



REVIEW ARTICLE

Oral adverse reactions due to cinnamon-flavoured chewing gums consumption

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Cinnamon-flavoured products (toothpaste, chewing gum, food, candy and mouthwash) can cause oral adverse reactions; among these, the most common is contact stomatitis (cinnamon contact stomatitis, CCS). Signs and symptoms of contact allergic reactions affecting the oral mucosa can mimic other common oral disorders, making diagnosis difficult. As CCS may be more prevalent than believed and its clinical features can frequently determine misdiagnosis, we reviewed case reports and case series of oral adverse reactions due to cinnamon-containing chewing gums, emphasizing clinical aspects, diagnostic and management procedures. We also proposed an algorithm to perform a diagnosis of CCS as in the previous published literature the diagnostic approach was not based on a harmonized and shared evidence-based procedure. Moreover, as patients can refer to different specialists as dentists, dermatologists and allergists, a multidisciplinary approach is suggested.

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Introduction

Chewing gum is typically manufactured using a water-insoluble gum base blended with soluble sweeteners and flavourings. Chewing gum bases may be made of a single ingredient or of a blend of ingredients, such as elastomers, resins, emulsifiers, waxes and fillers (Imfeld, 1999). Obviously, after the use, the insoluble gum base can be discharged (Gajendran *et al*, 2008; Heema and Stuti, 2010).

Chewing gum releases substances in a slow and continuous manner, for this reason pharmaceutical companies developed products that use this dosage to orally vehicle drugs, in addition to the most common tablets and capsules (Gajendran *et al*, 2008; Pagare *et al*, 2012). Chewing gums can contain active pharmaceutical ingredients (API) such as nicotine, aspirin, antihistaminics, but also vitamins, minerals, and/or food or food supplements such as cinnamon, passiflora, chamomilla (Gajendran *et al*, 2008).

Different factors can influence the oral delivery of substances contained in chewing gum, they depend on permeability and thickness of the mucosa, and eventually keratinization and composition, blood supply, blood/lymph drainage, cell renewal rate and enzyme content will also govern the rate and extent of substances absorption; also the oral pH and features of saliva can have impact. Further factors are duration and chewing rate, chewing frequency and chewing intensity, also physicochemical and solubility of ingredients released by the chewing gum (Rathbone, 1996).

Beside the well-known problems linked to the sugars and/or sweeteners contained in chewing gums, currently, there is poor information on safety issues related to chewing gum releasing foods or flavouring agents (Mayers, 2007). Among these, one of the most common flavouring agents is represented by cinnamon (*Cinnamomum verum* Presl. or *Cinnamomum zeylanicum* Blume).

The bark and essential oil of cinnamon (*Cinnamomi corticis aetheroleum*, *Cinnamomi cortex*) has a long tradition of use as flavouring agent and herbal medicine (Barnes *et al*, 2007). Cinnamon bark contains up to 4% of essential oil consisting primarily of cinnamaldehyde (60–75%), cinnamyl acetate (1–5%), eugenol (1–10%), β -caryophyllene (1–4%), linalool (1–3%) and 1,8-cineole (1–2%) (ESCOP Monographs, 2003). The dried bark possesses a characteristic and pleasantly aromatic odour and a pungently spicy and at the same time sweet taste (Bisset, 1994).

Other constituents are oligo polymeric procyanidins, cinnamic acid, phenolic acids, pentacyclic diterpenes

cinnzeylanol and its acetyl derivative cinnzeylanine and the sugars mannitol, L-arabino-D-xylanose, L-arabinose, D-xylose, α -D-glucan as well as mucilage polysaccharides (ESCAP Monographs, 2003). Especially the insulated compounds cinnamic alcohol and cinnamaldehyde are utilized in the food industry as flavours. They are also naturally present in *Myroxylonperei* (*balsam of Peru*) and are commonly used in chewing gums as flavouring agents resembling cinnamon (Bousquet *et al*, 2005).

Cinnamon-flavoured products can cause oral hypersensitivity reactions (Scully, 2006).

This oral contact allergy is a rare condition also known as cinnamon contact stomatitis (CCS). CCS has been described as a localized adverse reaction involving oral tissues and resulting by contact with a product containing a cinnamon-flavouring agent such as toothpaste, chewing gum, food, candy and mouthwash. It is believed to represent a form of intra-oral contact allergy caused by a delayed hypersensitivity (type IV) reaction (Haring, 1993; Tosti *et al*, 1997).

Other flavouring substances, such as menthol or peppermint essential oil, contained in chewing gums and other confectionary products or tooth pastes, can cause oral contact reactions (Morton *et al*, 1995; Sainio and Kanerva, 1995). Contact stomatitis can develop also in latex sensitive subjects due to latex contained in some chewing gums (Wolf *et al*, 2006). Moreover, oral contact allergy can be caused by metals present in dental amalgam or by chlorhexidine in wash-mouth and products containing propolis (Hay and Greig, 1990; Torgerson *et al*, 2007; Raap *et al*, 2012). These other forms of contact allergy may have either a different clinical presentation than CCS. For example, metal fillings can produce a lichenoid reaction or a reaction similar to that caused by cinnamon in gums. Oral mucosa lesions, usually localized in the area of contact with substance, can appear in the form of erythema, oedema, vesicles, bullae, erosions and ulcerations (Bakula *et al*, 2011).

Signs and symptoms of contact allergic reactions affecting the oral mucosa can mimic other common oral disorders, making diagnosis difficult (De Rossi and Greenberg, 1998). As CCS may be more prevalent than believed and its clinical features can frequently determine misdiagnosis, a review of this topic is highly desirable. The present article analyses case reports on oral adverse reactions due to cinnamon-containing chewing gums, emphasizing clinical aspects, diagnostic procedures and management.

Methods

A systematic search of the scientific literature, published prior to March 2013, was independently conducted by two investigators in the databases MEDLINE, Cochrane library, EMBASE and the search engine Google Scholar. Investigators inserted in the databases the following keywords or combination of them:

- Chewing gum
- Cinnamon gum
- Cinnamon-flavoured chewing gum
- Cinnamon adverse reaction
- Cinnamic acid

Cinnamaldehyde

Clinical features

This kind of reaction was first described in 1976 (Drake and Maibach, 1976). Clinical signs and lesions appearance of CCS are variable (Table 1). At clinical examination, the lesions can appear as erythematous patches often with associated keratosis or ulceration, leukoedema-like, lichen-like and lupus-like erosions or ulcerations, leukoplakia-like patches, white plaques with verrucous surface, swelling of the cheeks and gingival exfoliation (Allen and Blozis, 1988; Bousquet *et al*, 2005; Hoskyn and Guin, 2005; Tremblay and Avon, 2008; Kind *et al*, 2010). These lesions can be observed on lips, tongue, oral and gingival mucosa; their extent can vary, and they can be localized either on a limited or a wide area in the mouth of subjects (Endo and Rees, 2006). The exposure to cinnamon-flavouring agents can cause immediate symptoms such as urticaria, and it may mimic angioedema due to the accompanying swelling (Mathias *et al*, 1980; Cohen and Bhattacharyya, 2000; Diba and Statham, 2003), and they can be accompanied by sores and complaints such as mild pain, pruritus and burning sensation; symptoms in some cases can evolve in severe discomfort (Endo and Rees, 2006).

Medical history reveals as causative factor the consumption, in many cases daily, of cinnamon-flavoured chewing gum or other cinnamon-flavoured products. Subjects suffering of CCS can have a past or present clinical history of allergic diseases, but it is not a necessary condition to develop CCS. The duration of symptoms can be variable; it ranges from weeks to more than 1 year (Allen and Blozis, 1988). In the best part of cases, as the consumption of cinnamon-flavoured chewing gum has discontinued, the lesions of the buccal mucosa disappeared completely (Tremblay and Avon, 2008). In fact, it is quite common that patients reveal to have had symptomatic episodes separated by symptom-free periods; usually they occur in correspondence of a discontinuation of cinnamon-flavoured chewing gum consumption (Bousquet *et al*, 2005; Pollock, 2006). Anaphylaxis following the cinnamon exposure rarely occurs (Kind *et al*, 2010). In some cases, patients referred smoking habits for years, but it is not possible to state a certain association between smoking and cinnamon contact stomatitis (Haring, 1993). A case of oral leukoplakia caused by prolonged exposure to cinnamon-flavoured gum has been described; the biopsy showed a squamous epithelial dysplasia of the oral mucosa. (Mihail, 1992). Moreover, Westra *et al* reported a case of squamous cell carcinoma of the tongue associated with persistent and prolonged exposure of cinnamon-flavoured chewing gum (Westra *et al*, 1998).

Interestingly, most of the reactions reported occurred in females, both in single case reports (Haring, 1993; Westra *et al*, 1998; Bousquet *et al*, 2005; Pollock, 2006; Tremblay and Avon, 2008; Georgakopoulou, 2010; Kind *et al*, 2010) and in records (Allen and Blozis, 1988; Miller *et al*, 1992; Endo and Rees, 2006), where the reported rate female: male was 8:2 (Allen and Blozis, 1988), 6:4 (Miller *et al*, 1992, 6:2 (Endo and Rees, 2006)). This finding is

Table 1 Cases of contact stomatitis induced by cinnamon-flavoured chewing gums

Reference	Gender	Age	Duration of Symptoms	Location of Lesions	Clinical features	Biopsy	Patch test	Clinical recovery after discontinuation of cinnamon chewing-gums	Re-challenge	History of atopy	Tobacco
Allen and Blozis (1988)	F	36	4 months	Buccal mucosa (R)	Erythematous lesion, keratosis and ulceration, peeling off, burning sensation (in the article these data are not associated with a particular patient)	Performed only in two cases	Performed	Full recovery	Performed in several patients with reoccurrence even in 2 h	n.r.	n.r.
	F	50	6 months	Lateral tongue (L, R);			Performed	Full recovery		n.r.	n.r.
	F	38	4 weeks	Buccal mucosa (L, R)			n.p.	Full recovery		Yes	n.r.
	F	32	3 months	Buccal mucosa (L, R)			n.p.	Full recovery		n.r.	n.r.
	M	65	2 weeks	Buccal mucosa (L)			n.p.	Full recovery		n.r.	n.r.
	F	45	10 months	Buccal mucosa			n.p.	Full recovery		Yes	n.r.
	F	49	3 months	Buccal mucosa (L, R);			n.p.	Full recovery		n.r.	n.r.
	F	66	4 weeks	Lateral tongue			n.p.	Full recovery		n.r.	n.r.
	M	56	3 weeks	Buccal mucosa			n.p.	Full recovery		n.r.	n.r.
	F	48	15 months	Buccal mucosa;			n.p.	Full recovery		n.r.	n.r.
Mihail (1992) Miller <i>et al</i> (1992)				Lateral tongue (L)							
				Floor of the mouth							
	M	n.r.	n.r.	Buccal mucosa (L)	Leukoplakic	Performed	n.p.	Full recovery	n.p.	n.r.	n.r.
	F	55	6 months	Buccal mucosa	White lichenoid plaque, pain	n.p.	Performed	Full recovery	Positivity	Yes	None
	F	37	2 months	Palatal mucosa	White plaque	n.p.	Not performed	Full recovery	n.p.	n.r.	Cigarette
	F	56	3 weeks	Buccal mucosa (L)	Lichenoid patch	n.p.	Not performed	Major in 3 years	n.p.	n.r.	n.r.
	F	62	3 months	Buccal mucosa (L)	Lichenoid ulceration	n.p.	Not performed	Full recovery	n.p.	n.r.	None
	M	34	6–8 weeks	Buccal mucosa (L, R), ventral tongue and gingiva	White lacy ulcerated	n.p.	Not performed	Full recovery	Positivity	n.r.	None
	M	62	2 months	Buccal mucosa (L, R)	Red-white lichenoid ulceration	n.p.	Not performed	Full recovery	n.p.	n.r.	Cigar cess.
	M	60	4 months	Buccal mucosa (L, R)	White fissured	n.p.	Not performed	Full recovery	n.p.	n.r.	Cigarette
	M	40	6 weeks	Buccal mucosa (R), vestibule (R)	White striated	Performed	Not performed	Full recovery	n.p.	n.r.	Cigarette cess.
			5 months	Buccal mucosa (R), vestibule (R)	Red white pain	Performed	Not performed	Full recovery	n.p.	n.r.	Cigarette
				Buccal mucosa (L, R)	White plaque peeling						None
				Buccal mucosa (R), gingiva (R)							
Haring (1993)	F	39	2 months	Buccal mucosa (R)	Erythematous white-red patches, pain	n.p.	Not performed	Full recovery	n.p.	n.r.	Cigarette cess.
Westra <i>et al</i> (1998)	F	24	2 months	Tongue (R)	Squamous cell carcinoma	Performed	Not performed	Full after surgical excision	n.p.	n.r.	None
Bousquet <i>et al</i> (2005)	F	34	18 months	Buccal mucosa, tongue	Lichen-like lesion	n.p.	Performed	Full recovery	Positivity	n.r.	n.r.

(continued)

Table 1 (continued)

Reference	Gender	Age	Duration of Symptoms	Location of Lesions	Clinical features	Biopsy	Patch test	Clinical recovery after discontinuation of cinnamon chewing-gums	Re-challenge	History of atopy	Tobacco
Endo and Rees (2006)	F	26		Gingiva	Erythema, sloughing.	Performed	Performed	Full recovery	n.p.	n.r.	n.r.
	M	38		Buccal mucosa, tongue	White lesion	Performed	n.p.	Full recovery	n.p.	n.r.	n.r.
	F	61			Erythema	n.p.	Performed	Full recovery	n.p.	n.r.	n.r.
	F	58		Buccal mucosa	White lesion	Performed	n.p.	Full recovery	n.p.	n.r.	n.r.
	M	38		Buccal mucosa, tongue	Fissured tongue, erythema	Performed	n.p.	Full recovery	n.p.	n.r.	n.r.
	F	54		Tongue, gingiva	Erythema, welling, dry lip	n.p.	n.p.	Full recovery	n.p.	n.r.	n.r.
	F	51		Lip, labial mucosa, gingiva	Lip swelling, oedema	Performed	n.p.	Full recovery	n.p.	n.r.	n.r.
	F	58		Lip, tongue	Fissured tongue, erythema, sore mouth			Full recovery	n.p.	n.r.	Cigarette cess.
Pollock (2006) Tremblay and Avon (2008) Siqueira <i>et al</i> (2009) Kind <i>et al</i> (2010)	M	n.r.	n.r.	Buccal mucosa	Burning	n.p.	n.p.	Full recovery	n.p.	n.r.	n.r.
	F	42	n.r.	Buccal mucosa (L,R)	Red erosive lesion	Performed	n.p.	Full recovery	n.p.	n.r.	Cigar
	M	53	n.r.	Buccal mucosa	n.r.	n.p.	n.p.	n.r.	n.p.	n.r.	n.r.
	F	39	6 months	Buccal mucosa (L, R), white plaque, erythematous.	Burning, pain, swelling	n.p.	n.p.	n.r.	n.p.	Yes	n.r.
				Tongue (R)	Burning, elevated mucosal patches	n.p.	n.p.	Full recovery	n.p.	n.r.	None
	F	20	n.r.								

n.r., Not reported; n.p., Not performed.

supported by analysis of records published by Endo reporting a prevalence of females (32:5) in subjects affected by contact stomatitis caused by different cinnamon-flavoured products besides chewing gum (toothpaste and foods) (Endo and Rees, 2006). However, there is a lack of clear epidemiologic studies supporting prevalence of women in cinnamon-induced contact stomatitis. For this reason, we do not know whether our observation that female are more affected depends on the higher prevalence of contact stomatitis in females or on the higher use of cinnamon-flavoured products in females.

Diagnosis

In the analysed case reports, it appears clear that it is desirable to adopt a conservative approach in the diagnostic procedure of CCS. The main factor in diagnosing allergic contact stomatitis due to cinnamon-flavouring agents is the information purchased by patient, which should allow the clinician to associate consumption of the allergenic agent with development of symptoms (Tremblay and Avon, 2008). Clinical examination and medical history are sufficient, because CCS usually improves spontaneously after omission of the consumption of cinnamon-flavoured products; for this reason, performing expensive assessment as biopsy is advantageous only if the lesions do not improve spontaneously.

Patch testing is indicated in all lesions that are not clearly related to trauma or physical injuries or to confirm the suspected diagnosis of contact stomatitis. In some cases, the test was performed for fragrance mix, a mix of 8 ingredients including cinnamic alcohol, for cinnamic alcohol alone, cinnamic acid, trans cinnamic aldehyde and for cinnamon gum as is (Bousquet *et al*, 2005; Endo and Rees, 2006; Kind *et al*, 2010) with positive results. However, it is necessary to evaluate the connection between clinical manifestations and positive patch test result; this is

always very difficult and requires an interdisciplinary approach to the patient. False negative results to patch test can also occur because of the structural differences between the skin and the oral mucosa, and direct tests of the mucosa are difficult to perform and even more difficult to interpret (Regezi *et al*, 2003).

The histopathologic findings of CCS are not specific; they show inflammation in lamina propria with lymphocytes and plasma cells, hyperkeratosis and acanthosis, resembling to lichenoid reaction and plasma cell stomatitis. The histopathologic assessments indicate that CCS tissues reactions have not specific features, histopathologic changes can be suggestive of cinnamon-flavouring agents induced mucositis, but they are not pathognomonic (Allen and Blozis, 1988; Mihail, 1992; Westra *et al*, 1998; Regezi *et al*, 2003). In a case series published by Miller *et al*, the histopathologic tests show parakeratosis, acanthosis or orthokeratosis (Miller *et al*, 1992). Other authors have been suggested that cinnamon-flavoured chewing gum can induce precancerous lesions such as leukoplakia and also squamous cell carcinoma of the tongue (Mihail, 1992; Westra *et al*, 1998).

The differential diagnosis of CCS includes lichenoid reactions, leukoplakia, lupus-like oral eruptions, hairy leukoplakia, leukoedema, erythroplakia and hyperplastic candidiasis. Therefore, when the lesions present features resembling other oral diseases, in particular precancerous diseases, it is mandatory to perform a biopsy.

Based on a combination of history, clinical and histologic data and allergic tests, it is possible to differentiate the different conditions as proposed in the algorithm shown in Figure 1.

In most cases, information coming from a careful history and an accurate examination of the oral cavity will be sufficient to distinguish a possible contact stomatitis. The withdrawal of the suspected compound is the first step in the diagnostic process. The disappearance of lesions

Algorithm for diagnosis and clinical management of CCS

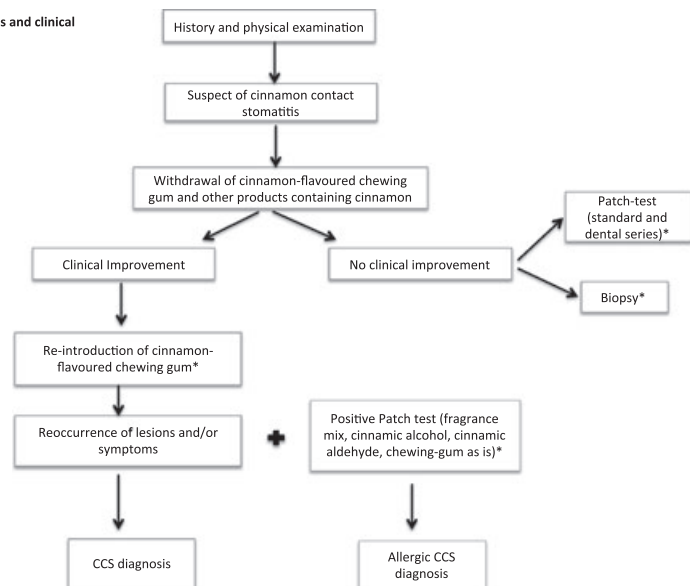


Figure 1 Algorithm for diagnosis and clinical management of cinnamon contact stomatitis (CCS). *Previous patient informed consent

*Previous patient informed consent

followed by a positive reintroduction use test (after obtaining patient's informed consent) results can lead to the diagnosis. In these cases, patch testing with fragrance mix, cinnamic alcohol, cinnamic aldehyde and with personal products supplied by the patient can confirm the diagnosis of an allergic CCS. In subjects with an unclear correlation between the lesions and the use of cinnamon-flavoured chewing gums or in patients with a clinical presentation similar to neoplastic diseases, a histopathologic assessment can be helpful, otherwise invasive and expensive examinations, as biopsy can be avoided.

Discussion

The worldwide use of cinnamon-flavoured products especially chewing gums has catalysed the attention on a spectrum of clinical conditions and their corresponding histopathologic features. The most studied compounds are cinnamonaldehydes and cinnamic acid; other cinnamon-flavoured compounds have recently come to light as chemical toxins able to promote reactions of the oral mucosa. These compounds released by chewing gum can act through cytotoxic mechanisms when excessive doses exceed threshold levels causing alterations of the oral mucosa (Miller *et al*, 1992; Koch and Bahmer, 1999; Moller, 2002). The hypothesized mechanism underlying the oral alterations, according to several authors, could be linked to contact allergy.

Contact allergies are common in the skin but rare in the mouth, probably it is due to the protective role of saliva against the accumulation of allergenic substances, but also the high vascularization in oral epithelium that prevents the long-term maintenance of allergens in contact with the mucosa by absorption and removal and the reduced activation of cellular immunity as less antigen-presenting cells are found in the oral mucosa in comparison with skin (Georgakopoulou, 2010).

Cinnamon contact stomatitis is a well-described clinical entity; for this reason, health professionals who observe the above-described lesions in the oral cavity of a patient should be aware of the importance to investigate on the usage of cinnamon-flavouring substances. Furthermore, the clinical resolution of lesions after the discontinuation of consumption of cinnamon is sufficient to diagnose cinnamon contact stomatitis.

According to the literature revised in some cases, it appears clear that the diagnostic approach was based on authors' professional background instead on a harmonized and shared evidence-based procedure. For example for a dentist is more common using bioptical evaluation, for an allergist or dermatologist using patch testing. A clinical management based on expensive investigations and therapies as first choice is not supported by evidence, because it is common that CCS spontaneously improves after the discontinuation of cinnamon-flavoured chewing gum exposure.

The proposed algorithm can offer an useful tool in diagnostic and care process to physicians, who should manage the oral adverse reaction to cinnamon-flavoured chewing gums with an approach borrowed from pharmacovigilance methodology.

Conclusion

The above-discussed and commented scientific literature suggests to clinicians who treat patients with oral conditions that they should be aware to correctly diagnose and manage CCS. In fact, this pathological entity could be under diagnosed and more frequent with respect to the supposed occurrence. Usually clinical examination and history taking are sufficient for diagnosis. A treatment consisting of omission of consumption of cinnamon-flavoured chewing gum can determine a prompt clinical recovery. The presence of an allergic mechanism can be proved by patch test. For this reason, it is crucial limiting invasive and expensive investigations, which are indicate only in the cases of persistence of the lesions after a prompt withdrawal of cinnamon exposure. Moreover, as patients can refer to different specialists as dentists, dermatologists and allergists, a multidisciplinary approach is suggested.

Author contributions

All authors drafted the manuscript.

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