

APPENDIX IV

Appendix IV

**Methemoglobinemia and Topical Benzocaine Use
Review and Expert Opinion by: Elliot V. Hersh, DMD, MS, PhD**

METHEMOGLOBINEMIA and TOPICAL BENZOCAINE USE

Review and Expert Opinion by: Elliot V Hersh DMD, MS, PhD
Professor Pharmacology
Associate Dean Clinical Research
University of Pennsylvania – School of Dental Medicine

Conclusion

Based on a review of the literature it is extremely unlikely that the current labeling of 20% benzocaine products for “adults and children 2 years of age and older for the temporary relief of toothache pain” could cause clinically significant methemoglobinemia.

Clinical Aspects of Methemoglobinemia

Acquired methemoglobinemia is considered an exceedingly rare event caused by the excessive oxidation of the ferrous (Fe⁺⁺) or reduced form of hemoglobin to the ferric (Fe⁺⁺⁺) or methemoglobin species.¹⁻⁴ The reduced form of hemoglobin has the ability to bind oxygen, transport it, and release it into tissues.⁵ Normally, methemoglobin represents less than 1% - 2% of the total hemoglobin species. It does not bind oxygen and when present in toxic concentrations, it essentially reduces the level of functioning hemoglobin. For example with a methemoglobin level of 50%, an original hemoglobin level of 12 gm/dl would decrease to a functional hemoglobin level of only 6 gm/dl.⁶ In addition during this state, the remaining reduced ferrous hemoglobin species develop an increased affinity to oxygen and do not readily release it into tissues.⁶⁻¹⁰ Symptoms and signs vary according to blood levels of the methemoglobin species. Methemoglobin levels above 10% produce visible signs of cyanosis in the buccal mucous membranes, lips, nose, cheeks, fingers and toes.^{1,6,11,12} In addition arterial blood takes on a distinctive chocolate brown appearance that fails to change color when exposed to air.^{11,12} At concentrations below 30%, methemoglobinemia is generally well tolerated with a lack of overt respiratory distress.^{1,6,11,12} At concentrations of 30-40%, symptoms include headache, weakness, dyspnea, tachycardia and dizziness.^{1,10,11} Methemoglobin concentrations above 50% are associated with lethargy, confusion, cardiac arrhythmias, and depression of consciousness followed by seizures.^{1,10-12} Death may occur at concentrations exceeding 70%.^{1,6,12} Intravenous methylene blue, a reducing agent is the treatment of choice for treating methemoglobin levels above 30%.¹⁻¹² While a few individuals (most often found in the Alaskan Eskimo, Navajo Indian and Siberian Yakutsk populations) possess a genetic deficiency in the enzyme nicotinamide adenine dinucleotide dependent methemoglobin reductase (NADH cytochrome b5 reductase),^{1,6} which continuously reduces methemoglobin to hemoglobin, most cases of methemoglobinemia are in fact drug-induced in individuals without this deficiency.

The table below lists various drugs and chemicals with the greatest risk of inducing methemoglobinemia.^{1,10,12} All of these drugs and chemicals share a common property; they can produce a dose-dependent oxidation of hemoglobin directly or through their metabolites. Two local anesthetic agents appear on this table, namely prilocaine and benzocaine.

GENERIC NAME	COMMON TRADE NAMES
Aniline	Various dyes and inks
Benzocaine	Americaine, Hurricaine
Ciprofloxacin	Cipro
Dapsone	Dapsone UPS
Flutamide	Eulexin
Metoclopramide	Reglan
Nitric Oxide	-----
Nitrates and nitrites	Nitrostat, Nitro-Dur, Isordil
Phenazopyridine	Urobiotic, Pyridium
Phenelzine	Nardil
Phenobarbital	Various generics
Prilocaine	Citanest
Quinine	Various generics
Resorcinol	Bensulfoid Cream
Trimethoprim/sulfamethoxazole	Bactrim

Benzocaine-induced Methemoglobinemia

Since first described by Bernstein in 1950,¹³ more than 60 cases of benzocaine-induced methemoglobinemia have been reported in the literature.⁵ It has been estimated that a threshold dose of 15 mg/kg benzocaine absorbed directly from mucous membranes, pulmonary membranes, abraded skin or ingested are necessary to produce overt cyanosis in most individuals.^{4,12} The table below summarizes the minimal dose of benzocaine required to produce clinically visible methemoglobinemia in individuals of varying body weights.

BODY WEIGHT (kg)	BODY WEIGHT (lbs)	Benzocaine Dose (mg)
25	55	375
50	110	750
70	150	1050

Methemoglobinemia Associated with Oral Health Care Products

Accidental ingestion by neonates and young children, or absorption from open wounds or mucous membranes account for several published reports of this phenomenon.^{5, 11, 14-17} In one such case it was estimated that 3300 mg of a 7.5% benzocaine gel (total benzocaine dose of 250 mg) had been applied intraorally to a 14 month old teething infant resulting in a methemoglobin level of 33%.¹⁶ This translated into a weight based dose of 25 mg/kg. While the child was markedly cyanotic, there was no evidence of respiratory distress. The child received 100% oxygen by mask for 3 hours and ascorbic acid 100 mg by mouth. Within 12 hours the child was clinically free of all signs of cyanosis and was discharged from the hospital a day later. Another case involved the accidental ingestion by a 2 ½ year old of approximately 560 mg or 40 mg/kg of benzocaine (7500 mg of a 7.5% gel).¹⁷ The child was markedly cyanotic with a quantitative methemoglobin level of 59%. Intravenous methylene blue 10 mg was administered due a methemoglobin level well over 30%, accompanied by oxygen. Within 8 minutes the cyanosis had visibly faded with methemoglobin levels being

reduced to 4.4% within 6 hours of methylene blue administration. Both of these reports describe benzocaine exposures significantly greater than the 15 mg/kg threshold reported to produce methemoglobinemia.^{4,12} One other case occurred in the out-patient hospital environment where oral and maxillofacial surgeons applied excessive amounts of 20% benzocaine to the oral mucous membranes of a 5 ½ year old, to facilitate the removal of maxillary and mandibular arch bars.¹⁵ The child was administered 20 mg of intravenous methylene blue and the cyanosis resolved within 15 minutes.

Over-the-counter benzocaine preparations in the form of gels and liquids have been widely used for the temporary relief of toothache pain for almost 80 years.¹⁸ However even with this wide spread use, only one case of benzocaine-induced methemoglobinemia has been reported in this patient population.¹⁹ The patient claimed to have used "the entire bottle of Anbesol" several hours before presenting to the emergency room due to a syncopial episode. Since the Regular Strength formulation of this product contains 10% benzocaine and the total volume of the bottle is 9 ml, total benzocaine exposure was 900 mg, resulting in a methemoglobin concentration of 46%. He was promptly treated with intravenous methylene blue and was discharged home the next day.

From the cases discussed above, it appears that the occurrence of methemoglobinemia due to benzocaine administration is typically due to an acute overdose of the drug.

Methemoglobinemia Associated with Other Benzocaine-containing Products

In reviewing the cases of benzocaine induced methemoglobinemia that appear in the literature, procedures involving the application of benzocaine via a spray for intubations, endoscopies, bronchoscopies and transesophageal echocardiography represent the vast preponderance of the cases.^{2-7, 9, 12, 13, 20-24} Estimated benzocaine dispersion rates can range from 200 – 295 mg/sec.⁷ In addition, these reports typically involve patients of advanced age and/or serious preexisting medical conditions. The table below summarizes some of these cases.

Age	Sex	Procedure	Concomitant Medical Conditions	Estimated Benzocaine Dose	Methemoglobin Level	Ref.
68	M	TEE	Cardiac arrhythmias	Unknown	31%	2
59	F	TEE	Atrial fibrillation, fever, dyspnea, renal transplant	Unknown	29%	2
71	F	Bronch	Severe anemia, esophageal ulcers, pulmonary infection	400 mg	23%	3
76	F	Intub	Rheumatoid arthritis	800 – 1600 mg	24%	4
76	F	Intub	Pneumonia, respiratory distress	Unknown	33%	5

65	M	Intub	Rheumatoid arthritis, peptic ulcer, spinal cord compression, dyspnea	600 mg	55%	6
71	M	TEE	Recent knee amputee, cardiac valvular sclerosis	Unknown	50%	7
65	M	TEE	TIA	Unknown	44%	7
50	M	Bronch	Lung cancer, lobectomy, mucus plug	Unknown	32%	7
51	M	Endos	Morbid obesity, gallstone	Unknown	Unknown	7
24	M	Intub	Drug/alcohol abuse, tracheal stoma	600 mg	23%	9
83	M	Intub	Alzheimer's, thyroid tumor	600 mg	54%	12
77	M	Bronch	Atelectasis	"Liberal"	51%	20
80	F	Bronch	Ischemic bowel	"Usual amount"	21%	20
41	M	Endos	GI bleeding, hereditary MetHb reductase deficient	1600	75%	21
52	M	Intub	Oral cancer, alcoholic, seizures, previous MI	160 mg*	26%	22
73	M	Endos	Esophageal carcinoma, chronic renal failure	800 mg	49%	23

61	M	Bronch	Oral cancer, lung cancer	> 1020 mg*	55%	24
----	---	--------	--------------------------	------------	-----	----

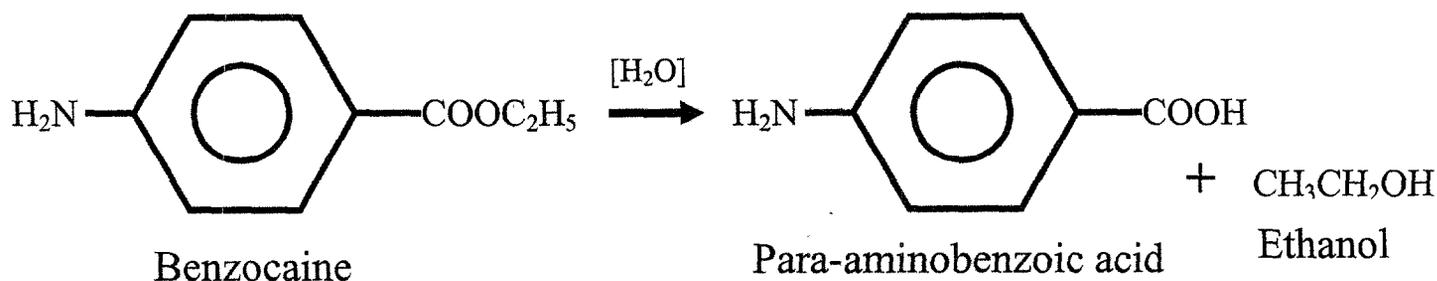
TEE = transesophageal echocardiography, Bronch = bronchoscopy, Endos = endoscopy, Intub = intubation, TIA = transient ischemic attack.

* Includes estimated butylaminobenzoate dose

Intubation, endoscopy, bronchoscopy and transesophageal echocardiography procedures account for the greatest number of cases because the doses that are employed are relatively high (each one-second spray of a 20% solution delivers approximately 200 mg of benzocaine), a large amount of the drug is absorbed from both the respiratory tree and the gastrointestinal tract, and many of these patients are of advanced age with serious concomitant medical conditions. In fact, following bronchoscopy procedures, the estimated incidence of methemoglobinemia after topical anesthesia is 1/7000 patients.¹ Uptake of local anesthetics from the tracheal mucosa is almost as rapid as intravenous administration.²⁵ The elderly and patients suffering from anemia and advanced cardiopulmonary diseases are more likely to develop methemoglobinemia when given high doses of oxidizing drugs.¹⁰ The increased susceptibility in the elderly is believed to be due to less efficient nicotinamide adenine dinucleotide phosphate methemoglobin reductase, delaying the conversion of methemoglobin back to the native non-oxidized species.⁷ In the one case where an adult patient received only 160 mg of benzocaine,²² excessive benzocaine absorption probably occurred due to the presence of a squamous cell carcinoma in the retromolar trigone region. The contributing factors of advanced age, poor overall health and drug overdose are further supported by the fact that in a study of 91 relatively healthy individuals age 20-81 years, a two-second spray of 20% benzocaine (approximate dose of 400 mg) did not produce clinically significant elevations or symptoms of methemoglobinemia in any of the subjects.⁸

Pharmacokinetics

The popularity of benzocaine as an intraoral topical anesthetic is a result of its limited systemic absorption following its application to mucous membranes.²⁶ Any drug that reaches the systemic circulation would be rapidly hydrolyzed by plasma esterases.²⁷



While direct pharmacokinetic studies of benzocaine in man are lacking, the related injectable ester procaine, is reported to have a plasma half-life of one minute or less.²⁷ It is possible that the para-aminobenzoic acid metabolite or a minor aniline metabolite contribute to the production of methemoglobinemia during a toxic overdose of benzocaine.⁸ The half-life of methemoglobin has been reported to be approximately 55

minutes in man.²⁸ Therefore if a patient self-medicating for toothache were to apply a supra-therapeutic dose of benzocaine and developed a sub-clinically evident, yet elevated methemoglobin level of 4%, within 2 hours of application the methemoglobin levels would be down to 1% which would be considered in the normal range. It is thus extremely unlikely that the current labeling of 20% benzocaine products for “adults and children 2 years of age and older: apply to the affected area up to 4 times daily or as directed by a doctor/dentist” could cause clinically significant methemoglobinemia. The dearth of case reports in toothache patients compared to other medical uses of benzocaine supports this assumption. Therapeutic dosing of up to 8 times per day would still be well within the margin of safety.

REFERENCES

1. Hall DL, Moses MK, Weaver JM, Yanich JP, Voyles JW, Reed DN. Dental anesthesia management of methemoglobinemia-susceptible patients: A case report and review of literature. *Anesth Prog* 2004;51:24-27.
2. Aepfelbacher FC, Breen P, Manning WJ. Methemoglobinemia and topical pharyngeal anesthesia. *N Engl J Med* 2003;348:85-86.
3. Nguyen ST, Cabrales RE, Bashour CA, Rosenberger TE, Michener JA, Yared J-P, Starr NJ. Benzocaine-induced methemoglobinemia. *Anesth Analg* 2000;90:369-371.
4. Ellis FD, Seiler JG, Palmore MM. Methemoglobinemia: A complication after fiberoptic orotracheal intubation with benzocaine spray. A case report. *J Bone Joint Surg Am* 1995;77:937-939.
5. Carlson G, Negri E, McGrew A, Plasier B. Two cases of methemoglobinemia from the use of topical anesthetics. *J Emerg Nurs* 2003;29:106-108.
6. Udech C, Bittikofer J, Sum-Ping STJ. Severe methemoglobinemia on reexposure to benzocaine. *J Clin Anesth* 2001;13:128-130.
7. Gupta PM, Lala DS, Arsura EL. Benzocaine-induced methemoglobinemia. *South Med J* 2000; 93:83-86.
8. Guertler AT, Pearce WA. A prospective evaluation of benzocaine-associated methemoglobinemia in human beings. *Ann Emerg Med* 1994;24:626-630.
9. Spielman FJ, Anderson JA, Terry WC. Benzocaine-induced methemoglobinemia during general anesthesia. *J Oral Maxillofac Surg* 1984;42:740-743.
10. Wilburn-Goo D, Lloyd LM. When patients become cyanotic: Acquired methemoglobinemia. *JADA* 1999;130:826-831.
11. Tush GM, Kuhn RJ. Methemoglobinemia induced by an over-the-counter medication. *Ann Pharmacother* 1996;30:1251-1254.
12. Rodriguez LF, Smolik LM, Zbehlik AJ. Benzocaine-induced methemoglobinemia: Report of a severe reaction and review of the literature. *Ann Pharmacother* 1994;28:643-649.
13. Bernstein BM. Cyanosis following use of anesthesin (ethylaminobenzoate). *Rev Gastroenterol* 1950; 17:123-124.
14. Adachi T, Fukumoto M, Uetsuki N, Yasui O, Hayashi M. Suspected severe methemoglobinemia caused by topical application of an ointment containing benzocaine around the enterostomy. *Anesth Analg* 1999;88:1190-1191
15. Klein SL, Nustad RA, Feinberg SE, Fonseca RJ. Acute toxic methemoglobinemia cause by a topical anesthetic. *Pediatr Dent* 1983;5:107-108.
16. Townes PL, Geertsma MA, White MR. Benzocaine-induced methemoglobinemia. *Am J Dis Child* 1977; 131:697-698.
17. Potter JL, Hillman JV. Benzocaine-induced methemoglobinemia. *J Am Coll Emerg Phys* 1979;8:26-27.
18. Hersh EV, DeRossi SS, Ciarrocca KN, Secreto SA, Ghassemi A. Efficacy and tolerability of an intraoral benzocaine patch in the relief of spontaneous toothache pain. *J Clin Dent* 2003;14:1-6.
19. Gilman CS, Veser FH, Randall D. Methemoglobinemia from a topical oral anesthetic. *Acad Emerg Med* 1997;4:1011-1013.

20. Douglas WW, Fairbanks VF. Methemoglobinemia induced by a topical anesthetic spray (Cetacaine). *Chest* 1977;71:587-591.
21. Collins JF. Methemoglobinemia as a complication of 20% benzocaine spray for endoscopy. *Gastroenterol* 1990;98:211-213.
22. Anderson ST, Hajduczek J, Barker SJ. Benzocaine-induced methemoglobinemia in an adult: accuracy of pulse oximetry with methemoglobinemia. *Anesth Analg* 1988;67:1099-1101.
23. Linares LA, Peretz TY, Chin J. Methemoglobinemia induced by topical anesthetic (benzocaine). *Radiother Oncol* 1990;18:267-269.
24. Vessely MB, Zitsch RP. Topical anesthetic-induced methemoglobinemia: A case report and review of the literature. *Otolaryngol Head Neck Surg* 1993;108:763-767.
25. Malamed SF. *Handbook of Local Anesthesia*. Ed 4, Mosby, St Louis, 1997, p 25.
26. Yagiela JA. Local Anesthetics. In *Pharmacology and Therapeutics for Dentistry*, Yagiela JA, Neidle EA, Dowd FJ eds. Ed 4, Mosby, St Louis, 1998, pp 217-234.
27. Yagiela JA. Pharmacokinetics: the absorption, distribution, and fate of drugs. In *Pharmacology and Therapeutics for Dentistry*, Yagiela JA, Neidle EA, Dowd FJ eds. Ed 4, Mosby, St Louis, 1998, pp 15-41.
28. Coleman MD, Coleman NA. Drug induced methemoglobinemia-treatment issues. *Drug Saf* 1996; 14:394-405.