. The product contains 0.4 mg of phentolamine mesylate (0.235 mg/ml) packaged in a 1.7 ml dental cartridge (Table 1). On 12 May 2008, the United States Food & Drug Administration (FDA) granted approval of phentolamine mesylate for use in dentistry. It is marketed under the proprietary name of OraVerse™. It is available in 1.7 ml cartridges containing 0.4 mg phentolamine mesylate. It is not recommended for use in children less than 6 years of age or weighing less than 15 kg due to lack of clinical trials.[1]

Like other competitive antagonists, phentolamine shares a structural similarity (Figure 1) with the agonist epinephrine but includes bulky side chains that are presumed to permit receptor binding yet prevent receptor activation.[2]

The idea of using phentolamine as a local anesthesia "reversal" agent began when Dr. Eckard Weber, an inventor, specialist in creating companies pursuing innovative drug therapies, and a former professor of pharmacology at the University of California, visited a dentist and wondered why patients were constrained to remain numb for hours after each dental appointment. Although the notion of using phentolamine after local anesthesia to hasten the return of normal sensation had been contemplated at least twice previously, Weber was the first to take action. In 2000 he co-founded Novalar Pharmaceuticals with the expressed purpose of developing phentolamine for dental use.

Table 1: Dosing information of OraVerse™

Amount of local Anaesthetic administered	Dose of OraVerse™ (mg)	Dose of OraVerse™ (Cartridge (s))
½ Cartridge	0.2	1/2
1 Cartridge	0.4	1
2 Cartridge	0.8	2

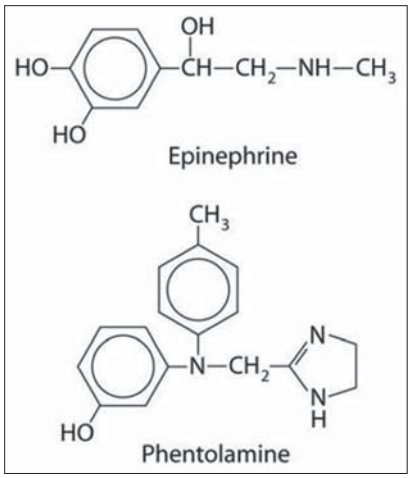

Figure 1: Structure of epinephrine and phentolamine[2]

MECHANISM OF ACTION

Phentolamine mesylate acts as a competitive inhibitor, blocking the effects of epinephrine, an active ingredient in some local anesthetics that causes vasoconstriction. Phentolamine blocks α-adrenergic receptors, causing smooth muscle relaxation. This relaxation will lead to greater blood flow, resulting in a more rapid systemic absorption of the local anesthetic. Thus, phentolamine mesylate is not an antagonist of the local anesthetic itself, but of the epinephrine added to prolong the effect of the local anesthetic. Therefore, phentolamine mesylate has not been tested for efficacy following use of local anesthetic without added vasoconstrictors.

The delivery method of phentolamine mesylate is similar to that of local anesthesia; it comes in a cartridge like that of regular local anesthetics. Each cartridge of 1.7ml Oraverse™ contains 0.4 mg of phentolamine mesylate. The amount of phentolamine mesylate delivered equals the amount of vasoconstrictor containing local anesthesia delivered during the appointment. In addition, the location for the delivery is the same as that used for the original local anesthesia. For example, delivery of three-fourths of a cartridge of lidocaine as an inferior alveolar block injection would require three-fourths of a cartridge of phentolamine mesylate to be delivered at the same inferior alveolar block injection site. The main challenge to the clinician using phentolamine mesylate is the timing of the injection. Since there is a delayed onset, the clinician needs to plan ahead to ensure that the client will regain sensation of soft tissue by the end of the dental appointment. Unlike local anesthesia, there are no known contraindications for phentolamine mesylate delivery.[3]

CLINICAL TRIALS

A phase 2 multicenter clinical trial, examined the reversal effect of phentolamine administered at the end of dental procedures in which local anesthesia was required intraoperatively but not postoperatively for pain relief. In addition to Lidocaine with epinephrine, vasoconstrictor containing formulations of articaine, mepivacaine, and prilocaine were tested. If a second cartridge of local anaesthetic was required to achieve adequate pain control, two doses of phentolamine (or placebo) were used as well. Table 2 displays the principal efficacy findings of this study with regard to lip sensation. This study demonstrated that phentolamine was effective in reversing soft-tissue anaesthesia caused by all tested local anaesthetic with vasoconstrictor formulations.[4]

Figure 2 illustrates the influence of phentolamine versus sham injection on recovery of lower lip sensation after mandibular injection of the same local anaesthetic formulations used in phase 2. Similar efficacies were observed for reversal of tongue anesthesia and, after maxillary injections tested in a separate phase 3 study, in the upper lip.[5]

A companion phase 2 trial extended the soft-tissue findings in children down to age 6. As shown in Figure 3, the reversal of lip anesthesia (in this case only Lidocaine with epinephrine was used) was more marked in the mandible than in adults, whereas the effect in the maxilla was less (not shown), yielding a combined median reduction of 75 minutes.[6]

Safety measures in all of these studies included the recording of vital signs at regular intervals, periodic assessments of pain at the injection and operative sites, the need for analgesic medications, visual assessments of the oral cavity, and reports of adverse events. No serious or severe adverse effects were noted during any of the studies nor were there any significant differences in vital signs, pain, or adverse events between phentolamine and sham-treated subjects.

Pharmacokinetic studies in adults and children support a low adverse potential of phentolamine used for reversal of local anesthesia.[7,8]

In recommended doses, the peak plasma concentrations of phentolamine are estimated to be about 100 times lower than those achieved in adults with medical doses of the drug infused intravenously. This difference explains the relative lack of cardiovascular effects with submucosal phentolamine.[9]

Table 2: Median times and treatment differences are in minutes (and percent difference)[4]

Location	Anaesthetic	Phentolamine		Placebo		Treatment difference
		n	Median	n	Median	
MAXILLA	Lidocaine/ epinephrine	7	35.0	8	150.0	115.0
	Articaine/ epinephrine	8	92.5	7	185.0	92.5.0
	Prilocaine/ epinephrine	7	35.0	6	113.0	78.0
	Mepivacaine/ levonordefrin	9	55.0	9	152.0	97.0
	All anesthetics*	31	50.0	30	155.0	105.5
Mandible	Lidocaine/ epinephrine	8	67.5	7	130.0	62.5
	Articaine/ epinephrine	7	135.0	8	160.0	25.0
	Prilocaine/ epinephrine	6	55.0	7	135.0	80.0
	Mepivacaine/ levonordefrin	9	120.0	9	190.0	70.0
	All anesthetics*	30	101.0	31	150.0	49.0
Combined	Treatment group total*	61	70.0	61	155.0	85.0

CLINICAL RELEVANCE

According to Rafique and colleagues 86% of patients receiving local anesthesia for dentistry report moderate dislike of postoperative numbness, and 14% report high dislike. In addition to the physical discomfort, some patients withdraw from public life while affected, refrain from eating (often appropriately) and drinking, or accidentally injure themselves by biting their lip or tongue. As a consequence, they may delay dental care or even refuse local anesthesia altogether.[10]

The only patient concern not addressed by the clinical development program for phentolamine was the drug's potential for According to a survey by College et al. lip biting after inferior alveolar nerve block occurs at the following rates in children: Under 4 years, 18%; 4 to 7 years, 16%; 8 to 11 years, 13%; and over 12 years, 7%. It is likely, but not certain, that these rates would fall in concert with the phentolamine-induced decrease in postprocedural numbness. Because the FDA has not approved the use of phentolamine reversal for children below 6 years of age, and safety data only extend down to children 4 years of age and 15 kg in weight, a study of young children is a pressing need to extend the benefit of phentolamine reversal to this important age group.[11]

Another issue of clinical relevance is the use of a 1:1 cartridge-dosing ratio. The notion that the volume of phentolamine injected should equal the amount of local anaesthetic administered was originally based on the

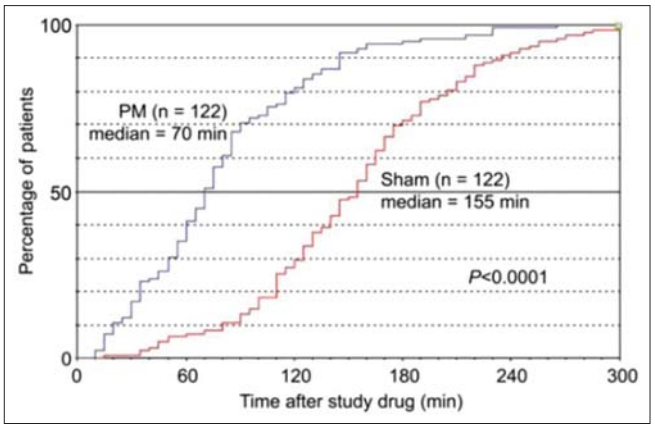

Figure 2: Percentage of adult and adolescent patients with normal lower lip sensation after phentolamine mesylate (PM) or sham injection[5]

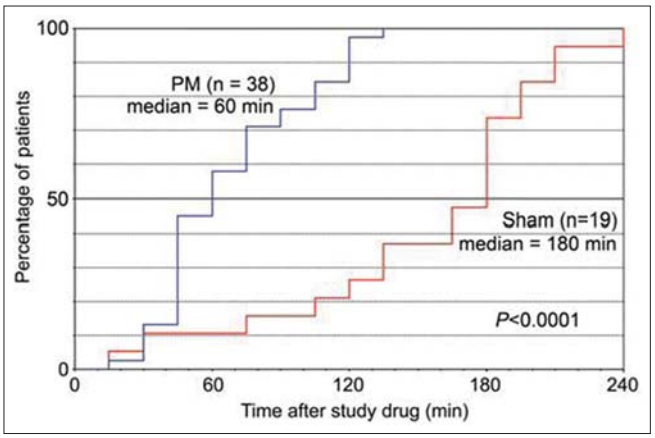

Figure 3: Percentage of children patients with normal lower lip sensation after phentolamine mesylate (PM) or sham injection[6]

assumption that phentolamine works by competitively blocking the injected vasoconstrictor. The actual mechanism probably derives more from the ability of phentolamine to block the actions of endogenously released norepinephrine and increase local blood flow.

This conclusion is based on (1) studies showing that submucosal epinephrine is absorbed quickly from oral tissues and would be mostly gone by the time phentolamine is injected, and (2) the pharmacokinetic indicating that phentolamine increases the systemic absorption of local anaesthetic remaining in tissues at the time of injection. If this mechanism is correct, there should be no need to give more than one dose of phentolamine per local anaesthetic injection site regardless of the number of local anaesthetic cartridges used there. Following this strategy would reduce the amount of phentolamine used and allow more local anaesthetic injections to be reversed without exceeding the maximum recommended dose of two cartridges. The proposed mechanism suggests that local anaesthetics without added vasoconstrictors can also be effectively reversed by phentolamine.[12,13]

CONCLUSION

The majority of dental treatments today are not so traumatic in nature as to require a patient to leave the dental surgery with residual soft-tissue anesthesia that commonly persists for many hours while gradually resolving. These include conservative dental restorations, crowns and periodontal maintenance procedures, such as scaling and root planing. In addition, paediatric patients, whether in the general dentistry or paediatric dentistry office, will benefit from the diminished soft-tissue duration associated with phentolamine mesylate administration. Patients with medical conditions requiring strict adherence to eating regimens, such as diabetics, will also benefit from the reversal of anesthesia.[14]

REFERENCES

1. Malamed S. Phentolamine mesylate for the reversal of residual soft tissue anesthesia. The Academy of Dental Therapeutics and Stomatology. 2008.
2. Malamed S. What's new in local anesthesia. SAAD digest, vol. 2, January 2009.
3. Wynn RL. Phentolamine mesylate - an old medical drug becomes a new dental drug. *Gen Dent*. 2009;57:200-2.
4. Laviola M, McGavin SK, Freer GA, et al. Randomized study of phentolamine mesylate for reversal of local anesthesia. *J Dent Res*. 2008;87(7):635-639.
5. Hersh EV, Moore PA, Papas AS, et al. Reversal of soft-tissue local anesthesia with phentolamine mesylate in adolescents and adults. *J Am Dent Assoc*. 2008; 139(8):1080-1093).
6. Tavares M, Goodson JM, Studen-Pavlovich D, et al. Reversal of soft-tissue local anesthesia with phentolamine mesylate in pediatric patients. *J Am Dent Assoc*. 2008;139(8):1095-1104.
7. Moore PA, Hersh EV, Papas AS, et al. Pharmacokinetics of lidocaine with epinephrine following local anesthesia reversal with phentolamine mesylate. *Anesth Prog*. 2008; 55(2):40-48.
8. Simone A. Clinical review NDA 22-159. OraVerse (phentolamine mesylate). Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research, Division of Anesthesia, Analgesia and Rheumatology November 15, 2010.
9. Hersh EV, Lindemeyer RG. Phentolamine mesylate for accelerating recovery from lip and tongue anesthesia. *Dent Clin N Am*. 2010; 54(4):631-642.
10. Rafique S, Fiske J, Banerjee A. Clinical trial of an airabrasion/ chemomechanical operative procedure for restorative treatment of dental patients. *Caries Res*. 2003;37(5):360-364.
11. 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.
12. Homma Y, Ichinohe T, Kaneko Y. Oral mucosal blood flow, plasma epinephrine and haemodynamic responses after injection of lidocaine with epinephrine during midazolam sedation and isoflurane anesthesia. *Br J Anaesth*. 1999;82(4):570-574.
13. Takahashi Y, Nakano M, Sano K, Kanri T. The effects of epinephrine in local anaesthetics on plasma catecholamine and hemodynamic responses. *Odontology* 2005;93(1):72-79.
14. Timothy R. Saunders, Gregory Psaltis. In-Practîce Evaluation of OraVerse for the Reversal of Soft-Tissue Anesthesia after Dental Procedures. *Compendium*. 2001;32:5.

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