Intranasal tetracaine and oxymetazoline (Kovanaze): a novel method of maxillary dental anesthesia

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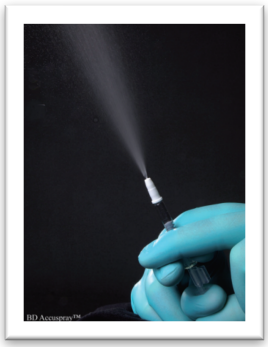
Introduction

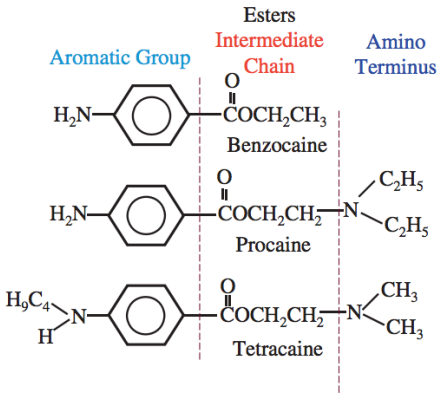
- For many patients, fear of injections represents a major barrier towards seeking and receiving dental treatment
- Providing needle phobic patients with an alternative to conventional dental injections may allow patients to seek treatment earlier, when the treatment required is a simple restoration. Thus a painless form of anesthesia may provide an avenue for major cost savings for this population and better oral health
- On 29 June 2016 the FDA approved an intranasal delivery system of local anesthesia consisting of 3% tetracaine and 0.05% oxymetazoline (Kovanaze)
- Indicated for single maxillary dental restorations on permanent premolars, canines and incisors in adults, and all maxillary deciduous teeth in children (>40kg)

Mechanism

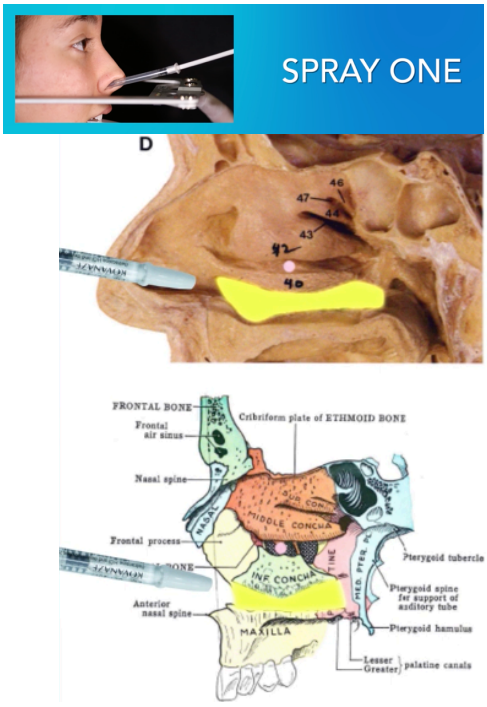
- Device uses a Becton Dickinson Accuspray device, which delivers the solution as a "plume" in the nostril, on the nostril ipsilateral to the teeth being treated



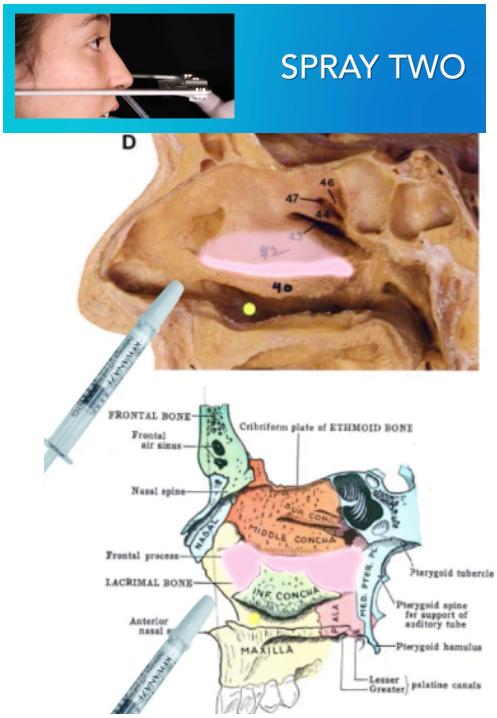
- It is proposed that the anesthetic spray penetrates the maxillary sinus and anesthetizes the anterior superior and middle superior alveolar nerves (innervate maxillary incisor, canine, premolars)
- Tetracaine – an ester local anesthetic. Employed routinely by otolaryngologists to anesthetize the nasal cavity. Structure is similar to benzocaine, but possesses additional tertiary amino group which enables additional carbon moieties that enhance lipid solubility. Improved lipid solubility allows greater protein binding and improved potency and duration of action of the anesthetic. Benozcaine lacks the amino group needed for solublity and thus must be dissolved in a polyethylene glycol vehicle for topical use.



- Oxymetazoline – post-synaptic alpha-adrenergic agonist that causes vasoconstriction. Established uses include treatment of epistaxis and over-the-counter nasal decongestant. Included in Kovanaze forumulation to slow redistribution of tetracaine and improve the efficacy and duration of anesthesia.
- Administered using two sprays delivered at two different angles to the sagittal plane. The first spray is parallel to sagittal plane, perpendicular to coronal plane, and 10-20˚ above the horizontal plane (palate or floor of nose), aiming for the inferior meatus. The second spray is delivered at 45˚ below the horizontal plane, aiming for the middle meatus. Must wait four minutes between each spray.
- **Spray One**



Spray Two



Methodology

- Literature review was conducted using search terms for intranasal delivery, tetracaine, oxymetazoline and dental local anesthesia using search engines PubMed Plus, Scopus and he Web of Science.
- Search limited to double-blind, randomized trials, excluding phase 1 and phase 2 pharmacokinetic and safety data. Five relevant publications were obtained.

Pharmacokinetics & Safety

- Quantity of delivered tetracaine and oxymetazoline per spray

Table 1. Conversion calculations from % to mg for tetracaine and oxymetazoline employing 0.2 ml spray volumes.

3% tetracaine = 3 grams/100 ml = 3000 mg/100 ml = 30 mg/ml
× 0.2 ml/spray = 6 mg/spray
2 sprays = 12 mg tetracaine
3 sprays = 18 mg tetracaine
6 sprays = 36 mg tetracaine
0.05% oxymetazoline = 0.05 grams/100 ml = 50 mg/100 ml = 0.5 mg/ml
× 0.2 ml/spray = 0.1 mg/spray
2 sprays = 0.2 mg oxymetazoline
3 sprays = 0.3 mg oxymetazoline
6 sprays = 0.6 mg oxymetazoline

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- Pharmacokinetic parameters

Table 2. Mean derived pharmacokinetic parameters (± SEM) from subject plasma samples.

Analyte/Dose Level	T_{max} (min)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Oxymetazoline/0.3 mg[a]	15 ± 0.8	1.45 ± 0.14	2.37 ± 0.27	2.32 ± 0.32
Oxymetazoline/0.6 mg[b]	26 ± 1.0	2.05 ± 0.22	3.51 ± 0.41	1.72 ± 0.018
Tetracaine/18 mg[a]	53 ± 13.8	0.24 ± 0.06	—	—
Tetracaine/36 mg[b]	83 ± 17.6	1.15 ± 0.93	—	—
PBBA[a]	45 ± 9.8	492 ± 55	862 ± 101	1.00 ± 0.12
PBBA[b]	47 ± 3.5	886 ± 84	1773 ± 322	1.01 ± 0.10

  - *Tmax* – time to max plasma concentration
  - *Cmax* – maximum plasma concentration
  - *AUCo*-oo – area under plasma concentration curve (t 0-> infinity)
  - *t1/2 – plasma half life*
  - There were insufficient number of subjects with measureable tetracaine plasma levels to calculate the plasma half life. This is likely due to the rapid degradation of tetracaine by plasma esterase. The proposed maximum recommended dose (MRD) of 18 mg tetracaine was insufficient in producing quantifiable plasma levels in the majority of participants.
- Safety
  - No serious adverse reactions were observed or reported with the MRD or twice the MRD in healthy participants. Common side effects included mild nasal runniness (50%), mild nasal stuffiness (33%) and headaches (25%).
  - Pulse oximetry revealed no oxygen desaturations. Vital signs, included systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) remained stable in a narrow range for both doses. A single 24-year-old male experienced a moderate pressor response, but resolved spontaneously.

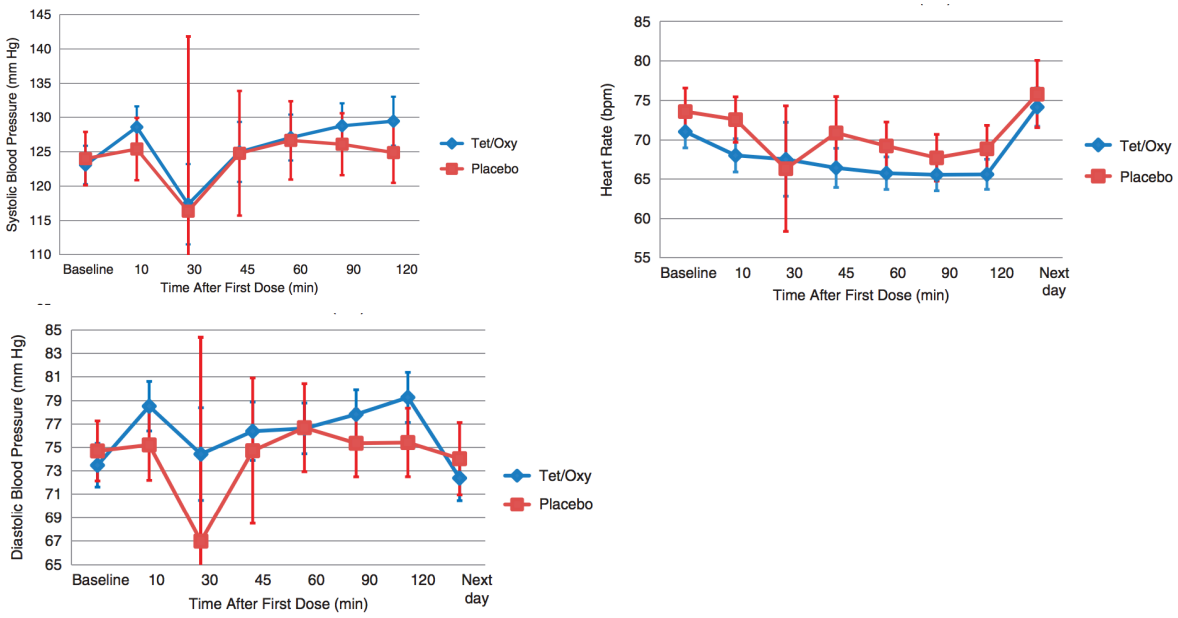

Figure 4. Mean changes in systolic and diastolic blood pressure (mmHg), and heart rate in patients receiving 3% tetracaine/0.05% oxymetazoline (Tet/Oxy) and placebo spray. Following drug administration vital signs were only taken after the completion of the dental procedure. At 10, 90, and 120 minutes, mean values represent 100 participants in the Tet/Oxy group and 50 participants in the placebo group. At 30 minutes, mean values represent 23 participants in the Tet/Oxy group and 3 participants in the placebo group. At 45 minutes, mean values represent 71 participants in the Tet/Oxy group and 18 participants in the placebo group. At 60 minutes, mean values represent 97 participants in the Tet/Oxy group and 44 participants in the placebo group. Error bars represent the 95% confidence intervals. Adapted with permission from Hersh EV, Pinto A, Saraghi M, et al. Double-masked, randomized, placebo-controlled study to evaluate the efficacy and tolerability of intranasal K305 (3% tetracaine plus 0.05% oxymetazoline) in anesthetizing maxillary teeth. J Am Dent Assoc 2016;147:278-87[20].

Efficacy for Dental Restorative Procedures

- Several studies evaluated the success rate of intranasal anesthesia. Success defined as ability to complete procedure without need for rescue local anesthesia. Rescue local anesthetic was 4% articaine (1:100,000 epinephrine)
- A single site proof-of-concept phase 2 study compared gold standard 1 mL infiltration of 2% lidocaine (1:100,000 epinephrine) to an MRD of 3% tetracaine/0.05% oxymetazoline as three pairs of 0.1 m: bilateral nasal sprays. N=30 for the spray and N=15 for the injection, with all patients undergoing routine single maxillary restorative procedure in incisors, canines, premolars or 1st molars. Success rate of intranasal route was 83% compared to 93% for injectable route. However, success rate of intranasal route rose to 90% if the maxillary first molars were excluded.
- A multisite phase 3, double-blind, placebo-controlled study found that application of spray to the ipsilateral nostril is sufficient for treating one half of the maxilla. The success rate was 88% for intranasal 3% tetracaine/0.05% oxymetazoline group versus 28% for placebo nasal spray. Subanalysis found a success rate of 96% for anterior teeth versus 79% for posterior teeth (premolars).
- A second phase 3 double-bind controlled study determined the necessity of 0.05% oxymetazoline in the formulation. The success rates were 84% for the combination of 3% tetracaine/0.05% oxymetazoline and only 27% for 3% tetracaine alone and placebo. Also, this study found that 3% tetracaine/0.05% oxymetazoline produced soft tissue anesthesia of the anterior palatal mucosa. Common adverse effects were nasal runniness (38.6%), nasal congestion (34.1%), nasal discomfort (25%), lacrimation (15.9%) and oropharyngeal pain (13.6%).

Discussion

- Intranasal administration of anesthetics may be an effective, safe alternative for needle-phobic patients in achieving dental anesthesia
- The tetracaine component of Kovanaze appears to degrade rapidly in the plasma; however, excessive use of topical tetracaine on the oropharyngeal membrane may produce symptoms of local anesthetic overdose, including disorientation, seizures, respiratory depression and death.
- Oxymetazoline is a vasoconstrictor included in the formulation to prevent rapid redistribution of tetracaine from the target site, and increase the depth and duration of anesthesia. Overall, the mean pressor effects of 0.05% oxymetazoline are relatively minor and do not seem to be clinically significant. However, patients with pre-existing conditions such as hyperactive thyroid disease, were found to experience clinically significant pressor reactions. Thus, relative contraindications for oxymetazoline use would also apply to the use of Kovanaze. Overall, oxymetazoline is used widely as a OTC nasal decongestant and cases of serious cardiovascular events are rare.
- The success rates suggest the intranasal system can provide sufficient anesthesia for completion of 83-90% of maxillary restorative procedures. The success rate appears greatest in anterior teeth (96-100%) versus the premolars (60-74%). This may be attributed to anatomical differences, where in 28% of people the middle superior alveolar nerve is absent, and thus the premolars may be innervation by the posterior superior alveolar nerve. Kovanaze does not appears to reliably anesthetize the PSA nerve due to limited penetration in the posterior regions o the maxillary sinus.

Summary

- Studies reveal 3% tetracaine and 0.05% oxymetazoline produced a success rate of 83-90% in sufficiently anaesthetizing the maxillary jpremolars, canines, and incisors to allow dental restoration
- Most common side effects include nasal runniness, stuffiness and stinging
- Cardiovascular effects were observed in only two individuals out of 186 subjects and can be attributed to the oxymetazoline component
- Current FDA indications are narrow, limited to single maxillary restorative procedures for patients at least 40 kg
- Future phase 4 clinical trials are required to assess whether the depth of anesthesia obtained is sufficient for more complex dental procedures (extractions, root canals) and to determine the effect of young children

Reference

Hersh, Elliot V., Mana Saraghi, and Paul A. Moore. "Intranasal tetracaine and oxymetazoline: a newly approved drug formulation that provides maxillary dental anesthesia without needles." *Current medical research and opinion*32.11 (2016): 1919-1925.