A Guidance on the Use of Topical Anesthetics for Naso/Oropharyngeal and Laryngotracheal Procedures

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and the National Center for Patient Safety

This guidance is based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment. The clinician must ultimately decide the course of therapy based on individual patient situations.

INTRODUCTION

Topical anesthetics have routinely been used to provide anesthesia for the skin, eyes, ears, nasal mucosa, oral mucosa and bronchotracheal area. Several local anesthetics are available; however, benzocaine, cocaine, lidocaine, prilocaine, and tetracaine are the only agents used for topical anesthesia. Cocaine was used widely in the past for nasopharyngeal anesthesia due to its vasoconstrictive properties. However, due to its Schedule-II status, its use is very limited. Prilocaine is only available as a topical anesthetic in a cream or ointment preparation, and hence, its use is also limited. The most commonly used topical anesthetics for naso/oropharyngeal, laryngotracheal and airway administration are benzocaine, tetracaine (in combination with benzocaine) and lidocaine.

Benzocaine and lidocaine preparations are often used for intubation, endoscopy, bronchoscopy, and other invasive procedures. The topical anesthetic agents have been used for many years with the ester-based anesthetics (benzocaine) being used initially, followed by the amide-based local anesthetic (lidocaine).[1] The toxicity of local anesthetics is well documented. The amount of drug administered as well as the route of administration influence the toxic or untoward effects of these agents. When assessing the risk of toxicity, primary considerations are the intended area of administration, underlying risk factors, as well as the amount administered. Administration of topical anesthetics should be performed with accuracy to ensure that a predetermined amount of drug is administered to allow for the intended effect while minimizing the risk of toxicity.

Local anesthetic toxicities include central nervous system (CNS) toxicity, cardiovascular (CV) toxicity, and methemoglobinemia (MHb). Benzocaine-acquired MHb has been thoroughly documented in the literature. Clinical MHb, unless reversed with methylene blue, is associated with increased morbidity and mortality. The symptoms of MHb correlate with the proportion of methemoglobin to total hemoglobin. The patients become hypoxic yet the symptoms are not relieved by 100% oxygen because the hemoglobin oxidized by the benzocaine cannot carry oxygen. Standard monitoring parameters are not sufficient in detecting MHb so it is not easily identified. Monitors such as the typical two wavelength pulse oximetry and arterial blood gases can be misleading because circulating methemoglobin interferes with the standard technology used to calculate or measure the actual oxygen level in the body. Although benzocaine is believed to exhibit negligible absorption, the number of benzocaine-acquired MHb cases appearing in the literature is in the hundreds. This number is a potential under-estimation of the actual number of cases as it reflects only cases published in the literature and those that are spontaneously reported to the Food and Drug Administration (FDA). Preliminary results from an unpublished informal survey within and outside of the Department of Veterans Affairs point to more cases of benzocaine-acquired MHb that were not previously found in the literature or FDA database. Benzocaine-acquired MHb can be attributed to several factors: variable amounts of drug delivered from the spray canister, liberal and excessive use by practitioners, and lack of awareness by practitioners of the dosage limits and toxic effects of benzocaine and the oxidizing effect of its active metabolite. Lidocaine is also associated with MHb, but it is less prevalent than with benzocaine (less than 10 case reports in the literature). In cases where the administered doses of lidocaine were known and reported, its use alone for topical anesthesia at recommended doses has not been associated with toxic levels of methemoglobin. Unlike the predictable CNS and CV toxicities associated with defined lidocaine serum concentrations, lidocaine-induced MHb is idiosyncratic and rare. Benzocaine acquired MHb however is not idiosyncratic, and is more prevalent.

In light of numerous case reports identifying toxicities associated with topical anesthetics, specifically benzocaine-acquired MHb, it is critical to evaluate the evidence supporting the safety and efficacy of topical local anesthetic agents. This is of primary concern for the use of these agents when applied to mucosal surfaces. The following guidance will focus on the most commonly used topical spray anesthetic agents, benzocaine and lidocaine.

Table 1 describes the topical local anesthetic agents available for naso/oropharyngeal and layrngotracheal use.

TABLE 1 TOPICAL ANESTHETICS FOR NASO/OROPHARYNGEAL AND LARYNGOTRACHEAL PROCEDURES[2-9]

Anesthetics Agent	Brand (Manufacturer)	Indication	Class	Formulations for Mucous Membrane
Benzocaine	Hurricaine® (Beutlich) Topex® (Sultan) Metered dose	Topical anesthetic to mucous membrane (except eyes) during surgical or other procedures in the ear, nose, mouth, pharynx, larynx, trachea, bronchi, and esophagus	Ester	• 20% topical spray
14% benzocaine , 2% tetracaine, 2% butamben combination	Cetacaine® (Cetylite)	Topical anesthesia of all mucous membrane except the eyes. The spray form is indicated for controlling pain or gagging. All forms are indicated for use in surgical or endoscopic or other procedures in the ear, nose, mouth, pharynx, larynx, trachea, bronchi, and esophagus	Ester	• Liquid (56 g) • Aerosol spray (56 g)
Lidocaine	Xylocaine® (AstraZeneca) and various generic manufacturers (e.g., Roxane)	Topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract	Amide	• 2% Jelly (lubricant for intubation) • 5% Ointment (lubricant for intubation) • 2% Viscous solution (20mL, 50mL, 100mL) • 4% Solution (50mL), (5mL ampules), (4 mL syringe)
Tetracaine	Pontocaine® (Hospira) and various generics	Topical anesthesia of accessible mucous membranes (larynx, trachea, esophagus)	Ester	• 0.5% solution (1mL, 2mL, 15mL) • 2% (30mL, 120mL)
Cocaine	Not Branded (Roxane)	Topical anesthesia of accessible mucous membranes of the oral, laryngeal and nasal cavities	Ester	• 4% solution (4mL, 10mL) • 10% solution

SUMMARY OF USES

The efficacy of naso/oropharyngeal and laryngotracheal uses of topical anesthetics is summarized by grade of recommendation with further explanation within this guidance document. The quality of the evidence, as depicted in Tables 2 and 3, was rated using the U.S. Preventive Services Task Force method.[10] Lidocaine (Table 3) has stronger evidence supporting its use as a topical anesthetic in the naso/oropharyngeal and laryngotracheal area compared to benzocaine (Table 2).

Table 2 Summary of uses for Topical Benzocaine by grade of recommendation

Grade A Strongly Recommend	Grade B Recommend	Grade C Consider	Grade I Insufficient Evidence
Indications always acceptable	*May be useful/effective*	*May be considered*	*Clinical judgment should be used*
	• Endoscopy in non-sedated patients[13,39]	• Endoscopy in sedated patients[12,14]	

Table 3 Summary of uses for Topical Lidocaine by grade of recommendation

Grade A Strongly Recommend	Grade B Recommend	Grade C Consider	Grade I Insufficient Evidence
Indications always acceptable	*May be useful/effective*	*May be considered*	*Clinical judgment should be used*
• Bronchoscopy in nonsedated patients[17,33,34] • Endoscopy in non-sedated patients[18,19,21,24]	• Bronchoscopy in sedated patients[16,40,41] • Awake intubation[27] • Intubation in sedated patients[25,26,28] • Insertion of NG tube[30-32,41] • Endoscopy in sedated patients[20,22,23]		• Nasendoscopy[29]

As a general rule, grades C and I uses are not routinely recommended, but they may be considered on an individual basis when other agents with evidence of efficacy are not effective, not tolerated, or contraindicated. The potential risks and benefits of using topical anesthetics for these indications should be discussed with the patient. The grades C and I uses and the anesthetic goals should be clearly articulated and documented in the patient's medical record.

Tables 2 and 3 demonstrate the evidence available for the use of benzocaine and lidocaine as topical anesthetics in the naso/oropharyngeal and larnygotracheal area. Stronger evidence is available to support the use of topical lidocaine in the various procedures listed. Even though insufficient efficacy evidence exists, due to lack of studies for the use of local anesthetics and nasoendoscopy, it remains a common practice and use of the safest agent available should be considered.

METHODS

A literature search was carried out in Medline 1966 to January 6, 2006 using the terms topical anesthetics, lidocaine, benzocaine, tetracaine, Cetacaine®, Topex®, oropharyngeal, esophageal, mucous membrane, pharmacokinetics, blood levels and methemoglobinemia. A search in the Cochrane Database of Systematic Reviews was performed in the English language for double-blind (DB) randomized controlled trials, quantitative systematic reviews or meta-analyses that involved benzocaine, lidocaine, tetracaine, or cetacaine and included, primarily or solely, the adult population.

The following tables are a compendium of what was reviewed.

TABLE 4 DOSAGE AND ADMINISTRATION[2-9]

Anesthetic Agent	Dosing and Administration	Comments
Benzocaine Hurricaine®	Apply spray for ≤ 1 second	1-second spray is designed to deliver 60mg but has been reported to deliver as much as 500mg-3300mg.[11,59,67] Toxicity has been observed with normal and excessive number of sprays.
Topex®	Delivers 45-55mg per spray	Metered dose at 50mg per spray
Cetacaine®	Apply spray for ≤ 1 second	Spraying in excess of 2 seconds is considered contraindicated. Product delivers 200 mg of benzocaine / butyl aminobenzoate / tetracaine residue per second
	Apply liquid form with cotton applicator	Cotton applicator should not be held in position for extended periods of time since local reactions to benzoate topical anesthetics are related to the length of time of application.
Lidocaine • 4% topical solution	Spray 1-5 mL (40-200mg lidocaine) with atomizer or apply with cotton applicator	Maximum adult dose: 10 ml of 4% solution (400mg lidocaine). Use extreme caution if there is sepsis or severely traumatized mucosa in the area of application since under such conditions there is the potential for rapid systemic absorption. Although the rate of absorption is relatively slow after spraying the laryngotracheal mucosa, there is the attendant risk that some solution may gravitate into the lower respiratory tract where surface area for absorption and tissue blood flow are much greater, resulting in unexpectedly rapid and high blood levels.
• 2% viscous solution	Gargle 15mL	Not to be administered at intervals of less than 3 hours and no greater than 8 doses in 24-hr period
• 2% jelly or 5% ointment	Apply a moderate amount of jelly or ointment to the external surface of the endotracheal tube shortly before use	No more than 600 mg or 30 mL of lidocaine 2% jelly should be given in any 12-hour period
Tetracaine • 2% solution • 0.5% solution	Apply with cotton pledgets Apply with cotton pledgets or inhale orally as nebulized 0.5% solution	The maximum recommended dose of tetracaine is 100-200mg. Tetracaine has a lower threshold for CNS symptoms.
Cocaine • 4% solution	Apply 1-4% solution TOPICALLY with cotton applicators or as a spray to mucous membranes; MAX 1-3 mg/kg (or 400 mg), generally 1 mg/kg sufficient; more pronounced effects may be achieved with a 10% solution with increased risk of toxic reactions	As with all topical anesthetic agents, use caution in patients with sepsis or severely traumatized mucosa in the area of application. Concentrations greater than 4% are generally not recommended because of difficulty in controlling dosage and the increased risk of toxic reactions.

CLINICAL TRIALS SUMMARY

BENZOCAINE AND CETACAINE® STUDIES

Few studies exist in the medical literature, which evaluate the efficacy of benzocaine used as a topical anesthetic agent on the naso/oropharyngeal mucosa, laryngotracheal region and airway. Table 5 describes 3 studies and Table 9 details the fourth. Only one lower level evidence study evaluating the safety of benzocaine was identified in the literature. The details of that study, which depict the ideal but not typical method of topical spray benzocaine administration, are summarized in Table 6. Additional safety reports on the risk of MHb are detailed in Appendix I.

TABLE 5 EFFECTIVENESS STUDIES FOR USE OF BENZOCAINE

Procedure	Available Evidence	Comments
Upper Endoscopy	**Large* DB randomized placebo-controlled** Level 1 evidence (n=150; Lachter)[12]	No difference in cough, gag, or difficulty in patients receiving benzocaine compared to placebo in sedated patients. Benefit only in patients undergoing endoscopy for the first time (p<0.03). Variation was minimized with only 4 endoscopists performing all 150 procedures.
	Large DB randomized placebo-controlled Level 1 Evidence (n=252; Campo)[13]	Comparison of benzocaine to placebo in unsedated patients. Visual Analog Scale showed intubation and examination were tolerated better in benzocaine treated patients (p=0.0001) compared to placebo. Degree of retching for intubation and examination was significantly less in the treatment group as well (p=0.0001, p=0.02, respectively).
	Small ** DB randomized placebo-controlled Level 1 Evidence (n=95; Davis)[14]	Comparison of benzocaine/tetracaine to placebo in sedated patients. No difference in patient and physician rating for all measures between benzocaine/tetracaine and placebo group.

*** Large = ≥ 100 patients; ** Small=< 100 patients; DB = Double-blind**

TABLE 6 SAFETY/PHARMACOKINETIC STUDIES FOR BENZOCAINE

Procedure	Available Evidence	Comments
Upper Endoscopy	**Prospective Cross Over Convenience** Level II-3 Evidence (n=91; Guertler)[15]	Safety of topical 20% benzocaine spray was evaluated in healthy adult and patient volunteers. A 2-second spray of 20% benzocaine applied to the oropharynx induced a statistically significant but clinically insignificant increase in methemoglobin levels between baseline (0.8+/-0.2%) and 20-, 40- and 60-minutes measurements (0.9+/-2%; p<0.05)

LIDOCAINE STUDIES

Several well-designed efficacy and safety studies have been conducted with lidocaine used as a topical anesthetic on the naso/oropharyngeal mucosa, laryngotracheal region and airway. Many of the efficacy studies compare lidocaine to placebo and examine different methods of administration. The safety studies evaluate lidocaine serum levels to confirm the safety of lidocaine when administered in different doses and by various methods. Tables 7 and 8 describe the efficacy and safety studies found in the literature. Table 9 details the only comparative study identified with benzocaine.

TABLE 7 EFFECTIVENESS STUDIES FOR USE OF LIDOCAINE

Procedure	Available Evidence	Comments
Bronchoscopy	**Large DB randomized placebo-controlled** Level 1 Evidence (n=150; Stolz)[16]	Comparison of different routes of lidocaine administration and placebo in sedated patients. Additional nebulized lidocaine did not increase benefit in patients under combined sedation and already receiving nasal and oropharyngeal lidocaine spray.
	Small randomized Level 1 Evidence (n=40; Kortilla)[17] Comparing spray to nebulized lidocaine. No placebo.	Comparison of different routes of lidocaine administration in unsedated patients. Lidocaine spray provided better anesthesia and patient cooperation than nebulized lidocaine (p<0.05).
Endoscopy	**Large DB randomized placebo-controlled** Level 1 Evidence (n=252; Ristinkankare)[18]	Comparison of lidocaine spray to placebo spray and control group with no spray. Lidocaine spray showed no benefit except when compared to no spray control group (p<0.01) but not to placebo group.
	Large DB randomized placebo-controlled Level 1 Evidence (n=167; Hedenbro)[19]	Comparison of lidocaine to placebo in unsedated patients. Patient rated less discomfort with lidocaine spray than placebo. Physician rated less difficult exam in lidocaine group than placebo (p=0.0014).
	Large DB randomized placebo controlled Level 1 Evidence (n=111; Gordon)[20]	Comparison of lidocaine to placebo in sedated patients Patient and physician rated tolerance better in lidocaine group (p<0.005 both), but no difference in gag reflex.
	Large DB randomized Level 1 Evidence (n=114; Mulcahy)[21] Comparing low and high dose lidocaine. No placebo.	Comparison of two doses of lidocaine in unsedated patients. Patients in high dose (100mg) group reported less discomfort during swallowing than low dose (30mg) (p<0.002). Overall satisfaction similar between both groups.
	Large DB randomized placebo-controlled Level 1 Evidence (n=154; Dhir)[22]	Comparison of lidocaine to placebo in unsedated patients. Lidocaine spray did not facilitate procedure in absence of IV sedation. No health related outcomes assessed.
	Small SB randomized Level 1 Evidence (n=60; Jameson)[23] Comparing 50mg, 100mg, and 200mg lidocaine.	Dose ranging study comparing 3 doses of lidocaine in sedated patients. 100mg and 200mg groups tolerated procedure better than 50mg group (p<0.05) and had fewer gags per minute.
	Small Open Label Level II evidence (n=25; Williams)[24] No comparison group. Evaluating nebulized lidocaine.	Evaluation of nebulized lidocaine in unsedated patients. VAS ratings showed lidocaine nebulization was acceptable to unsedated patients.
Intubation	**Descriptive Case Series** Level III Evidence (n=3; Sutherland)[25] Lidocaine 4% nebulized, 2% through bronchoscope, and 4% nebulized as needed	Descriptive report of different methods of lidocaine administration. Received lidocaine through spray and nebulizer which provided successful anesthesia and minimized discomfort. However, no clear measurable outcomes provided.
	Open Label Level II Evidence (n=20; Stoelting)[26] Comparing lidocaine gargle and spray to historical control	Comparison of topical lidocaine to historical control in sedated patients. Lidocaine attenuated BP response but had minimal effect on HR compared to historical control. Larger sample size needed to adequately compare to historical control.
	Randomized Single Blind Crossover in healthy volunteers Level 1 Evidence (n=11; Sitzman)[27] Comparing 3 routes: swish/gargle, spray, and glossopharyngeal nerve block	Comparison of different methods of lidocaine administration in healthy volunteers. Swish and Gargle plus spray and glossopharyngeal nerve block was significantly better than the swish and gargle alone (p<0.05) based on VAS. Majority patients preferred swish and gargle plus spray method (p<0.05) compared to the other 2 methods.

	DB randomized placebo controlled Level 1 Evidence (n=19; Polassani)[28]	Comparison of lidocaine to placebo in unsedated patients. Lidocaine significantly attenuated BP (p<0.001) and HR (p<0.005) compared to control group. Paroxysmal ventricular contractions occurred during intubation in the control group but not in the lidocaine group.
Nasendoscopy	**Small DB randomized placebo controlled** Level 1 (n=82; Frosh)[29]	Comparison of lidocaine to placebo. Patient rated lidocaine spray worse for taste, pain, and experience vs. placebo. No physician ratings.
NG tube placement	**Small DB randomized placebo controlled** Level 1 Evidence (n=50; Cullen)[30]	Comparison of lidocaine to placebo. Patients in nebulized lidocaine group reported less discomfort than placebo (difference between mean VAS 21.6mm, 95% CI 5.3 to 38.0 mm). Lidocaine group experienced more frequent epistaxis.
	Small DB randomized placebo controlled Level 1 Evidence (n=40; Wolfe)[31]	Comparison of lidocaine to placebo. Patients in atomized lidocaine group reported less pain then placebo (difference between mean VAS 27.1mm, 95% CI 14.8 to 39.4mm).
	Small DB randomized triple crossover in healthy volunteers Level 1 Evidence (n=30; Ducharme)[32] Comparing atomized lidocaine, atomized cocaine, and lidocaine gel. No placebo.	Comparison of two methods of lidocaine administration and cocaine in healthy volunteers. Patient rated no difference in nasal pain on VAS, but global discomfort was less with lidocaine gel than atomized cocaine or lidocaine (p<0.017)

DB = Double-blind; SB = Single-blind

TABLE 8 SAFETY/PHARMACOKINETIC STUDIES FOR LIDOCAINE

Procedure	Available Evidence	Comments
Bronchoscopy	**Small DB randomized** Level 1 Evidence (n=96; Mainland)[33] Comparing various strengths of lidocaine. No placebo.	Evaluation comparing different strengths of lidocaine. 33 patients consented to blood draws in this study which used dosage strengths not commercially available in U.S. 2 patients exceeded toxic conc. (5.02 and 6.28 mcg/mL with no signs of toxicity.) Recommended 1% lidocaine.
	Small DB randomized placebo controlled Level 1 Evidence (n=15; Groeben)[34] Evaluating effects of 3 concentrations of lidocaine in mild asthmatics.	Evaluation comparing 3 different strengths of lidocaine in asthmatic patients. Lidocaine concentrations remained below toxic threshold. 2mg/kg of 4% solution significantly attenuated bronchial hyperactivity with profound anesthesia and least airway irritation.
	Open Label Level II Evidence (n=51; Langmack)[35] Observational study evaluating lidocaine dose needed for optimal anesthesia and safety. No comparison group.	Evaluation of the optimal dose of lidocaine in asthmatic patients. The average dose of lidocaine was 600mg with no signs and symptoms of toxicity. Serum conc. were <5mcg/mL (toxic range is > 5 mcg/mL). Toxic range could not be adequately confirmed due to first level being obtained 30 minutes after administration missing peak concentration times and obtaining first level during the predominant elimination phase. Mild to moderate asthmatic population.
	Open Label Level 1 Evidence (n=40; Kortilla)[17] Observational study evaluating spray and nebulized lidocaine for safety.	Evaluation of two methods of lidocaine administration. Peak concentration for the spray group (total dose 439+/-85mg) was 2.54mcg/mL at 15 minutes ; for the nebulized group, it was 1.17mcg/mL at 5 minutes (total dose 462+/-81mg).
Endoscopy	**Open Label** Level II Evidence (n=25; Williams)[24] No comparison group. Evaluating nebulized lidocaine.	Evaluation of nebulized lidocaine in unsedated patients.. 200mg nebulized lidocaine, followed by 2mL lidocaine 5% sprayed into nose and 10% sprayed into oropharynx resulted in rapid absorption with all levels less than toxic threshold of 5mcg/mL. Peak concentrations were 4.5 mcg/mL and 3.5 mcg/mL. Serum levels should have been collected more frequently immediately after administration to adequately capture onset and peak conc. Number of levels available allowed for a more detailed analysis yet not conducted by authors.
	Small SB Randomized Level 1 Evidence (n=60; Jameson)[23] Comparison of 50mg, 100mg, and 200mg lidocaine. No placebo.	Comparison of three doses of lidocaine. All serum levels were less than 5 mcg/mL (toxic range), however levels were drawn q 20min., and therefore potentially missing peak concentrations.
Intubation for laryngoscopy	**Open Label** Level II Evidence (n=22; Kotaki)[36] Safety and pharmacokinetic study. No comparison group.	Safety study evaluating dose and serum levels of lidocaine. Total doses of 127-260mg resulted in serum levels below toxic range. Serum levels should have been drawn more frequently.
	Randomized Single Blind Crossover Level 1 Evidence (n=11; Sitzman)[27]	Comparison of different methods of lidocaine administration. Serum concentrations were significantly higher in the glossopharyngeal nerve block arm compared to the swish and gargle lidocaine or swish and gargle plus spray lidocaine. Full pk analysis and sampling times not conducted.
Intubation for orthopedic surgery	**Randomized Open Label** Level 1 Evidence (n=41; Morrell)[37] Comparing two methods of lidocaine administration.	Comparison of two methods of lidocaine administration. Mean plasma levels after 4% lidocaine spray were significantly higher in patients under controlled ventilation at 20 minutes than patient under spontaneous ventilation. Peak concentration occurred at 15 minutes in both group and mean levels were below toxic range. Number of levels available allowed for a more detailed analysis yet not conducted by authors.
NG tube placement	**Open Label** Level II Evidence (n=10; Watson)[38] Comparison of pharmacokinetics in young versus elderly patients.	Comparison of lidocaine serum levels in young versus elderly patients. No significant difference in peak plasma concentrations or concentrations over time between young (25-37 yrs) and elderly (60-68 yrs) however sample size is too small to find significant difference.

DB = Double-blind; SB = Single-blind

TABLE 9 COMPARATIVE EFFICACY – DRUGS

Agents compared	Procedure	Finding	N	Notes
Part I: Four separate days volunteers received 6 sprays of 1) 1% phenylephrine + placebo 2) 4% lidocaine + placebo, 3) 1% phenylephrine + lidocaine 4) 5% cocaine plus placebo to the nasal passageway. Following spray all volunteers received 10 mL viscous lidocaine to nares. Part 2: Patients received 1 of the following sprayed anesthetic regimens; 1) 1% phenylephrine + placebo 2) 4% lidocaine + placebo, 3) 1% phenylephrine + lidocaine 4) 5% cocaine plus placebo to the nasal passageway. Following the spray all patients received 10 mL of 2% viscous lidocaine instilled. All patients received conscious sedation with meperidine or midazolam	Part 1: NG tube insertion Part 2: Nasal bronchoscopy	Comparison of lidocaine and cocaine with and without vasoconstricting agents to placebo. Part 1:Vasoconstriction obtained in phenylephrine and cocaine groups. Depth of insertion of NG tube was significantly greater ($p<0.04$) for all regimens following viscous lidocaine instillation. Serum lidocaine levels in selected patients were <0.5 mg/L Part 2: No significant difference between regimes for nasal resistance to insertion of bronchoscope or patient discomfort. Conclusion: *Topical cocaine offered no advantage over lidocaine; sprayed nasal anesthetics were not superior to viscous lidocaine instillation; absorption following topical application of viscous lidocaine was negligible.* Authors adopted method of 1% phenylephrine spray for vasoconstriction followed by 10 mL of 2% viscous lidocaine application prior to nasal bronchoscopy.. Additive effect of spray anesthesia plus lidocaine not adequately evaluated.	Part 1:7 Part 2: 99	Level 1 Evidence Middleton[41]
Part 1: each subj. received 1 of 4 drugs on 4 separate scopes within 2 wks. 2-sec. Cetacaine® spray, 2 sec. Hurricaine® spray, 2% lidocaine green gargle, and 1 :1 dilution of 2% lidocaine green mouthwash gargle. Part 2:each received 1 of 4 drugs on 4 separate scopes within 2 wks: 2-4 squirts 10% lidocaine, preferred agent from part 1 (Cetacaine®), 2% lidocaine red gargle, and 1 :1 dilution of 2% lidocaine red mouthwash gargle	Upper GI endoscopy	Comparison of lidocaine to benzocaine. Part 1: Taste = Green lidocaine gargle most favored followed by Hurricaine® but not significant. Effectiveness=Cetacaine® was better than Hurricaine®, green gargle and 2% lidocaine gargle (all $p<0.05$). Ease of scope = no difference between; Preference = Cetacaine® preferred 2:1 over both gargles. No subj. preferred Hurricaine®. Part 2: Taste = 1% lidocaine red gargle preferred over Cetacaine® or 2% lidocaine gargle. 10% lidocaine spray preferred over Cetacaine® spray. Effectiveness = 10% lidocaine spray better than 1% lidocaine red gargle. Ease of scope = no difference between agents. Preference = 10% lidocaine spray in 7 subj. and Cetacaine® spray in 2 subj. Overall preference for spray form.	Part 1: 14 Part 2: 9	Level II-3 Evidence Smith[39]
Two benzocaine lozenges for all 3 groups prior to procedure. Group1- Lidocaine 40 mg (4 sprays) on posterior pharynx and lidocaine 80 mg (4 mL) jelly placed on nasal passages followed by 4 ML of 2.5% cocaine through bronchoscope onto cords and into the bronchial tree (via inspiration). Group 2 - Transtracheal injection (TI) of 2.5% cocaine through cricotyroid membrane into the upper trachea; Group 3 - Lidocaine 4% (mL) via nebulizer x 15 min; All 3 groups received 1% lidocaine solution as needed during procedure. Conscious sedation with fentanyl and droperidol	Bronchoscopy	Comparison of three different methods of lidocaine administration in combination with benzocaine lozenges. Mean cough count significantly lower with TI versus BI($p<0.01$) or NEB ($p<0.05$). VAS scores (patients and broncoscopists) significantly favored TI compared to nebulized lidocaine ($p<0.01$, $p<0.001$) or bronchoscopic injection ($p<0.01$, $p<0.001$). Overall TI of 2.5% cocaine produced better anesthesia than nebulized lidocaine or bronchial injection of cocaine. This study evaluated nebulized lidocaine, the recommended method of delivery of lidocaine for these procedures is atomization.	53	Level 1 Evidence Graham[40]

DISCUSSION OF STUDIES

Benzocaine Efficacy

Benzocaine and lidocaine are frequently used for topical anesthesia of the naso/oropharyngeal mucosa, laryngotracheal region and airway. Although benzocaine is the prototypical topical anesthetic, very few studies are available supporting its efficacy. In a literature search conducted from 1966 though Jan 2006, only four studies evaluating the efficacy of benzocaine for naso/oropharyngeal administration were identified.[12-14,39] Two were well designed and supported the efficacy of benzocaine as a topical anesthetic for endoscopies.[12,13] One did not support its use in sedated patients.[14] A fourth study comparing benzocaine with other topical anesthetics resulted in a positive response from patients but the design and supporting evidence were weak.[39] The evidence from these studies resulted in Grade B and C recommendations for benzocaine use in unsedated and sedated patients undergoing endoscopies.

Benzocaine Safety

In contrast to the paucity of studies that exist describing the efficacy of benzocaine, close to two hundred case reports exist describing the association of benzocaine and methemoglobinemia.[42-65] Only one study evaluating the safety of benzocaine has been identified in the literature. The study evaluated the safety of benzocaine by measuring methemoglobin levels after a 2-second spray in volunteers which resulted in statistically significant higher methemoglobin levels after the second spray.[15] The dose and regimen administered in the study is recommended but is not reflective of clinical practice. It is important to note that benzocaine-acquired MHb has been thoroughly documented. It was once believed that negligible absorption of benzocaine occurred with topical administration, and hence, the risk of MHb was perceived to be low. However, the number of case reports implicating benzocaine in acquired MHb proves this to be a concern greater than originally anticipated. While many of the reports show benzocaine-acquired MHb following more than 1 spray in the allotted period, several reports identify MHb in patients receiving normal doses.[(> 1spray 44-48,53-54, 59,62,64-65; normal dose 42,49)] Methemoglobinemia most likely occurs due to the variable amount of drug delivery, its liberal use by practitioners, and the oxidizing effect of its active metabolite.[66] This problem is principally associated with the benzocaine 20% spray, Hurricane®. As established by Khorasani et. al. the variable delivery of benzocaine results in large amounts delivered based on canister content and orientation and hence, by minimizing this problem, the occurrence of MHb may be minimized.[67] Although MHb can occur at normal doses, administering a defined and accurate amount via a metered dose method should decrease the risk. However, it should be noted that simply having the drug delivered in metered doses does not prevent the clinician from administering excessive sprays.[11] Unfortunately, studies showing that metered dose administration of benzocaine is safer have not been published. To date only one agent, Topex®, is available as a metered dose spray and is used most often for dental procedures.[7]

Lidocaine Efficacy

Lidocaine is also used for topical anesthesia in the naso/oropharyngeal, laryngotracheal and airway region. In contrast to benzocaine, several studies exist in the literature which supports its safety and efficacy as a topical anesthetic. Many well designed studies document the efficacy of lidocaine as a topical anesthetic for endoscopic procedures and nasogastric tube placement.[19-21,23,30-31] The evidence for these studies suggests that lidocaine should always be used in non-sedated patients and may have some advantages in sedated patients. Lidocaine has also proven to be effective as a topical local anesthetic in bronchoscopy procedures[16-17, 40-41]. The evidence for these studies resulted in Grade A recommendations of lidocaine use for non-sedated patients undergoing bronchoscopies and Grade B recommendations for sedated patients.[(non-sedated 17,33,34; sedated 16,40,41)] This information was important as it identified the benefits of lidocaine-induced anesthesia such as decreased cough, decreased gag reflex and overall decreased airway hyper-reactivity, enhancing patient and practitioner compliance and satisfaction, respectively. Lidocaine effectiveness studies were also conducted in the anesthesia area where awake intubations and standard laryngoscopy for endotracheal intubations in the anesthetized patients were conducted.[26-28] The results of those well designed studies resulted in Grade B recommendations for awake intubations, laryngoscopies and endotracheal intubations. The advantage of lidocaine in the awake intubation is a safer and easier intubation secondary to decreased cough and gags. The advantage of lidocaine for standard endotracheal intubations can be realized by decreased airway reactivity and decreased hemodynamic response to laryngoscopy. This may translate clinically to being advantageous in patients with asthma as well as in patients at risk for increased intracranial pressure, intraocular pressure or increased heart rate and blood pressure.

Lidocaine Safety

In addition to the several efficacy studies available, many safety studies have also been conducted with lidocaine to establish its therapeutic index. The toxicity of lidocaine has been extensively documented such that levels greater than 5

mcg/mL are associated with increased toxicity.[68] Serum lidocaine levels between 6 and 10 mcg/mL are associated with visual disturbances, muscle twitching, unconsciousness and seizures. Serum levels of approximately 15 mcg/mL have been associated with coma, and serum levels >20 mcg/mL are associated with cardio and respiratory arrest. Because lidocaine given topically usually results in levels below the toxic range (<5mcg/mL), it is relatively safe. The maximum recommended dose of lidocaine given for regional or peripheral blocks is 400 mg (maximum dose is based on infiltration). The pharmacokinetics of lidocaine are linear, hence increased doses result in increased serum concentrations. The most common toxicity reported with lidocaine is CNS toxicity which can be seen with topical administration. Hence the dose administered must always be calculated. Several studies have been conducted evaluating the safety of lidocaine to ensure that the dose and method of administration resulted in serum lidocaine levels below the toxic range.[17,23-24,27,33-34,36-38]

Although CNS toxicities are the most common toxicities associated with lidocaine (they have also been identified with tetracaine),[69] they are fully predictable and based on a maximum dose or level. Other idiosyncratic toxicities such as MHb can also occur with lidocaine as seen in a few case reports.[70-74] The occurrence, however, is far less prevalent with lidocaine than benzocaine. It should also be noted that in many of the case reports implicating lidocaine and MHb, the patient was also on a concurrent agent known to be associated with MHb (i.e. – nitrates, sulfonamides, benzocaine, and tetracaine), had risk factors for MHb (congenital MHb), or ingested large amounts of lidocaine. Additionally, the levels of MHb were clinically insignificant when lidocaine was used alone in normal doses. A maximum dose has not been identified and a therapeutic index has yet to be established for lidocaine and MHb; however, based on the current literature this should not be an issue when lidocaine is used alone in normal doses.

One relevant study, although conducted in animals, warrants mentioning as it directly compares lidocaine and benzocaine induced MHb in three different species of Macaques. The study compared low dose benzocaine (56 mg), high dose benzocaine (280 mg) and lidocaine(40 mg). Methemoglobin and sulfhemoglobin levels (a more dangerous form of altered hemoglobin) were serially measured in each arm following benzocaine or lidocaine administration. The results showed that benzocaine significantly increased MHb levels ($p<0.05$) in both dose ranges. In addition, sulfhemoglobin levels were detectable after both doses of benzocaine. In contrast, lidocaine did not result in MHb or sulfhemoglobin formation above baseline levels. The study resulted in the recommendation that benzocaine topical sprays should be replaced with lidocaine in the macaque species.[75]

Lidocaine Dosing and Pharmacokinetics

The efficacy and safety of lidocaine has been presented in the previous studies; however, the optimal dose and concentration of lidocaine has not been firmly established. The majority of studies were conducted with the 4% lidocaine solution which is commercially available in an ampule, bottle, and syringe with an atomizer attached. However, many studies used different methods of administration, such as spraying with an atomizer, nebulizing (there are different atomizers available for lidocaine administration such as metered-atomization-devices (MAD) and different nebulizers such as Devilbliss), swishing and gargling, gel swabbing, or oropharyngeal blocks. Nebulized lidocaine is generally not appropriate for providing topical anesthesia to the mucous membranes of the oropharynx, nasopharynx, and airway since it is more likely to be inhaled and absorbed in the lung, and thus not produce anesthesia to the desired area, while increasing the blood level of lidocaine, which is an undesirable effect. Moreover, when different administration methods were used, varying concentrations were evaluated as well. Although the 1% and 2% solutions are not commercially available, some studies diluted the 4% to make a less concentrated solution for evaluation. In one study by Mainland et al., the efficacy and safety of the different solutions were evaluated, and it was concluded that the 1% may be most effective and least toxic.[33] The limiting factor with the study was the method of aspiration administration which is not used as a method of choice in the U.S. Further studies are needed to evaluate the 1% solution. Although several safety studies have been conducted with lidocaine and full serial blood samples have been obtained, many studies did not obtain optimal samples due to prolonged waiting for the initial level or increasing the interval between levels. This resulted in the inability to adequately characterize onset and exact peak concentrations, as well as to conduct proper pharmacokinetic analyses. Moreover, in some studies, optimal serum samples were obtained but the proper pharmacokinetic analysis was not conducted.[24,27,37]

COMPARATIVE PHARMACOKINETICS[2-6]

The comparative pharmacokinetics for the available topical anesthetic agents are described in Table 10. In the product Hurricaine®, benzocaine has a very fast onset with a shorter duration of action. The addition of tetracaine increases the duration of action of Cetacaine®, which contains both benzocaine and tetracaine. Lidocaine's onset of action is slightly delayed, but the duration of action is long. While the duration of topical anesthesia may be limited, the sequela of the acquired MHb may extend for longer periods. Thus, with the shorter acting topical anesthetics such as benzocaine, repeated administrations to achieve the desired level of anesthesia pose an even greater risk for MHb and at higher levels.

TABLE 10 COMPARATIVE PHARMACOKINETICS[2-6]

Anesthetic Agent	Onset (minutes)	Duration (minutes)
Benzocaine 20% (Hurricaine®)	½	10 to 15
Cetacaine® (benzocaine 14%, tetracaine 2%, butamben)	½	30 to 60
Lidocaine 2%, 4%	2 to 5	15 to 60
Tetracaine 2%	3 to 8	30 to 60
Cocaine	1 to 5	30 to 60

MANAGEMENT OF METHEMOGLOBINEMIA[42-45,54]

What is methemoglobinemia (MHb)?

Normal hemoglobin (Hb) contains iron in the ferrous form (Fe^{2+}). Methemoglobinia (MHb) results from the oxidation of the iron in the hemoglobin from the ferrous (Fe2+) state to the ferric (Fe3+) state which renders it unable to bind oxygen. In addition, MHb shifts the oxygen dissociation curve of the remaining Hb to the left thereby impeding the unloading of oxygen from Hb to the tissues. Less than 1% methemoglobin is present in normal red blood cells and is rapidly converted back to hemoglobin by reduced cytochrome b5. MHb may be attributable to genetic causes (deficiency of NADH-MetHb or abnormal Hb such as HbM). However, by far the most common cause is exposure to drugs or chemicals which accelerate the hemoglobin oxidation rate (Appendix II). Risk factors for the development of MHb are outlined in Table 13.

What is the reported incidence with benzocaine?

All the topical anesthetics can cause MHb, but there are more reports in the literature associated with benzocaine due to its widespread and long-standing use. Moreover, a metabolite that is thought to be an N-hydroxy derivative appears to exert the toxic effects of benzocaine because of its oxidizing capabilities. Onset of MHb is within minutes of benzocaine administration. In most cases excessive amounts were employed, but MHb has occurred following application of normal doses. As little as 15-25 mg/kg benzocaine is capable of inducing MHb and producing recognizable cyanosis.

Out of 198 FDA reported adverse events associated with benzocaine from November 1997 through March 2002, 132 cases (66.7%) involved definite or probable MHb.[42] One hundred and seven cases (81.1%) were classified as serious, and 2 (1.5%) resulted in death. The majority (93.2%) of cases involved the spray product. Of the 69 cases that specified a dose, 37 (53.6%) indicated application of a single spray which is consistent with the recommended amount. The incidence of MHb is most likely under-reported due to the voluntary and spontaneous nature of reporting. Hence, the clinical significance of this problem is greater than these figures would indicate.

In a retrospective series analysis of 138 cases of acquired MHb, 5 were attributed to the use of benzocaine 20% spray.[77] Despite the small number, these cases were associated with the most severely elevated methemoglobin levels, with a mean of 43.3%.

A literature review of 44 cases of benzocaine-induced MHb showed that intubation, endoscopy/bronchoscopy, and ingestion were the most common procedures in which benzocaine administration produced MHb (Table 11).[43] Infants and elderly accounted for greater than half of the reported cases, possibly demonstrating the increased susceptibility of these populations. Other possible identified risks include patients with breaks in the mucosal barrier (Table 13). A representative, but not exhaustive, summary of case reports found in the literature is detailed in Appendix I.

TABLE 11 DISTRIBUTION OF CASES ACCORDING TO PROCEDURE REQUIRING BENZOCAINE ANESTHESIA (N=44)[43]

Procedure	Cases
ET/NT intubation	8
Endoscopy	9
Bronchoscopy	5
Esophageal Stethoscope	1

Rectal Probe	1
Ingestion (accidental and therapeutic)	8
Teething gel	2
Suppository	4
Skin Application	7

ET/NT=endotrachel tube/nasotracheal

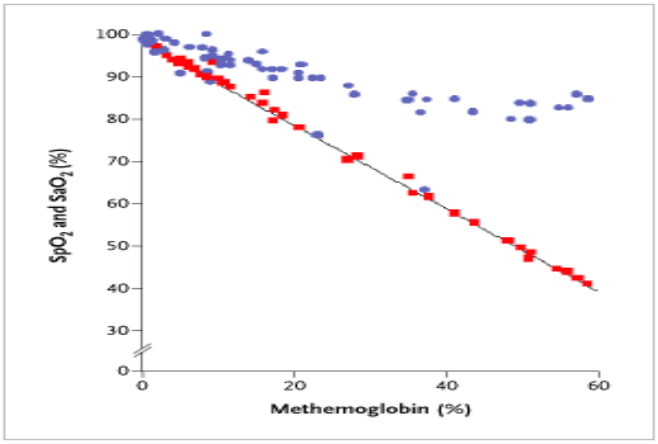
What are the signs/symptoms of MHb?

Symptoms of MHb correlate with the proportion of MHb to total hemoglobin, as outlined in Table 12, and are not relieved by 100% oxygen. Arterial blood appears chocolate brown and will not change to red upon exposure to air. Many signs of acute MHb are masked by general anesthesia, making the use of topical anesthetics in the preanesthesia setting of particular concern. Monitoring parameters such as pulse oximetry and arterial blood gases are misleading because circulating MHb interferes with the standard technology used to calculate or measure the actual oxygen level in the body. The absorbance spectra needed to accurately measure oxygenation during MHb are not available in two wavelength pulse oximeters resulting in falsely elevated O_2 readings in patients with MHb. The discordance in methemoglobin and oxyhemoglobin wavelengths and effect of methemoglobin on oxygen saturation are depicted in Figure A.[76] Standard two wavelength pulse oximetry is not accurate in detecting MHb. This type of pulse oximetry limits the nadir of oxygen saturation readings. These readings do not go below 80-85% even though the actual oxygen saturation may be as low as 40-50%. Co-oximetry is a more accurate way of measuring methemoglobin levels and thus, diagnosing the disorder.

TABLE 12 CORRELATON OF SYMPTOMS AND METHEMOGLOBIN LEVELS

MHb Level	Symptoms
<1%	Normal range
>10%	Clinical cyanosis
>30	Weakness, tachycardia, dyspnea, nausea, vomiting
>55%	Lethargy, dizziness, stupor
55-70%	Circulatory failure, cardiac arrhythmias, seizures, coma
>70%	Death

Figure A Effect of Methemoglobin in Oxygen Saturation As Measured by Pulse Oximetry[76] *Note: the blue circles provided below represent data from standard two wavelength pulse oximetry; the red squares represent data from a co-oximeter and indicate the actual oxygenation. These values assume no other underlying pathology such as anemia or compromised pulmonary function. See Table 13.*



What causes MHb?

MHb is attributable to 3 main causes:

1) Deficiency of NADH-MetHb due to hereditary or age-related enzyme system changes. Susceptible populations are neonates, elderly, and Native Americans of Alaskan or Inuit descent.
2) Genetic variation in hemoglobin structure resulting in abnormal hemoglobin (e.g. Hemoglobin M).
3) Exposure to drugs or chemicals which accelerate hemoglobin oxidation rate. Appendix II provides a list of agents associated with MHb. Absorption of benzocaine through broken skin and mucosa or absorption through the gastrointestinal tract is believed to be the main route of systemic access. Table 13 lists potential risk factors for MHb.

TABLE 13 POTENTIAL RISK FACTORS FOR METHEMOGLOBINEMIA[11]

Elderly – Due to multiple oxidant medications and comorbidities, in addition to increased fetal hemoglobin, the elderly may be placed at risk.
Infants – Infants have increased fetal hemoglobin and immature hepatic enzyme systems whereby hemoglobin is converted to methemoglobin more easily, and recovery mechanisms are not adequately developed
Heart Disease/Anemia – Including congestive heart failure, ischemic heart disease, electrical and mechanical disorders, and cardiomyopathy. These conditions may decrease hepatic blood flow to cause decreased metabolism of absorbed anesthetic.
Excessive Doses or absorption of topical anesthetic – Large doses of anesthetics and the presence of multiple oxidizing agents may lead to cumulative hematologic effects. Patients with traumatized tissue such that there are breaks in the mucosal barrier may experience increased absorption of topical anesthetics.
Respiratory Diseases – These patients may have altered oxygen delivery.
Lung Transplant Recipient – Patients may have limited functional reserve as oxygen delivery may continue to be compromised, rendering the patient more susceptible to conditions that may alter oxygenation. Moreover, transplant patients are often on multiple oxidizing drugs, such as sulfonamide antibiotics and dapsone for *Pneumocystis jirovedi* prophylaxis.

What is the treatment for MHb?

Treatment of acute MHb is directed at restoring the oxygen-carrying capacity of the blood and is most easily accomplished with methylene blue 1 to 2mg/kg (0.1 to 0.2 mL of 1% solution) given by slow intravenous push over 5 to 10 minutes. Methylene blue acts as a cofactor to greatly accelerate NADPH methemoglobin reductase in the reaction converting methemoglobin to hemoglobin. Methylene blue is reduced to leukomethylene blue by accepting electrons from NADPH. Leukomethylene blue donates an electron to reduce methemoglobin to hemoglobin. MHb is usually reduced by 50% within 30-60 minutes. Rebound MHb can occur several hours after successful treatment and repeat administration of methylene blue may be required. If response to methylene blue is poor, treatment alternatives include blood transfusion, exchange transfusion, and hemodialysis. Ascorbic acid 300-1000mg/day IV in divided doses may be given but works slowly and probably is of no benefit in acute situations. It should also be noted that methylene blue at high doses (7mg/kg) may also precipitate MHb. Lower doses of methylene blue 1% (0.3-0.5 mg/kg)should be administered in patients with G6PD deficiency . In asymptomatic patients with methemoglobin levels <30%, treatment may not be necessary since the half-life of benzocaine is approximately 55 minutes, and most cases resolve within 24-72 hours.

DRUG COSTS

TABLE 14 DRUG ACQUISITION COSTS

Drug	Acquisition Cost per unit
Benzocaine (Hurricaine®) 60mL	$19.42
*Cetacaine® 50 mL	$58.50
Lidocaine 4% Solution 50mL	$3.02
Lidocaine 4% Solution 4 mL SYRINGE	$2.62
Lidocaine 4% Solution 5 mL ampule	$1.12
Lidocaine 2% Viscous Solution 100mL	$1.76
Lidocaine 2% Jelly 30mL	$2.89
Lidocaine 5% Ointment 37.5GM	$1.56
Tetracaine 2% Solution	$8.56
Cocaine 4% Solution 4mL	$13.67
Cocaine 10% Solution 4mL	$28.59

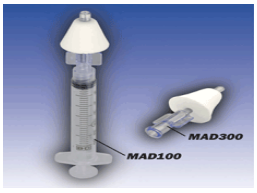
*Retail cost. Not a VA contracted item.

TABLE 15 COST OF DEVICE/SUPPLIES

Supplies	Cost
*MAD100 nasal drug delivery w/ 3mL syringe http://www.wolfetory.com/nasal.html	$3.12
*MAD300 nasal drug delivery w/o syringe	$2.60
*MAD-gic® MAD600 laryngo-tracheal drug delivery system w/ 3mL syringe (25) http://www.wolfetory.com/madgic.html	$4.72
*MAD-gic® MAD700 laryngo-tracheal drug delivery system w/o syringe (25)	$4.19
MADett® MAD710 ET tube drug delivery system http://www.wolfetory.com/madett.html	$10.55
Laryng-O-Jet Kit 4% Lidocaine (4mL) http://www.ims-limited.com/anesthetic.htm	$2.62
LTA® Prefilled 4% lidocaine HCl topical solution with syringe and cannula (160mg/4mL) NDC 0074-4698-01 *(picture not included)* http://www.hospira.com/products/productcatalog.aspx	$3.46

*MAD = metered atomization device
Note: cost of all devices based on retail cost

MAD100/300



MAD600/700

MAD710

Laryng-O-Jet

CONCLUSION

There are several local anesthetics that are available for topical use in the naso/oropharyngeal, laryngotracheal region and airway. Due to the safety issues associated with cocaine, in addition to its FDA classification as a Schedule II agent, its use is not as prevalent as in the past. Tetracaine is used in the combination product Cetacaine® with benzocaine. Benzocaine and lidocaine remain the topical anesthetics most commonly used.

Although benzocaine is commonly used, there is a lack of efficacy studies and a large number of safety reports implicating benzocaine and MHb. The reason MHb occurs with this agent is most likely secondary to the variable amount of drug delivery associated with the currently available dosage form, its liberal use by practitioners, and the oxidizing effect of its active metabolite. These reasons are compounded by the false sense of security that the two-wavelength pulse oximetry can provide. The liberal use by practitioners, often in excess of the recommended doses, may be the most pertinent reason. Also, due to the short duration of action of benzocaine (Hurricaine®), many practitioners may re-spray at shorter intervals and more often than indicated, resulting in larger amounts of benzocaine being delivered. Non-metered dose delivery systems further exacerbate the attendant risk of clinically significant MHb. A potential decrease in risk of MHb may be accomplished with metered dose delivery by delivering an accurate amount. This is based on the presumption that practitioners adhere to the dosage recommendations and do not exceed the maximum dose of benzocaine. However, this will not completely eliminate the risk of MHb and hence, awareness of the signs and symptoms of MHb, as well as knowledge of reversal with methylene blue, will remain paramount. Currently, a metered dose product for benzocaine is available; however, benzocaine's place in therapy remains questionable due to the dearth of efficacy studies in the literature.

An abundance of published studies have evaluated the safety and effectiveness of lidocaine as a topical anesthetic. *Good evidence supports its used for various procedures, and its clinical grade of effectiveness is stronger than that of benzocaine.* Lidocaine-associated MHb has not been consistent nor well documented in the absence of other agents which enhance its risk of MHb. In the four case reports identified in the literature and one from the manufacturer, only three reports identified lidocaine as the only agent potentially responsible for methemoglobinemia. In one of those three cases, the patient suffered from congenital MHb and received IV lidocaine, while the patient in the second case actually ingested 15mL of lidocaine. The dose of lidocaine was not reported in the case that was received from the manufacturer. The evidence currently available does not indicate it is a clinically significant cause of acquired MHb. Thus it is reasonable to conclude that lidocaine has less risk for methemoglobinemia compared to benzocaine. CNS toxicity is well documented with lidocaine and the therapeutic index has been well defined. Hence, dosing of lidocaine for specific procedures is more accurate, safer and effective than benzocaine when clinicians adhere to recommended dosing guidelines.

RECOMMENDATIONS

An ideal topical anesthetic should have rapid onset, adequate duration, and minimal or predictable systemic absorption, with the ability to be accurately administered. Due to the supporting efficacy studies and established therapeutic index for its common toxicities, it is recommended that the Veterans Health Administration adopt the use of topical lidocaine for naso/oropharyngeal and laryngotracheal procedures, and strongly discourage or prohibit the routine use of topical benzocaine for this purpose. To date, some VA Healthcare centers as well as non-VA medical centers, have removed benzocaine from their facility and use lidocaine as the sole topical anesthetic for naso/oropharyngeal and laryngotracheal administration. Currently, lidocaine is commercially available in a 4% solution and 2% viscous solution. The 4% lidocaine solution is available in a spray or can be delivered via a mucosal atomizing device (MAD), and thus, can be used as an acceptable replacement for benzocaine. Four percent lidocaine has an onset of 2 to 5 minutes, reaches a peak concentration at 15 to 20 minutes, and has a duration of action of 30 to 60 minutes.

From the supporting reasons above, it is recommended that lidocaine be used as the preferred topical local anesthetic for naso/oropharyngeal, laryngotracheal and airway applications. The recommended dosing for lidocaine is 40-200mg (1-5mL of the 4% solution) for anesthesia of the naso/oropharyngeal and laryngotracheal mucosa surface. The maximum recommended dose of lidocaine is 400mg (or 10mL of the 4% solution). Plasma levels should remain below the toxic threshold of <5mcg/mL.

Prepared: February 2006. Contact persons: Fran Cunningham, Pharm.D. and Muriel Burk, PharmD

Appendix I. Summary of Acquired Methemoglobin Cases Associated with Topical Anesthetics

Pt. Characteristics	Implicated Drug	Dose	Concomitant meds	Type of Procedure	Outcome	MHb level
83 y/o male; alzheimer's, thyroid adenoma	benzocaine 200mg/5mL (4%)	3x1sec spray (600mg)	4mL 5% cocaine, 1mL 4% lidocaine; anesthesia w/ fentanyl, midazolam, vecuronim, thiopental, nitrous oxide	intubation	prolonged hospitalization w/ slow neurologic recovery due to hypoxic injury.	54.10%
67 y/o male w/ lung mass	20% benzocaine	2 sprays	viscous lidocaine	fiberoptic bronchoscopy	uneventful after second bronch next day w/ 4% lido	35.40%
66 y/o male h/o CAD, lung carcinoma and necrotizing pneumonia	20% benzocaine	2 sprays	viscous lidocaine	fiberoptic bronchoscopy	normalized	
77 y/o female h/o HTN, CHF, COPD admitted for pneumonia and resp. failure	Cetacaine twice (2nd time 10 days later)	2 sprays	cefuroxime, albuterol, nifedipine, NTG oint previously on, cimetidine, heparin	naso/orotracheal intubations	recovered 1st time w/ methylene blue; recovered 2nd time spont. w/o methylene blue;	39.2%, 23.6% 2nd time
77 y/o male s/p hernia repair w/ atelectasis of LLL	Cetacaine	"Liberal" prep	meperidine, atropine, gentamicin, diazepam, KCl, aspirin, bisacodyl	bronchoscopy	recovered	4.45
80 y/o female	Cetacaine	"Usual" amt	KCl, meperidine, atropine	oro/endotracheal intubation for laparotomy	cyanotic for 21hrs b/f tx w/ methylene blue; irreversible shock & died	2.52
previously healthy 36 y/o male s/p syncope w/ abnorm mental status and cyanotic nails; smoker	Anbesol	"entire bottle"	acetaminophen, oxycodone, Nyquil®	none	recovered and d/c's home	46%
59 y/o female h/o CHF, bronchial asthma, peptic esophagitis w/ stricture s/p bowel resection, hysterectomy, cholecyst.	benzocaine 20%	gargled 30mL, portion swallowed X2 (total 12g)	furosemide, digoxin, cimetidine, isosorbide dinitrate, prednisone, quinidine, NTG oint.	esophagogastroduodenoscopy	recovered	67%
77 y/o female h/o CHF, pulm edema, mitral valve prolapse, NIDDM, HTN, cholecystect.	20% benzocaine	1-sec spray	digoxin, lisinopril, indapamide; gentamicin vancomycin, meperidine, midazolam	cholangiopancreatogram	recovered	32% after 1st methylene blue 50mg
24 y/o male h/o 10 operations to correct deformities from gunshot wound to face; h/o drug and EtoH abuse, and psych illness	20% benzocaine	not stated	imipramine, disulfiram, thiothixene; Inovar, cocaine 4% 3mL		recovered	
78 y/o male w/ fever/chills s/p ruptured appendix and abdominal abscess complicated by post-op sepsis and resp failure; h/o valve replacement, CAD, A-fib, HTN, COPD	Cetacaine	unclear	warfarin, atenolol, furosemide, inhaled albuterol/ipratropium; midazolam	TEE to r/o bacterial endocarditis	recovered	51%

70 y/o female h/o idiopathic neutropenia	xylocaine	not stated	Midazolam, meperidine	endoscopy	recovered	46%
71 y/o male s/p upper lobectomy	20% benzocaine	not stated	Midazolam	bronchoscopy	recovered	19.40%
36 y/o male h/o refactory AML	20% benzocaine	2-3 sprays on 2 occasions	acetaminophen	orogastric intubation	died of his illness	40%
73 y/o male h/o adv esophageal adenocarcinoma, CRF,	20% benzocaine	4 sprays		endoscopy	recovered	48.50%
26 y/o female	benzocaine	not stated	Meperidine, midazolam	esophagogastroduodenoscopy	recovered	23.60%
68 y/o male	20% benzocaine	not stated	Midazolam, fentanyl	TEE	recovered	31%
59 y/o female	20% benzocaine	not stated	Midazolam, fentanyl	TEE	recovered	29%
72 y/o male h/o HTN, CAD, s/p repair of thoracoabdominal arotic pseudoaneurysm	20% benzocaine	not stated		TEE	recovered	41.80%
65 y/o male s/p aortic valve replacement/ h/o atrial flutter	20% benzocaine	not stated	Furosemide, diltiazem	TEE	recovered	37.00%
23-mth female	OTC anesthetic	ingested			recovered	55.20%
56 y/o female	benzocaine spray	not stated	Midazolam,succinylcholine	intubation	recovered	33%
76 y/o female h/o RA, instability of cervical spine, s/p replacement of arthroplasties	20% benzocaine	4 sprays, 1-2 sec each		fiberoptic intubation	recovered	24%
69 y/o female (175 lb); h/o IHD, post bypass surgery, HTN, postmenopausal hyperlipidemia, type 2 DM, obesity, and symptomatic A-fib.	20% benzocaine	not stated		TEE	recovered	41.10%
73 y/o female	benzocaine spray	not stated		intubation	recovered	43.70%
40 y/o male h/o lung transplant admitted for respiratory distress w/ development of pneumonia	20% benzocaine	2-3 sprays		intubation	recovered	51.20%
Missing	benzocaine spray	not stated		endoscopy	recovered	45.00%
Missing	benzocaine spray	not stated		endoscopy	recovered	38.00%
Pt. h/o congenital MHb	lidocaine IV	1mg/kg IV		intubation	recovered	19.40%

Missing	2% lidocaine	10mL	SMX/TMP	bronchoscopy	recovered	14.00%
Missing	2% lidocaine and 4% spray	15mL swallowed; 3 sprays	Midazolam, meperidine	esophagogastroduodenoscopy	recovered	37.00%
Missing	2% lidocaine	15mL swallowed; 2 sprays	Isosorbide mononitrate; midazolam, meperidine	TEE	recovered	25.30%
68 y/o male admitted for possible stroke, h/o MI, partial colectomy	20% benzocaine	4 sprays, 2 sec each	Disulfiram	TEE	recovered	47.20%
52 y/o male admitted for increasing dyspnea	20% benzocaine	not stated		TEE	cardiac arrest and died	51.00%
64 y/o male h/o CAD and aortic stenosis referred for bypass grafting and aortic valve replacement	20% benzocaine; 10% lidocaine	1-2 sprays, 1-2 sec each; 3-4 metered sprays	Midazolam	TEE	recovered	45.00%

APPENDIX II. AGENTS ASSOCIATED WITH METHEMOGLOBINEMIA

TABLE A

Drugs or toxins that cause MHb			
Nitrates/nitrites	Local Anesthetics	Chlorates	Hydroxylamine
Amyl nitrate	Benzocaine	Chloroquine	Metoclopramide
Sodium nitrite	Prilocaine	Chromates	Methylene blue
Nitroglycerin	Lidocaine	Clofazimine	Naphthalene
Nitroprusside	Acetanilide	Dimethyl sulfoxide	Paraquat
Silver Nitrate	Aminobenzenes	Dinitrophenol	Phenacetin
Nitrofuran	Dapsone	Exhaust fumes	Phenazopyridine HCl
Nitric Oxide	Alloxan	Sodium Valproate	Phenol
Nitrobenzenes	Anilin (dyes, ink)	Smoke inhalation	Phenytoin
Phenacetin	Arsine	Sulfasalazine	Rifampin
Pyridium	Bivalent copper	Trinitrotoluene	Silver Nitrate
Primaquine	Bismuth subnitrate	Ferricyanide	Sulfamethoxazole
Resorcinol	Bupivacaine HCl	Flutamide	Sulfonamides

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