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Dentifrices - an update

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Abstract

Objectives; The objective of this paper was to review the published evidence concerning the efficacy and potential for adverse reactions of modern dentifrices toothpastes. Data sources; Publications cited on MEDLINE since 1990. Some further pre-1990 publications are also referenced. Data selection; Studies concerning the efficacy of dentifrices and their components and any related putative adverse incidents. Data extraction; Papers were scrutinised for scientific and trial data. Data synthesis; Data concerning the efficacy of dentifrice components were summarised. Conclusions; The efficacy of fluoride salts in dentifrices in reducing dental caries is well established. Toothpastes, containing triclosan, are effective in improving plaque control, gingivitis and periodontal health. Other toothpaste formulations are effective in reducing the formation of calculus, extrinsic tooth stain, dentine sensitivity and oral malodour. The consumer now has available a range of toothpastes which deliver oral health benefits. Adverse reactions to toothpastes are rare but should be considered in unexplained skin or respiratory allergies and gingival or lip lesions.

Key words: *Dentifrices, dentistry.*

Introduction

Toothpastes are used almost universally in the developed world but, in some groups and cultures, people still practice traditional toothbrushing without dentifrice with, for example, a miswak or salt. Dentifrices (toothpastes) have been used since antiquity but recently, formulations which deliver active compounds aimed at preventing and/or treating oral diseases have been developed. The history of toothpastes is reviewed elsewhere.(1)

Toothpastes; their regulation

A toothpaste may be classed as either a cosmetic or a medicine depending on the claims that are made and the level of certain constituents.

The primary function of a toothpaste is to clean the teeth which is considered to be a cosmetic benefit. The use of words such as 'protects', 'cleans', 'freshens breath', 'fights bacteria which may cause gum problems', 'whitens' or 'fights tartar' are considered to be cosmetic claims. Toothpastes that contain up to 1500 ppm F can make claims such as, 'cavity protection', 'helps prevent tooth decay' and 'fights tooth decay' all of which are cosmetic claims. Cosmetic products can be marketed without clearance from any regulatory body but the manufacturer has an obligation to ensure that such products are safe and do not cause damage to health under normal conditions of use. The EEC Cosmetics Directive now obliges the manufacturer to include full ingredient listing in descending order or level in the product. A full dossier on the product containing information on the raw materials, manufacturing, safety and proof of claims must be available at a specific address for inspection by a competent authority.

A medicine is considered to be any substance used wholly or mainly for the purpose of treating or preventing disease. Claims such as 'reduces hypersensitivity, 'reduces gingivitis', 'reduces gingival bleeding' or 'controls periodontitis', "prevents/treats dental caries" are medicinal claims and must be approved by the Medicines and Healthcare Products Regulatory Agency (MHRA), formerly known as the Medicines Control Agency, who require evidence to support the effectiveness and safety of such products. This takes the form of an application for marketing authorisation to sell the product.

There are three types of Product Licence:

- General Sales Licence (GSL),
- Pharmacy (P)
- Prescription only (POM).

A fluoride toothpaste containing up to1500 ppm F may be classed as either a cosmetic or medicine depending on the claims made for the product. Toothpastes containing more than 1500 ppm F are classed automatically as prescription only medicines.

Toothpaste constituents

Although toothpastes must by law be labelled with active and inactive ingredients, not all components are always clear from the labelling. Toothpastes usually contain excipients and active principles. Excipients and the reasons for their inclusion are shown in Table 1. Some toothpastes contain 'glycerin', which may be manufactured synthetically or derived from animal fat. The latter are contraindicated for use on religious or cultural grounds.

The first active principle added to toothpaste was fluoride - introduced in the USA in 1955 as an anti-caries agent (in the UK in the mid-1960s). Many toothpastes now deliver multiple benefits in addition to caries control. Such toothpastes need to be carefully formulated to ensure that active ingredients are not inactivated. For example, calcium carbonate binds sodium fluoride to render it fairly ineffective as an anti-caries agent; sodium monofluorophosphate on the other hand is not inhibited.

Anticaries agents in toothpastes

-Fluoride (F)

Systematic reviews (2,3) have concluded that fluoride toothpastes are effective in reducing caries. Fluoride toothpastes reduce caries in the deciduous dentition by 37% and by 24% in the permanent dentition of children and adolescents (3). A meta-analysis also concluded that fluoride is effective in preventing caries in adults of all ages (4). The effectiveness of fluoride toothpastes are concentration dependent (3,5-7). Brushing with a fluoride toothpaste should be recommended twice daily, whilst rinsing with large volumes of water should be discouraged (8).

Various forms of fluoride, such as amine fluoride, stannous fluoride, sodium fluoride and sodium monofluorophosphate, have been used in toothpaste formulations. The relative effectiveness of these different fluoride salts has been the topic of much debate (9,10) but a systematic review concluded that they were equally effective (3).

Dentifrices containing fluorides in concentrations >1500ppm are classed as prescription only medicines (POM) and should be used only above the age of 10 years and for the management of high caries risk individuals such as those with xerostomia or root surface caries.

-Non-fluoride anti-caries components

Non-fluoride anti-caries agents within toothpaste formulations include agents containing calcium, phosphorus (phosphates; trimetaphosphates, pyrophosphates, glycerophosphates), metals (zinc, tin, aluminium, iron, manganese, molybdenum) and various antimicrobials. (11). Although many agents have been identified in various models few have been taken forward to clinical trials in humans.

Calcium carbonate (chalk) is a common dentifrice abrasive and has dental plaque pH-raising properties(12) and may also raise plaque calcium levels, and help in remineralisation (13).

Table 1. Toothpaste excipients.

Abrasives	**Surfactants**	**Humectants**
Alumina	Amine fluorides	Glycerol
Aluminium trihydrate	Dioctyl sodium sulfosuccinate	PEG 8 (polyoxyethylene glycol esters)
Bentonite	Sodium lauryl sulfate (SLS)	Pentatol
Calcium carbonate	Sodium N lauryl sarcosinate	PPG (polypropylene glycol ethers)
Calcium pyrophosphate	Sodium stearyl fumarate	Sorbitol
Dicalcium phosphate	Sodium stearyl lactate	Water
Kaolin	Sodium lauryl sulfoacetate	Xylitol
Methacrylate		
Perlite (a natural volcanic glass)		
Polyethylene		
Pumice		
Silica		
Sodium bicarbonate		
Sodium metaphosphate		
Gelling or binding agents	**Flavours**	**Preservatives**
Carbopols	Aniseed	Alcohols
Carboxymethyl cellulose	Clove oil	Benzoic acid
Carrageenan	Eucalyptus	Ethyl parabens
Hydroxyethyl cellulose	Fennel	Formaldehyde
Plant extracts (alginate, guar gum,	Menthol	Methylparabens
gum arabic)	Peppermint	Phenolics (methyl, ethy, propyl)
Silica thickeners	Spearmint	Polyaminopropyl biguanide
Sodium alginate	Vanilla	
Sodium aluminum silicates Viscarine	Wintergreen	
Xanthan gum		
Colours	**Film agents**	**Sweeteners**
Chlorophyll	Cyclomethicone	Acesulfame
Titanium dioxide	Dimethicone	Aspartame
	Polydimethylsiloxane	Saccharine
	Siliglycol	Sorbitol

Antiplaque agents in toothpastes.

Most antiplaque agents in oral use are antiseptics or antimicrobials used in an effort to prevent attachment of biofilms, to influence bacterial proliferation, or to remove established dental plaque and/or alter its pathogenicity. Most successful antiplaque agents have prolonged retention on oral surfaces by adsorption followed by slow desorption (substantivity). They should have a broad antibacterial spectrum, with low toxicity, compatibility with other toothpaste components and be of low toxicity.

-*Triclosan*

Triclosan ((2,4,4' trichlor-2'-hydroxydiphenyl ether) is a non-ionic chlorinated bisphenol widely used in personal products such as deodorants and soaps and appears to be safe, effective and well tolerated. It is compatible with toothpaste components such as fluoride and surfactants and, by virtue of its inhibition of cyclo-oxygenase/lipoxygenase pathways, is also anti-inflammatory.

However, triclosan per se has only moderate substantivity and is not retained sufficiently long to have a significant antibacterial effect, However, when combined with a co-polymer, polyvinylmethyl ether maleic acid (PVM/MA or Gantrez) its oral retention is significantly increased (14).

Triclosan functions by inhibiting the enoyl-reductase enzymes of type II fatty acid synthases in susceptible bacteria, damaging the bacterial cytoplasmic membrane, leading to leakage. It has a broad spectrum of antibacterial activity and a significant anti-plaque effect, without staining the teeth.

Systematic reviews of six-month clinical studies have concluded that formulations containing triclosan and copolymer significantly improve plaque control and periodontal health (15-17). Toothpastes containing triclosan and zinc citrate are also effective in improving plaque control and gingival health (18-21).

-*Chlorhexidine*

Early studies indicated anti-plaque activity of chlorhexidine (CHX) toothpastes (22), but it is inactivated by other constituents in conventional formulations.

Other anti-plaque ingredients

A systematic review concluded that toothpastes containing stannous fluoride improve plaque control and gingivitis (23).

Herbal toothpastes have rarely been shown to have significantly greater anti-plaque activity than conventional pastes (24).

A zinc citrate/bromochlorophene/triglyceride formulation has been reported to inhibit both plaque and gingival inflammation (25).

Whitening toothpastes

The evidence to date suggests that that the primary stain removal ingredient in toothpaste is the abrasive but some toothpastes do contain additional chemical agents that augment the abrasive cleaning. A number of the whitening ingredients that have been assessed include enzymes, peroxide, surfactants, citrate, pyrophosphates and hexametaphosphate. Whitening dentifrices may contain

- Enzymes (such as natural fruit enzymes of the Bromaine complex in Janina Diamond® and Opale® toothpastes, and citroxain in Rembrandt toothpaste®)
- Peroxide (for instance, in Colgate Simply White Toothpaste®)
- Sodium hexametaphosphate (polypyrophosphate) or
- Sodium tripolyphosphate.

A number of the whitening toothpaste ingredients are effective at stain removal in laboratory studies (26) but evaluating their clinical benefit is problematic. A toothpaste containing 0.5% calcium peroxide significantly reduced tooth stain after 6 weeks of product use (27). A toothpaste packaged as a dual chambered container where one stream contained 1% hydrogen peroxide the other phosphate salts, manganese gluconate and silica removed significant amounts of extrinsic tooth stain after 6 weeks (28). A clinical study demonstrated that dentifrices containing 0.234% sodium fluoride with copolymer, tetrasodium pyrophosphate, and sodium tripolyphosphate in a silica base, or 0.243% sodium fluoride with copolymer, tetrasodium pyrophosphate, and sodium tripolyphosphate in a silica base were more effective in preventing natural extrinsic staining compared with a control dentifrice (29. A double-blind clinical study indicated that Colgate Tartar Control® with Baking Soda & Peroxide Fluoride Toothpaste is significantly better at control of extrinsic tooth stain than is Crest Regular Fluoride®, a sodium fluoride/silica dentifrice (30).

Anti-calculus toothpastes (tartar control toothpastes)

Supragingival calculus is mineralised plaque and one approach to its control is the inhibition of mineralisation by crystal growth inhibitors. Such inhibitors include chemicals such as pyrophosphates, phosphonates zinc salts and a copolymer of methyl vinyl ether and maleic anhydride (31). A clinical trial of a toothpaste containing zinc citrate trihydrate and triclosan in a silica-base containing 1450 ppm F significantly reduced calculus (32). A number of studies have assessed dentifrices containing 3.3% soluble pyrophosphate and reported significant reductions in calculus (33-37). The addition of a copolymer (polyvinyl ether and maleic acid) to formulations containing pyrophosphate has been found to improve their effectiveness in reducing calculus (38,39). Clinical studies have established that a toothpaste containing triclosan/copolymer is effective in reducing calculus (40,41).

Anti-malodour toothpastes

A toothpaste containing triclosan/co-polymer/sodium fluoride (Colgate®, Total®, Advanced Fresh) is effective in reducing oral bacteria and malodour as well as reducing the volatile sulphur compounds implicated in malodour (42,43).

Desensitising toothpastes

Exposed root surfaces due to gingival recession are a major predisposing factor to dentinal root sensitivity which is often exacerbated after periodontal treatment. Two groups of products are used to treat sensitivity; those that interfere with the transmission of neural impulses and those that block and occlude the dentinal tubules.

Potassium nitrate (5%), potassium chloride (3.75%) and potassium citrate (5.5%) are used interchangeably in many countries since each of these salts provides 2% potassium ion which acts to block neural transmission.

In clinical trials, potassium based toothpastes have been shown to take at least two weeks of twice daily use to provide measurable reductions in sensitivity. Clinical data indicate that all three forms of potassium are effective in reducing sensitivity when compared to a regular fluoride toothpaste (44-48). However, a systematic review questioned the effectiveness of potassium containing formulations (49).

Strontium chloride and stannous fluoride both involve the principle of occluding tubules. These products provide significant reductions in hypersensitivity after four weeks of twice daily use (50-52).

Recently a novel formulation has been launched whose mode of action is to occlude dentinal tubules. The dentifrice contains 8% arginine, calcium carbonate and 1450 ppm fluoride as sodium monofluorophosphate. Several clinical studies have demonstrated the effectiveness of this product (53,54). Using a range of techniques such as confocal laser scanning electron microscopy and atomic force microscopy the formulation was shown to occlude the dentinal tubules (55).

Interactions of dentifrices with other oral health care products

Toothpastes may interact with, for example, cetylpyridinium chloride mouthrinses to reduce the plaque-inhibitory effects (56).

It may be sensible therefore, to leave a period of a couple of minutes between use of mouthwashes and toothpastes.

Possible adverse effects of dentifrices

Toothpaste ingredients may be ingested, particularly by children or people with learning disability, and may contribute to damage to hard tissues (abrasion, staining) and occasionally soft-tissues.

-Fluoride

Fluoride may be ingested from toothpaste, particularly by young children and fluorosis can result (57-59). The risk of fluorosis is related to the dose of fluoride ingested ie the fluoride concentration x amount. The amount of toothpaste poses a greater risk than the fluoride concentration and parents should be advised to supervise toothbrushing, place only a small amount of toothpaste on the toothbrush and encourage the child to spit out excess. A recent publication by the Department of Health and the British Association for the Study of Community Dentistry, entitled " Delivering Better Oral Health: An evidence based toolkit for prevention" recommends a smear of toothpaste containing at least 1000 .ppm fluoride for children aged up to 3 years and for those aged 3 to 6 years a pea sized amount of toothpaste containing 1350-1500 ppm fluoride (60). Toothpaste alone was responsible for an average of 81.5% of the daily fluoride intake in pre-school Brazilian children (61).

-Sodium lauryl sulfate

Sodium lauryl sulphate (SLS) is a detergent commonly used in toothpastes and may occasionally cause mucosal desquamation or ulceration (62-64).

-Triclosan

In 2005, a "toothpaste cancer alert" appeared in some newspapers after a report that triclosan can react with water to produce chloroform (65) which, if inhaled in large enough quantities, can cause depression, liver problems and, in some cases, cancer. However, other studies suggest that triclosan may have chemotherapeutic potential against cancer (66).

-Soft tissue reactions

Soft tissue reactions may arise, most often to essential oils, flavourings, cinnamonaldehyde, benzoates, or carvone, and manifest as direct irritants or allergic reactions in the mouth, lips as contact cheilitis (67). Rarely allergic rhinitis (68) or asthma (69) may occur.

Essential oils, such as peppermint, anethole, cinnamon, cloves and spearmint and antimicrobial agents can cause cheilitis or circumoral dermatitis (70). Carvone is a common constituent of essential oils and may be implicated.

Some toothpaste constituents have been implicated in other reactions. Tartar-control pyrophosphate dentifrices occasionally cause erythema, scaling and fissuring of the perioral area, sometimes with cheilitis, gingivitis (71) and circumoral dermatitis (72) and other reactions. Herbal toothpastes occasionally produce similar reactions (73).

Conclusion

The clinical team has a responsibility to keep up-to-date with the ever-increasing development and marketing of dentifrices. In the past the profession has had to rely on data obtained from clinical trials some of which

were of poor quality. The regulatory bodies have done much to improve the quality of trials and review and approve claims made by the manufacturers. The Cochrane Oral Health Group has been at the forefront in publishing systematic reviews of randomised controlled clinical trials involving toothpastes. Clinicians can feel confident that the advice derived from such reviews is sound and based on a rigorous process of appraisal. Until recently toothpastes, notably those containing fluoride, delivered the single benefit of caries prevention. Today the composition of toothpastes is complex often delivering several oral health benefits. Much of the improvement in the oral health of individuals, communities and populations can be attributed to the widespread availability and use of safe and effective toothpastes.

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