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Review Article

Local anesthesia reversal— A review

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ABSTRACT

Local anesthetic agents are widely used in dentistry. It has major role in all field of dentistry especially in oral surgery, Pediatrics, Endodontics, Periodontics etc. The only drawback associated with LA is that occurrence of soft tissue anaesthesia can persist for three to five hours, while the procedure itself usually lasts for less than an hour. Patients experience limitation of function in terms of speech difficulty, drinking neating etc. All these events leave negative impact on minds of patients; hence they avoid visiting dental offices. In order to reverse these events, a new drug named OraVerse (phentolamine mesylate) is available to us. This drug is known for its LA reversal ability and effects of local dental anaesthetic.

1. Introduction

Local anesthetic (LA) solutions are routinely used in dental practice in order to relieve pain lined with various dental procedures since 19^{th} century.[1] An adequate profound anesthesia is the foremost requirement for starting any endodontic or operative dental procedure. Local anesthetic agents are extensively used in dentistry.[2]

It is complaint by most of the patients that numbness associated with soft tissues restricts their normal daily activities in three specific areas viz. perceptual, sensory and functional. Patients may experience altered physical appearance, feel deficiency of sensation and altered capacity to smile, drink, drooling and speach.[3]

Inability to speak confidently, lack of eating capacity is among few findings of most of the patients after their dental visits. The effect of LA is for several hours and numbness of lip and tongue remains there even after dental procedure is over. This is the one of the factors for which patient deny dental visits.[4] In children administration of LA in mandible could results in 13% injuries to tissues as reported by study.[3]

After statistical analysis of the 923 consecutive cases, the overall complication rate was 5.3%. All of the complications were considered to be mild to moderate, and there were no severe event reports.

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. A OraVerse is the first and only local dental anesthesia reversal agent in the market proven to accelerate the reversal of anaesthetic effect (numbness) after dental procedures.

Till date, there is no therapeutic modality to accelerate the return of normal sensation and function after local

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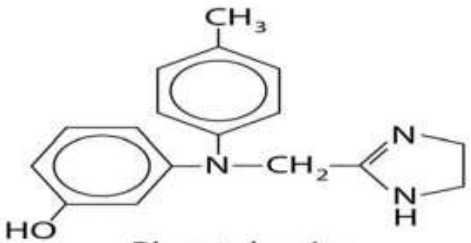
anesthetic injection. It is further observed that loss of sensation related to lips and tongue is not observed throughout the day as there in availability of new anesthetic reversal agent called OraVerse. It is the first and only local dental anesthesia reversal agent available to speed up the reversal of anaesthetic effect after dental interventions.[4]

The present review article covers the indications, dosage, mechanism of action, pharmacokinetics, complications and adverse effects of phentolamine mesylate for the reversal of soft tissue anesthesia.

2. Chemistry

Chemically, phentolamine is 3-[N-(4,5-dihydro-1H-imidazol-2-ylmethyl)-4 methylanilino] phenol having molecular formula C17H19N3O. The molecular weight is 281.35226 g/mol. 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). Phentolamine mesylate is phenol, 3-[(4,5-dihydro-1H-imidazol-2-yl)methyl] (4-methyl-phenyl)amino] methanesulfonate with the empirical Formula C17H19N3O·CH4OS. It is a white to off-white, odorless crystalline powder with a molecular weight of 377.46g/mol.[5]



Phentolamine

3. Mechanism of Action

Phentolamine is a nonselective a-adrenergic receptor antagonist that competitively prevents the capability of sympathomimetic amines like norepinephrine and epinephrine to excite vascular contraction. The smooth muscles of vascular beds such as of oral mucosa, contain α-receptors and vasodilation is the eventual effect of α-receptor blockade. It causes vasodilation at the site of administration resulting into improved absorption of local anesthetic and hence shortens the duration of anesthesia. In another study on dog animal, it found to increase local blood flow in submucosal tissue when given after an intraoral injection of lidocaine 2% with 1:100,000 epinephrine.[6,7]

4. Pharmacokinetics

Phentolamine mesylate got FDA recommendation on May 12, 2008 is available under proprietary name OraVerse. It causes reversal of lip and tongue numbness and the associated functional deficits resulting from a local dental anesthetic containing a vasoconstrictor. After administration of agent, peak concentrations are attained within 10-20 minutes. The oral submucosal injections dose of phentolamine is 0.2-0.8 mg. The elimination half-life was approximately 2 to 3 hours. The concentration of lignocaine increases after phentolamine injection suggesting that it encourages clearance of lidocaine from oral tissue into systemic tissues.[8,9]

5. Absorption

T max is the time essential to attain maximum drug concentrationin systemic circulation is thought to be10–20 minutes.

6. Elimination

It is eliminated in urine and approximately 13% is passed out unchanged. Half-life is 19 minutes (IV) and 2–3 hours.[4,8]

Table 1: Classification local anesthetic agents[10] JISPPD 2015

Local anesthesia agents	Chemical structure	Duration
Lidocaine	Amide	Intermediate (180-300 min)
Prilocaine	Amide	Intermediate (180-300 min)
Mepivacaine	Amide	Intermediate (180-300 min)
Bupivacaine	Amide	Long acting (240-720 min)
Etidocaine	Amide	Long acting
Articaine	Amide with an ester as side chain	Intermediate (180-300 min)
Procaine	Ester	Short acting (90-120 min)
Chloroprocaine	Ester	Short acting (90-120 min)
Tetracaine	Ester	Long acting

7. General Dosing Information

The recommended dose of OraVerse in adults is 0.4 to 0.8 mg and in children is 0.2 to 0.4 mg in age range 4-11 years. It also depends on number of cartridges of local anesthetic with vasoconstrictor administered. At this dosage safe and effective reversal of soft issue anesthesia have been acheived.[5,9]

The administration of drug should follow same method and location as employed for local anesthetic solution. Either block injection or infiltration may be used.[11,12]

Table 2: Duration of action for several local anesthetic agents [10]

Agent	Approximate duration of anesthesia	
	Pulpal anesthesia	Soft tissue anesthesia
Bupivacaine hydrochloride		
0.5 % with epinephrine 1: 200,000	>90 min	240-720 min
Lidocaine hydrochloride		
2% without vasoconstrictor	< 10 min	30-45 min
2% with epinephrine 1:50,000	60 min	180-300 min
2% with epinephrine 1:100,000	60 min	180 -300 min
Mepivacaine hydrochloride		
3% without vasoconstrictor	5-10 min	90-120 min
2% with levonordefrin 1:20,000	60 min	180-300 min
Prilocaine hydrochloride		
4% without vasoconstrictor	40-60 min	120 -240 min
4% with epinephrine 1:200,000	60 -90 min	180-480 min
Articaine		
4% with epinephrine 1:100, 000	45- 60 min	180 – 240 min

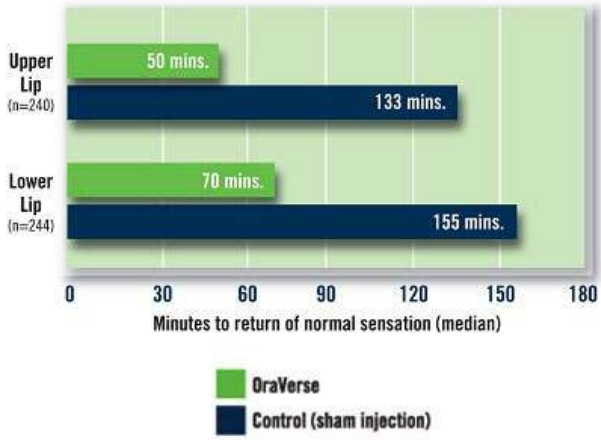


Fig. 1:

Table 3: Recommended dose of phentolamine meslylate [11]

Amount of local Anesthetic Administered	Dose of Phentolamine mesylate [mg]	Dose of Phentolaminemesylate [Cartridge]
$\frac{1}{2}$ Cartridge	0.2	$\frac{1}{2}$
1 Cartridge	0.4	1
2 Cartridges	0.8	2

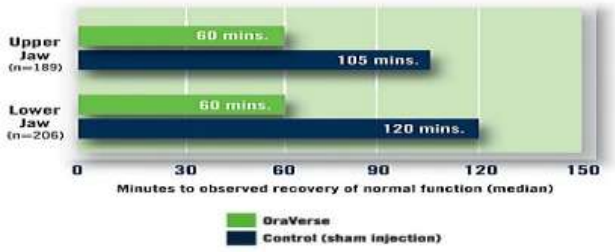


Fig. 2:

7.1. Points to remember

1. In case of presence of discoloration or particulate matter the administration of OraVerse must be avoided. [13]
2. Changing of skin colour from normal colour to blanching is indicative of effectiveness of drug.
3. Multiple small injections should be used with 27 or 30 gauge needles for infiltrating the area. Avoid occurence of compartment syndrome with swelling of the extremity. Consultation of vascular surgeon is mandatory when infiltration is severe. [10,14]

7.2. Indications

1. Treatment of dermal necrosis resulting from the extravasation of the vasoconstrictors norepinephrine and epinephrine.
2. Second indication is timely diagnosis of hypertension in patients with pheochromocytoma.
3. Management of catecholamine-induced hypertensive crises.
4. Treatment of impotence caused by alpha-adrenergic blockade in penile blood vessels. [15]

7.3. Contraindications

1. Children younger than 6 years of age or weighing less than 15 kg is strict contraindication. [12]
2. Patients allergic to phentolamine or related compounds
3. Subjects with previous history of myocardial infarction (MI), coronary insufficiency, angina pectoris, or coronary artery disease (CAD). [2]

7.4. Overdosage

There are no reports of mortality linked with acute poisoning. Overdosage with systematically administered phentolamine may lead to arrhythmias, tachycardia, hypotension, and shock.

Patients may experience headache, sweating, nausea, diarrhoea, visual disturbances, contraction of pupils and low blood glucose level. Management of these symptoms

comprised of appropriate monitoring and supportive care.[7]

8. Usage in Specific Conditions

8.1. Children

The maximum dose of recommended is 1/2 cartridge (0.2 mg) in children weighing 15-30 kgs.[4,5]

A dose of > 1 cartridge [0.4 mg] has not been studied in children < 12 years of age.

8.2. Pregnancy

Pregnancy Category C

Till date, no adequate and effective study is available mentioning its use in pregnant women.

8.3. Nursing mothers

Excretion of this drug in human milk is doubtful. The unknown risks of limited infant exposure to drugvia breast milk following a single maternal dose should be weighed against theknown benefits of breastfeeding.

8.4. Non clinical toxicology

So far, no data and research is available showing its carcinogenic nature. Phentolamine was not mutagenic in the in-vitro bacterial reverse mutation (Ames) assay.[11]

8.5. Clinical trials outcomes

Administration of this drug in dental patients in a dose of 0.2, 0.4 or 0.8 mg resulted in mild symptoms and resolved within 48 hours. There were no reports of serious adverse reactions and discontinuations due to adverse reactions.[4,5]

Table 4: Clinical trails with phentolamine mesylate[11]

Adverse event	OraVersetotal N0= 418 Patients	Controltotal No = 338 patients
Post procedural pain	8%	6%
Injection site pain	5%	4%
Headache	3%	4%
Bradycardia	2%	0.3%

OraVerse appears to be harmless and efficient in reducing soft tissue anesthesia in adults and children. The drug has beneficial role in dentistry and can be used to improve the patient experience.

9. Source of Funding

None.

10. Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Malamed SF. Handbookof Local Anesthesia. 5th ed. St. Louis: Mo: Mosby; 2004.
2. Koller C. Historical notes on the beginning of local anesthesia. *J Am Med Assoc*. 1928;90:1742–3.
3. Moore PA, Hersh EV, Papas AS, Goodson JM, Yagiela JA, Rutherford B, et al. Pharmacokinetics of Lidocaine With Epinephrine Following Local Anesthesia Reversal With Phentolamine Mesylate. *Anesth Prog*. 2008;55(2):40–8. doi:10.2344/0003-3006(2008)55[40:polwef]2.0.co;2.
4. Prasanna JS. OraVerse: Reverses Numbness After Dental Procedures. *J Maxillofac Oral Surg*. 2012;11(2):212–9.
5. Hersh EV, Moore PA, Papas AS, Goodson JM, Navalta LA, Rogy S, et al. Reversal of Soft-Tissue Local Anesthesia With Phentolamine Mesylate in Adolescents and Adults. *J Am Dent Assoc*. 2008;139(8):1080–93. doi:10.14219/jada.archive.2008.0311.
6. Goswami A, Bora A, Kundu GK, Ghosh S. Reversal of Residual Soft-Tissue Anesthesia: A Review. *Int J Sci Study*. 2014;2(3):86–9.
7. Saunders TR, Psaltis G, Weston JF, Yanase RR, Rogy SS, Ghalie RG. In-practice evaluation of OraVerse for the reversal of soft-tissue anesthesia after dental procedures. *Compend Contin Educ Dent*. 1995;32(5):58–62.
8. Moore PA, Hersh EV, Papas AS, Goodson JM, Yagiela JA, Rutherford B, et al. Pharmacokinetics of Lidocaine With Epinephrine Following Local Anesthesia Reversal With Phentolamine Mesylate. *Anesth Prog*. 2008;55(2):40–8. doi:10.2344/0003-3006(2008)55[40:polwef]2.0.co;2.
9. Urech E, Marxer A, Miescher K. 2-Aminoalkyl-imidazoline. *Helvetica Chimica Acta*. 1950;33(5):1386–1407. doi:10.1002/hlca.19500330539.
10. Saksena N, Grover HS, Gupta A, Saini N. Phentolamine mesylate: It′s role as a reversal agent for unwarranted prolonged local analgesia. *J Indian Soc Pedod Prev Dent*. 2015;33(4):265. doi:10.4103/0970-4388.165646.
11. Shijineed TK, Vadakkepurayil K, Mereesha K, Kumar TVA, Beegum PKF. Reverse the Adverse - Reversing Agent (Phentolamine Mesylate)for Local Anaesthesia. *IOSR*. 2017;16(4):134–7.
12. Babaei M, Nourbakhsh N, Shirani F. Effect of phentolamine mesylate on duration of soft tissue local anesthesia in children. *J Res Pharm Pract*. 2012;1(2):55–9. doi:10.4103/2279-042x.108371.
13. Hersh EV, Lindemeyer RG. Phentolamine Mesylate for Accelerating Recovery from Lip and Tongue Anesthesia. *Dent Clin N Am*. 2010;54(4):631–42. doi:10.1016/j.cden.2010.06.004.
14. Urech E, Marxer A, Miescher K. 2-Aminoalkyl-imidazoline. *Helvetica Chimica Acta*. 1950;33(5):1386–1407. doi:10.1002/hlca.19500330539.
15. Tavares M, Goodson JM, Studen-Pavlovich D, Yagiela JA, Navalta LA, Rogy S, et al. Reversal of Soft-Tissue Local Anesthesia With Phentolamine Mesylate in Pediatric Patients. *J Am Dent Assoc*. 2008;139(8):1095–1104. doi:10.14219/jada.archive.2008.0312.

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