European Review for Medical and Pharmacological Sciences 2017; 21: 4930-4934

Drug-related oral malodour (halitosis): a literature review

M. TORSTEN, G. GÓMEZ-MORENO, A. AGUILAR-SALVATIERRA

Pharmacological Research in Dentistry Group, Faculty of Dentistry, University of Granada, Granada, Spain

Abstract. **Dry mouth (xerostomia), is a fairly common, well-researched condition, which is an indirect cause of oral malodour. This systematic literature review looked into another cause of bad breath: adverse drug reactions in the orofacial region causing halitosis. The study focused on extraoral halitosis, and its subdivisions, particularly blood borne halitosis in which malodourous compounds in the blood stream are carried to the lungs, passively diffused across the pulmonary alveolar membrane to enter the breath. An electronic search was conducted in various databases. Inclusion criteria were: editorials, case control studies, retrospective studies and randomized double-blind studies published in English between 1983 and March 2017. The search identified a total of 23 articles. According to these, drug-related halitosis may be caused by nine medications. Dimethyl sulfoxide, cysteamine and suplatast tosilate are metabolised to dimethyl sulfide, a malodourous compound that is stable in blood and is transported into the breath. Disulfiram is reduced to carbon disulfide, also a stable compound in blood. Nitric oxide reacts with foul-smelling volatile organosulfur compounds. The degradation of penicillamine raises the pH level, favouring the growth of gram-negative bacteria in the oral cavity producing halitosis. Chloral hydrate, phenothiazine, and paraldehyde could not be related to halitosis. The analysis showed that halitosis can be caused by medication but does not correlate to any specific disease or specific form of drug therapy. The pharmacological compounds identified as causes of halitosis are administered to treat a broad spectrum of diseases, or in therapeutic regimes.**

Key Words
Halitosis, Oral malodour, Drugs, Blood-borne halitosis, Pharmacological compounds.

Introduction

Post-industrial societies in the 21st century aspire to ideal lifestyles and maximum personal appeal. In this context, bad breath constitutes a source of anxiety among a large sector of the population. Halitosis is an oral health condition in which the sufferer consistently emits odourous breath. The range of terms used in scientific literature – *halitosis, bad or foul breath*, *oral malodour*, *fetor ex ore*, *fetor oris* – all describe unpleasant breath exhaled from the sufferer's mouth, although the source of malodourous substances may be oral or non-oral[1,2]. This may be caused by a range of factors including the use of certain medications, poor oral hygiene, decreased salivary flow rate, certain foods, frequent alcohol ingestion, smoking, and/or systemic medical conditions[3,4].

Adverse drug reactions in the orofacial region can cause dry mouth (xerostomia), an indirect cause of oral malodour. Other drugs can be a direct cause of halitosis[5].

Halitosis – Short overview

The International Society for Breath Odor Research (ISBOR) has established a simple means of classifying halitosis based on its origins. This system serves as the global standard for classifying halitosis[6]. Halitosis can be classified into three main categories: genuine halitosis, pseudo-halitosis, and halitophobia.

In genuine halitosis, the patient presents obvious oral malodour with an intensity beyond socially acceptable levels. This is subdivided into pathological halitosis (of intra- and extra-oral origin) and physiological halitosis in which malodour originates from sources within the oral cavity and is not associated with a pathologic condition or with a specific disease. Temporary halitosis, due to dietary factors, can be excluded from definitions of genuine halitosis[2].

Some patients are mistakenly convinced that they present oral malodour; in this case, the patient is diagnosed as having pseudo-halitosis. If, after treating a case of genuine or pseudo-halito-

Corresponding Author: Gerardo Gómez-Moreno, DDS, Ph.D, MS; e-mail: ggomez@ugr.es

sis, the patient still believes that he/she has halitosis, this is diagnosed as halitophobia.

Intra-oral Halitosis

Up to 80% of malodour originates from sources within the oral cavity[1,3] and is associated with poor oral hygiene, dental plaque, dental caries, gingivitis, stomatitis, periodontitis, tongue coating, oral carcinoma, and/or xerostomia[1].

Normal saliva has a pH of approximately 6.5; this acidic pH suppresses the growth and proliferation of the anaerobic Gram-negative oral microorganisms responsible for bad breath. An alkaline pH favours Gram-negative bacteria that allow the activation of the enzymes required for putrefaction of the sulphur-containing amino acids cysteine and methionine to foul-smelling volatile sulfur compounds (VSCs) hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH) and dimethyl sulfide (CH_3SCH_3)[1-3] (Table I).

These gram-negative bacteria species include *Bacteroides loescheii, Centipeda periodontii, Eikenella corrodens, Enterobacteriaceae, Fusobacterium nucleatum*, *Porphyromonas endodontalis, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythensi* and *Treponema denticola*[4]. Oral malodour derives from multiplex interactions between several oral bacterial species. These bacterial interactions are most likely to occur in the gingival sulcus and periodontal pockets. Bad breath can also arise from the posterior dorsal tongue area. Because of its large and papillary surface area, the deep crypts at the base of the tongue can retain large amounts of microorganisms[3,4].

Bad breath does not always originate from organosulfur compounds. Other malodourous molecules produced by saliva or tongue coatings can be the cause of halitosis, including polyamines (putrescine and cadaverine), phenyl compounds (indole, skatole, and pyridine), and nitrogen-containing compounds (urea and ammonia)[6].

Extra-oral Halitosis

An estimated 10-20% of halitosis has non-oral causes. Many cases of extra-oral halitosis are a manifestation of a systemic disease and cannot be treated successfully[1]. Cases of acetone breath are mainly with a biomarker of type 1 diabetes[7], while kidney failure and uremia result in an odor of ammonia in urine. A fresh cadaver smell is characteristic of severe hepatic failure leading to *fetor hepaticus*. The breath of patients with rheumatic fever is described as an acid sweet breath, while patients with lung abscess present a smell of rotting meat. Other diseases and conditions causing bad breath are toxemia, gastrointestinal disorders such as hemorrhage and indigestion, vitamin C deficiency, anaerobic infections, ulcerations, and/or cancer located in the upper/lower respiratory tract[8].

Certain medications are potential sources of blood-borne halitosis, in which malodourous compounds in the blood stream are carried to the lungs and enter the breath.

Materials and Methods

A systematic electronic search was performed in the PubMed database and Wiley Online Library. The search strategy was adapted to suit each database, applying key search terms alone or in combination: halitosis, oral malodour, bad breath, odor, adverse drug reaction, drugs and medication. Secondary data from publications identified were also evaluated.

Inclusion criteria were as follows:

- Articles published in English between 1983 and March 2017;
- Articles with adequate documentation and relevant information about halitosis including editorials, case control studies, retrospective studies and randomized double-blind studies.

Exclusion criteria were:

- Articles published before 1983;
- Studies published in a language other than English.

The titles and abstracts identified that were considered reliable were carefully reviewed to select the most relevant studies for inclusion in the review.

Table I. Pharmacological compounds and their odor characteristics[1].

Name	Smell
Hydrogen sulfide (H_2S)	Rotten eggs
Methyl mercaptan (CH_3SH)	Pungent
Dimethyl sulfide (CH_3SCH_3)	Unpleasant sweet
Dimethyl disulfide (CH_3SSCH_3)	Pungent
Carbon disulfide (CS_2)	Slightly pungent
Ammonia (NH_3)	Pleasantly sweet
Dimethylamine ($(CH_3)_2NH$)	Fishy, ammoniacal
Allyl mercaptan ($CH_2=CHCH_2SH$)	Garlic-like
Allyl methyl sulfide ($CH_2=CHCH_2SCH_3$)	Garlic-like

Results

The initial electronic search identified a total of 58 articles of potential interest. Of these, two articles were excluded because they were not in English, and seven articles were excluded because they were published before 1983. After reading and evaluating the full texts, 34 studies were excluded because they were not related to the generic mode of action of drugs producing halitosis. Finally, 23 articles were included in the present review and underwent a process of information extraction, making it possible to condense a large amount of relevant clinical information.

Blood Borne Halitosis

Hydrogen sulfide (H_2S) and methyl mercaptan (CH_3SH) comprise about 90% of the volatile organosulfur compounds (VSCs) found in exhaled air and constitute major contributors to the objectionable odors that are present in halitosis of intra-oral origin[6]. These breath volatile sulfur compounds are not be found in blood-borne halitosis caused by drug administration. Neutral molecules such as dimethyl sulfide (CH_3SCH_3), a minor component of intra-oral halitosis, are stable in blood, absorbed into the blood stream and later transferred to the pulmonary alveoli. Pulmonary excretion of these volatiles into the alveolar air then causes halitosis, providing the malodourous volatiles are present in the breath in sufficient concentrations to become objectionable[1,3].

Halitosis Induced by Medication

According to the results of the present literature review, the following drugs may be directly responsible for oral malodour: dimethyl sulfoxide[3,5,9,10], cysteamine[1], nitrates and nitrites (isosorbide dinitrate)[3,5,10], disulfiram[1,3,5,9,10], penicillamine (penicillin)[3], chloral hydrate[3,10], phenothiazine[3,10], suplatast tosilate[10], and paraldehyde[10].

Dimethyl Sulfoxide

A significant side-effect of dimethyl sulfoxide (DMSO) is an odor and taste in the mouth similar to garlic due to the pulmonary excretion of a small percentage of DMSO as dimethyl sulfide[11].

The volatile sulfur compounds (VSCs) methyl mercaptan (CH_3SH) and hydrogen sulfide (H_2S) contain a free thiol (-SH group), which immediately reacts with blood, resulting in irreversible binding and oxidation, thereby preventing transportation from the blood into the alveolar air and thus into the breath. But dimethyl sulfide (CH_3SCH_3), a neutral molecule that is stable in blood, is transported from the blood into alveolar air and breath. The neutral nature of most volatiles found in halitosis makes them difficult to remove from breath, unlike the very reactive thiol methyl mercaptan (CH_3SH) and hydrogen sulfide (H_2S) also found in halitosis[1,12].

Cysteamine

Cysteamine is used to treat patients with nephropathic cystinosis and can be metabolized to dimethyl sulfide (CH_3SCH_3), a malodorous compound stable in blood[13].

Nitrates and Nitrites

Nitrates are used to treat or prevent angina and the chest pain caused by heart disease. In the oral cavity, anaerobic bacteria in the deep crypts at the base of the tongue reduce nitrate to nitrite in the course of respiration. Some of this nitrite is reduced to nitric oxide (NO) in the oral cavity[14], contributing to levels of NO measured in exhaled breath; NO reacts with foul-smelling volatile organosulfur compounds[15,16].

Disulfiram

Disulfiram (Antabuse) is used in the treatment of alcohol dependence. Carbon disulfide (CS_2) is a product of the metabolism of disulfiram; it is stable in blood and can be transported from the blood into alveolar air and breath. Acetone is a product of normal metabolism and appears in the breath of all individuals, but disulfiram increases acetone levels in blood[17].

Penicillamine

Penicillamine has proved an essential drug for treating rheumatoid arthritis[18] and is a degradation product of penicillin antibiotics. It has a close structural relation to cysteine, a sulphur-containing amino acid. The microbial degradation of both cysteine and penicillamine produces hydrogen sulfide (H_2S) and sulfhydryl anion (HS^-), a strong reducing agent that decreases the redox potential within the tongue biofilm, and so raises the pH favouring the growth of Gram-negative bacteria and activating enzymes including serine protease, important in the putrefaction process. Bacterial interactions with specific substrates – amino acids such as cysteine, methionine, tryptophan, arginine, and lysine – biotransform them into odourous compounds that may cause oral malodour[3,18,19].

Chloral hydrate

Chloral hydrate is a widely used sedative agent in pediatric dentistry[20]. It is a colorless substance with a penetrating acrid odor and a slightly bitter taste[21]. Although it is cited in two articles (3, 10), they do not describe its generic mode of action that produces halitosis.

Phenothiazine

Although this drug is cited in two of the articles reviewed[3,10], they do not describe its generic mode of action that produces halitosis.

Suplatast Tosilate

Suplatast tosilate is an anti-allergic agent that suppresses cytokine production. Dimethyl sulfide (CH_3SCH_3), metabolized from suplatast tosilate, is a potential cause of halitosis due to the volatile (CH_3SCH_3) dissolved into the blood and exhaled through alveolar gas exchange[22].

Paraldehyde

Paraldehyde is administered intravenously for the emergency treatment of epilepsy. It is a colorless liquid with a pungent odor and a disagreeable taste[23]. Although it is cited in one article reviewed[10], its generic mode of action producing halitosis has not been described.

Conclusions

The present literature review only evaluated articles from journals with high impact factors. Analysis of the information drawn from the articles clearly showed that drug-related halitosis can be caused by medications even though they do not correlate to any specific disease or to any specific form of drug therapy. The pharmacological compounds identified in the review as associated with medication-induced halitosis are applied in a broad spectrum of diseases or therapeutic regimens. Dimethyl sulfoxide, cysteamine, and suplatast tosilate are metabolized to dimethyl sulfide (CH3SCH3), a malodourous compound stable in the blood which is transported from the blood into alveolar air and breath. Disulfiram is reduced to carbon disulfide (CS2), also a compound stable in blood. Nitric oxide reacts with the foul-smelling volatile organosulfur compounds, contributing to levels of nitric oxide measured in exhaled breath. The degradation of penicillamine raises the pH favouring the growth of Gram-negative bacteria in the oral cavity producing halitosis.

This review was limited by the fact that although the drugs chloral hydrate, phenothiazine, and paraldehyde were mentioned in several articles, their action was not described. Moreover, to date, only a small number of articles have been published on the topic of medication-induced halitosis.

Nevertheless, this review provides relevant clinical information, which could be used to monitor patients' medication history, and so avoid those drugs that act directly to cause halitosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Tangerman A. Halitosis in medicine: a review. Int Dent J 2002; 52: 201-206.
2) Murata T, Yamaga T, Iida T, Miyazaki H, Yaegaki K. Classification and examination of halitosis. Int Dent J 2002; 52: 181-186.
3) Scully C, Greenman J. Halitology (breath odour: aetiopathogenesis and management). Oral Dis 2012; 18: 333-345.
4) Cortelli JR, Barbosa MD, Westphal MA. Halitosis: a review of associated factors and therapeutic approach. Braz Oral Res 2008; 22: 44-54.
5) Scully C, Bagan JV. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med 2004; 15: 221-239.
6) Loesche WJ, Kazor C. Microbiology and treatment of halitosis. Periodontol 2000 2002; 28: 256-279.
7) Rydosz A. A Negative Correlation Between Blood Glucose and Acetone Measured in Healthy and Type 1 Diabetes Mellitus Patient Breath. J Diabetes Sci Technol 2015; 9: 881-884.
8) Scully C, el-Maaytah M, Porter SR, Greenman J. Breath odor: etiopathogenesis, assessment and management. Eur J Oral Sci 1997; 105: 287-293.
9) Tack DA, Rogers ES. Oral drug reactions. Dermatol Therap 2002; 15: 236-250.
10) Aylikci BU, Colak H. Halitosis: From diagnosis to management. J Nat Sci Biol Med 2013; 4: 14-23.
11) Santos NC, Figueira-Coelho J, Martins-Silva J, Saldanha C. Multidisciplinary utilization of dimethyl sulfoxide: pharmacological, cellular, and molecular aspects. Biochem Pharmacol 2003; 65: 1035-1041.
12) Zheng Y, Yu B, De La Cruz LK, Roy Choudhury M, Anifowose A, Wang B. Toward Hydrogen Sulfide Based Therapeutics: Critical Drug Delivery and Developability Issues. Med Res Rev 2017. doi: 10.1002/med.21433.
13) Dohil R, Rioux P. Pharmacokinetic studies of cysteamine bitartrate delayed-release. Clin Pharmacol Drug Dev 2013; 2: 178-185.

14) Marteus H, Törnberg DC, Weitzberg E, Schedin U, Alving K. Origin of nitrite and nitrate in nasal and exhaled breath condensate and relation to nitric oxide formation. Thorax 2005; 60: 219-225.

15) Mochalski P, Unterkofler K, Španěl P, Smith D, Amann A. Product ion distributions for the reactions of NO(+) with some physiologically significant volatile organosulfur and organoselenium compounds obtained using a selective reagent ionization time-of-flight mass spectrometer. Rapid Commun Mass Spectrom 2014; 28: 1683-1690.

16) Whittle CL, Fakharzadeh S, Eades J, Preti G. Human breath odors and their use in diagnosis. Ann N Y Acad Sci 2007; 1098: 252-266.

17) Bloor RN, Španěl P, Smith D. Quantification of breath carbon disulphide and acetone following a single dose of disulfiram (Antabuse) using selected ion flow tube mass spectrometry (SIFT-MS). Addict Biol 2006; 11: 163-169.

18) Muijsers AO, van de Stadt RJ, Henrichs AM, Ament HJ, van der Korst JK. D-penicillamine in patients with rheumatoid arthritis. Serum levels, pharmacokinetic aspects, and correlation with clinical course and side effects. Arthritis Rheum 1984; 27: 1362-1369.

19) Sissons CH, Yakub S. Suppression of urease levels in Streptococcus salivarius by cysteine, related compounds and by sulfide. Oral Microbiol Immunol 2000; 15: 317-324.

20) Hosey MT; UK National Clinical Guidelines in Pediatric Dentistry. UK National Clinical Guidelines in Paediatric Dentistry. Managing anxious children: the use of conscious sedation in paediatric dentistry. Int J Paediatr Dent 2002; 12: 359-372.

21) Wang C, Shi J, Sun B, Liu D, Li P, Gong Y, He Y, Liu S, Xu G, Li J, Luo A, Li E. Breath pentane as a potential biomarker for survival in hepatic ischemia and reperfusion injury--a pilot study. PLoS One 2012; 7: e44940.

22) Murata T, Fujiyama Y, Yamaga T, Miyazaki H. Breath malodor in an asthmatic patient caused by side-effects of medication: a case report and review of the literature. Oral Dis 2003; 9: 273-276.

23) Bruni J. Treatment of status epilepticus in adults. Can Med Assoc J 1983; 128: 531-533.