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Reverse The Adverse - Reversing Agent (Phentolamine Mesylate) For Local Anaesthesia

Shijineed.T.K[1], Kannan Vadakkepurayil [2], Mereesha. K[3], Anupam Kumar T.V[4], Faseela Beegum P.K [5]

(Junior Resident, Department of Pedodontics, Govt Dental College, Calicut [1]
Professor & Head, Department of Pedodontics, Govt Dental College, Calicut [2]
Senior Resident, Department of Pedodontics, Govt Dental College, Trissur [3]
Additional Professor, Department of Pedodontics, Govt Dental College, Calicut [4]
Junior Resident, Department of Oral Pathology & Microbiology, Govt Dental College,Calicut [5])

Abstract: *Although pain control remains the cornerstone of any oral and dental procedure, prolonged local anesthetic effects may be undesirable in many instances in dental clinical practice. Soft tissue anesthesia can lead to uncontrolled drooling, patient's perceived sense of altered appearance, self inflicted injuries and thermal or chemical burns. Phentolamine mesylate, a nonselective α adrenergic blocking drug is the first therapeutic agent marketed for the reversal of soft tissue anaesthesia and the associated functional deficits resulting from an intraoral submucosal injection of a local anaesthetic containing a vasoconstrictor. This article reviews the indications, recommended dosage, mechanism of action, pharmacokinetics, clinical studies, complications and adverse effects of phentolamine mesylate for the reversal of soft tissue anesthesia.*

Keywords: *anaesthesia reversal, phentolamine mesylate, α adrenergic block*

I. Introduction

Local anesthesia forms the backbone of pain-control techniques in dentistry.[1] Usually teeth recover more quickly than surrounding bone and soft tissues such as lips and tongue. The soft tissue anesthesia lasts approximately 3 to 5 hours [2] and frequently is longer than necessary for completion of many routine dental procedures. Patients report that lingering anesthesia interferes with normal activities such as speaking, drinking and eating. The most embarrassing and disturbing side effect is drooling.[3] Residual anesthesia is of particular concern in pediatric patients who may chew a bitten lower lip because of its numbness, causing ulceration of the oral mucosa. One recent study measured a 13% incidence of injury after mandibular anesthesia in pediatric patients.[4]

At present, no therapeutic modality exists to hasten the return of normal sensation and function after local anesthetic injection. Recently, the search for a pharmacologic means of minimizing postoperative anesthesia has focused on Phentolamine Mesylate, which is a nonselective competitive α adrenergic antagonist. It has been demonstrated to reverse vasoconstriction in rats, cats, and dogs resulting from nerve stimulated release of nor epinephrine or locally applied nor epinephrine or epinephrine.[5-7]

II. Review Of Literature

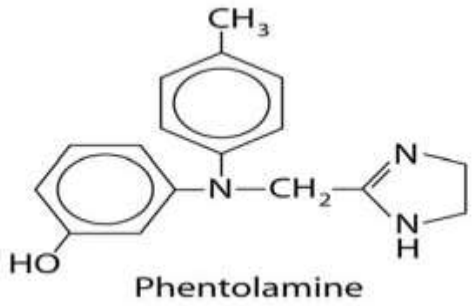
In a review article **J S Prasanna** says," Phentolamine mesylate injection – the first and only proven safe and effective product of its kind. It can quickly reverse the effects of local dental anesthetics. So, patient can carry on without impairment of talk, smile and drink after dental procedures". Studies also have shown that there are no known drug interactions and evident toxicity or contraindications for using Phentolamine mesylate Another study by **Saunders TR et al** investigated the pattern of use, dentist evaluation, and patient assessment of Phentolamine mesylate. In this clinical evaluation, times to return to normal oral sensation and function after Phentolamine mesylate administration were consistent with those reported in randomized clinical studies. Both patient and dentist satisfaction rates were high.[9]

Hersh EV et al conducted two multicentered, randomized, double blinded, controlled Phase III clinical trials to study the efficacy and safety of Phentolamine Mesylate in shortening the duration and burden of soft tissue anesthesia. Phentolamine Mesylate was efficacious and safe in reducing the duration of local anesthetic induced soft-tissue numbness and its associated functional deficits.[10]

Chemistry

Chemically, phentolamine is 3-[N-(4,5-dihydro-1H-imidazol-2-ylmethyl)-4 methylanilino] phenol and has a molecular weight of 281.35226 g/mol with the molecular formula $C_{17}H_{19}N_3O$. It was first synthesized by

Miescher, Marxer and Urech and patented with the United States Patent Office on April 4, 1950 (Patent number 2503059, filing date January 27, 1948, issue date April 4, 1950)**.**[11] Phentolamine mesylate is phenol,3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4-methyl-phenyl) amino]-methanesulfonate with the empirical formula $C_{17}H_{19}N_3O{\cdot}CH_4O_3S$. It is a white to off-white, odorless crystalline powder with a molecular weight of 377.46 g/mol.



Phentolamine

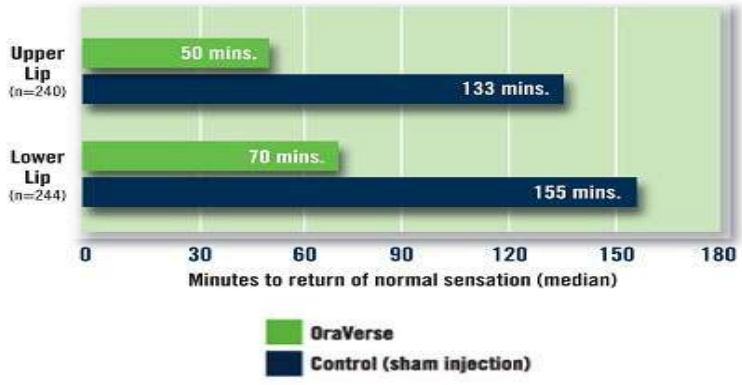
Mechanism of Action

The mechanism by which Phentolamine mesylate accelerates reversal of soft tissue anesthesia and the associated functional deficits is not fully understood. Phentolamine mesylate produces an α adrenergic block of relatively short duration resulting in vasodilatation when applied to vascular smooth muscle. In an animal model it increased local blood flow in submucosal tissue of the dog when given after an intraoral injection of lidocaine 2% with 1:100,000 epinephrine.

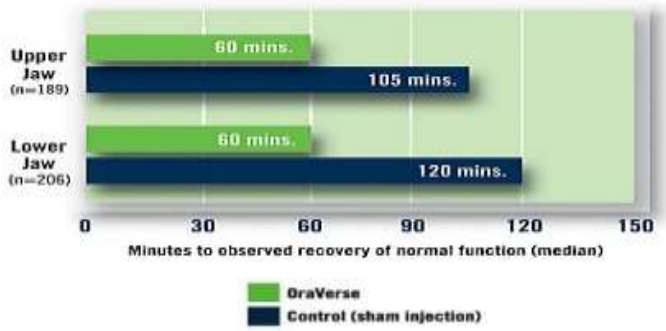
Pharmacokinetics

Following administration phentolamine is 100% available from the submucosal injection site and peak concentrations are achieved 10 to 20 minutes after injection. Phentolamine systemic exposure increased linearly after 0.8 mg compared with 0.4 mg intraoral submucosal injection. The terminal elimination half-life of phentolamine in the blood was approximately 2 to 3 hours. The lidocaine concentration increased after phentolamine injection, which suggests that it promotes clearance of lidocaine from oral tissue into systemic circulation.[12]

Efficacy
Median Time to Normal Lip Sensation[10]
(Adult and Adolescent Clinical Trials)



Median Time to Recovery of Normal Function[10]



General Dosing Information

Phentolamine mesylate, at dosages from 0.4 to 0.8 mg in adults and adolescents and at dosages from 0.2 to 0.4 mg in children aged 4 to 11 years, has been proven to be safe and effective for the reversal of soft tissue anesthesia.[13] The recommended dose of Phentolamine mesylate is based on the number of cartridges of local anesthetic with vasoconstrictor administered.[14]

Amount of Local Anesthetic Administered	Dose of Phentolamine mesylate [mg]	Dose of Phentolamine mesylate [Cartridge]
½ Cartridge	0.2	½
1 Cartridge	0.4	1
2 Cartridges	0.8	2

Phentolamine mesylate should be administered following the dental procedure using the same location(s) and technique(s) (infiltration or block injection) employed for the administration of the local anesthetic.

Overdosage:

No deaths due to acute poisoning with phentolamine have been reported.[15] Overdosage with parenterally administered phentolamine is characterized chiefly by cardiovascular disturbances, such as arrhythmias, tachycardia, hypotension, and possibly shock. In addition excitation, headache, sweating, pupillary contraction, visual disturbances, nausea, vomiting, diarrhea or hypoglycemia may occur. There is no specific antidote. Treatment consists of appropriate monitoring and supportive care. Substantial decreases in blood pressure or other evidence of shock-like conditions should be treated vigorously and promptly.[16]

III. Use In Specific Populations

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers

It is not known whether phentolamine is excreted in human milk. The unknown risks of limited infant exposure to phentolamine through breast milk following a single maternal dose should be weighed against the known benefits of breastfeeding.

Pediatric use

In pediatric patients weighing 15-30 kg, the maximum dose of Phentolamine mesylate recommended is 1/2 cartridge (0.2 mg).

Use in pediatric patients under 6 years of age or weighing less than 15 kg (33 lbs) is not recommended.[17] A dose of more than 1 cartridge [0.4 mg] of Phentolamine mesylate has not been studied in children less than 12 years of age.

Non Clinical Toxicology

Carcinogenicity studies with Phentolamine mesylate have not been conducted. Phentolamine was not mutagenic in the in-vitro bacterial reverse mutation (Ames) assay.

Clinical Trials Experience

Dental patients were administered a dose of 0.2, 0.4 or 0.8 mg of Phentolamine mesylate. The majority of adverse reactions were mild and resolved within 48 hours. There were no serious adverse reactions and discontinuations due to adverse reactions.

Adverse Event*	OraVerse®	Control
	Total (N=418 patients)	Total (N=359 patients)
Post procedural pain	6 %	6 %
Injection site pain	5 %	4 %
Tachycardia	5 %	6 %
Headache	3 %	4 %
Bradycardia	2%	0.3%

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IV. Conclusion

The results of clinical trials with phentolamine mesylate in anesthetized patients demonstrate that its administration after routine dental or periodontal maintenance procedures should yield a significant benefit. Faster recovery of normal sensation of lip and tongue, as well as a faster return to normal ability to smile, speak, drink, and to refrain from drooling and inflicting self-injury are highly desirable. The prevention of self-injury resulting from lingering soft tissue anesthesia, particularly in pediatric patients, is an additional important clinical benefit. The high probability that phentolamine mesylate administration would safely accelerate the recovery of both observed and perceived normal sensation and function significantly compared to the current standard of care with minimal risk will likely be perceived as both desirable and beneficial by many dental patients and clinicians.

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