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Chlorhexidine-containing chewing gum

Clinical documentation

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Summary

A clinical documentation on chlorhexidine containing chewing gum is presented on the occasion of the launch of CHewX®, a chewing gum containing 5 mg of chlorhexidine diacetate in Switzerland. Following an overview on functional chewing gum, the mechanism of action of chlorhexidine (CHX), its toxicity and safety are summarized and a review of clinical studies performed with CHX-containing chewing gum given. Indication, dosage, precautions and benefits of CHX chewing gum are described.

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Introduction

Chewing gum with chlorhexidine

In spring 2006, CHewX®, a chewing gum containing 5 mg chlorhexidine diacetate per pellet, was introduced to the Swiss market by the distributor firm heicoDent. The following clinical documentation for the chlorhexidine containing chewing gum will present the mechanism of action of chlorhexidine (CHX), its toxicity and safety along with a review of clinical studies performed with CHX chewing gum. Indications, dosage, precautions and benefits of this new galenic form of CHX, CHewX®, will be described.

Chlorhexidine

Dental plaque, a bacterial biofilm, is one of the major etiologic agents involved in the initiation and progression of dental caries, gingivitis and periodontal disease. The recognition of the role of microorganisms as the major cause of chronic gingivitis was early established (ASH et al. 1964; LÖE et al. 1965; THEILADE et al. 1966). The association of particular organisms with caries and periodontal disease has since been described. Owing to the strong association between oral microorganisms and caries as well as periodontal diseases, the dental profession has been increasingly interested in the topical use of antimicrobial agents. Chemical therapy has, however, primarily been used as an adjunct to mechanical therapy.

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CHX was the first antimicrobial agent shown to inhibit dental plaque formation and the development of chronic gingivitis (Löe & Schiott 1970). CHX is not effective against systemic infections following parenteral dosing. Its use is restricted to prophylactic antisepsis by topical or oral application.

CHX is a cationic chlorophenyl bisbiguanide antiseptic. Bisbiguanides are the primary second-generation antiplaque agents exhibiting considerable substantivity and very broad antibacterial properties. CHX is a strong base and, at physiologic pH, is a large dicationic molecule [1,6-di(4-chlorophenyl-diguanido) hexane] with two positive charges distributed over the nitrogen atoms on either side of the hexamethylene bridge (Jones 1997; Albert & Sargeant 1962). By virtue of its positive charge, CHX has the ability to bind to negatively charged surfaces such as the bacterial cell wall (Koontongkaew & Jitpukdeebodintra 1995). Since most intraoral surfaces are negatively charged the drug gets well distributed in the oral cavity and is not easily displaced (Loesche 1976). Once bound, it can exert its bacteriostatic and bactericidal effects. The substantivity of CHX is given by the fact that once adsorbed to intraoral surfaces it gets only slowly displaced by calcium ions from saliva. The dicationic nature making CHX extremely interactive with anions is not only relevant to its efficacy, safety, but also to local side effects and difficulties with product formulation.

CHX is available as digluconate, acetate or hydrochloride salt. Digluconate and acetate salts are water soluble, CHX hydrochloride is weakly soluble in water. CHX, developed by Imperial Chemical Industries, GB, after intensive investigations of the biological properties of polybiguanide compounds, was first marketed as an antiseptic for skin wounds in 1953. It has undergone extensive laboratory testing.

Current applications of CHX in general medicine include: Skin disinfection, surgical hand disinfection, hygienic hand disinfection, preoperative whole-body disinfection, urology (irrigant, lubricant and antiseptic), obstetrics and gynecology (irrigant and antiseptic), nasal cavity and throat, wounds and burns.

In dental medicine, CHX was initially used for presurgical disinfection of the mouth and in endodontology. Plaque inhibition by CHX was already investigated in 1962 (Schröder 1969) but the first controlled clinical study was performed by Löe & Schiott (1970). This study showed that rinsing for 60 sec, twice per day with 10 ml of a 0.2% (20 mg dose) CHX gluconate solution, in the absence of normal toothcleaning inhibited plaque regrowth and the development of gingivitis. Numerous studies have followed such that CHX is one of the best investigated compounds in dentistry and to date still remains the gold standard to which other antiplaque and antigingivitis agents are compared. Reviews have been published by Gjermo, 1989; Addy et al. 1994 and Moshrefi 2002. For purposes of dental medicine, CHX is marketed and routinely used in various galenic forms such as mouthrinse, toothpaste, spray, gel, varnish and pastille or lozenge.

Functional chewing gum

1. Medicinal chewing gum

Although the first medicated chewing gum, Aspergum®, was introduced in the USA as early as 1924, the great potential of chewing gum as a galenic form for drug delivery has gone fairly unnoticed to date. Chewing gum is, however, listed as a dosage form in pharmaceutical guidelines and as a standard in the European Pharmacopoeia (Commission of the European Communities 1991; European Department for the Quality of Medicine 2001). The advantages of chewing gum as a carrier for drugs are obvious: Chewing gum can be used without water, at any time, and everywhere. Product stability is good, because incorporated therapeutic agents are protected from oxygen, light and water. Chewing gum as a drug delivery system has been reviewed by Rassing (1994; 1996) and a representative list of medicinal chewing gums sold worldwide was published by Imfeld (1999).

2. Dental chewing gum

Chewing gum as a delivery system for various topical dental prophylactic and therapeutic agents has been repeatedly studied, and a few dental chewing gum products are registered and marketed in various countries (Imfeld 1999). Thus, there are gums containing fluoride, enzymes, mineral salts, metal salts, xylitol, carbamide and CHX diacetate.

Mechanism of action of CHX

CHX has a broad spectrum of antimicrobial activity including a wide range of Gram-positive and Gram-negative bacteria (Wade & Addy 1989), yeasts, dermatophytes and some lipophylic viruses including HBV and HIV (Denton 1991).

The antibacterial action of CHX shows different effects at different concentrations. At low concentrations, the agent is rapidly bacteriostatic, and at higher concentrations, it is bactericidal (Jones 1997). CHX's antimicrobial activity is based on its membrane binding activity. As the CHX molecule is positively charged, it binds strongly to the negatively charged bacterial cell membranes. The binding is specific and strongly adsorptive to phosphate-containing compounds. At low concentration, the binding results in a disorientation of the lipoprotein structure of the cell membrane thus inducing an increased membrane permeability and leakage of intracellular components including potassium (Hugo & Longworth 1964, 1965). At higher concentration, the molecule binds to phospholipids in the inner membrane, leading to increased permeability of the latter and leakage of low-molecular-weight molecules. This causes precipitation of bacterial cytoplasm and cell death (Hugo & Longworth 1966). Cells treated with bacteriostatic levels of CHX can recover viability despite having lost up to 50% of their potassium storage (Denton 1991). As the concentration of the compound increases, higher molecular weight cellular constituents, such as nucleotides, appear in the supernatant fluid surrounding the bacterial cell. Levels of CHX producing this effect are bactericidal (Denton 1991).

In the mouth, CHX readily adsorbs to negatively charged surfaces, including the mucosa and pellicle-coated teeth. Unlike most other antiseptics, once adsorbed, CHX still remains bacteriostatically active. A single rinse with 0.2% (Europe) or 0.12% (USA) CHX will maintain substantivity at antibacterial levels within the saliva for up to five hours (Roberts & Addy 1981; Schiott 1973). Persistence at the oral surfaces has been shown to suppress salivary bacterial counts for over 12 hours (Schiott 1973).

Studies with radiolabelled CHX suggested a slow release of the antiseptic from surfaces (Bonesvoll et al. 1974). Approximately 30% of the dose, i.e. 5.5 to 6.0 mg CHX, is retained after a 60-sec mouth rinse with 10 ml of a 0.2% solution (Bonesvoll 1977). It was hypothesised that this leads to a persistent antibacterial milieu in the mouth (Gjermo et al. 1974). Jenkins et al. (1989) suggested that the plaque inhibitory action of CHX is derived only from the CHX adsorbed to the tooth surface. It is possible that the molecule attaches to pellicle on the tooth surface by one cation, leaving the other cation free to interact with bacteria at-

tempting to colonize. The same mechanism is most probably associated with toothstaining. This would explain why anionic substances such as sodium lauryl sulfate, contained in most toothpastes, reduce the plaque inhibition of CHX if the latter are used shortly after rinses with the antiseptic (Barkvoll et al. 1989). Short-term use of CHX causes a striking reduction in the number of oral microorganisms. In the absence of other oral hygiene measures, CHX has been shown to reduce the number of bacteria in saliva by 85% after only 24 hours. A maximum reduction of 95% occurred after around five days. After this the numbers of bacteria gradually increased, but an overall reduction of 70–80% was maintained at 40 days. Cessation of CHX mouth rinses results in a return of normal salivary bacterial counts. Plaque inhibition by CHX mouthrinses appears to be dose related (Cancro et al. 1974; Jenkins et al. 1994; Agerbaek et al. 1975). The best results have been obtained when using two daily rinses with an aqueous solution of CHX gluconate (Gjermo et al. 1970; Löe & Schiott 1970; Cancro et al. 1972; Madsen 1974). Similar effects as seen with 10 ml rinses of 0.2% solutions (20 mg CHX) can also be achieved with high volumes of low concentration solutions (Cumming & Löe 1973; Agerbaek et al. 1975; Lang & Ramseier-Grossman 1981). It is, however, noteworthy that a considerable plaque inhibition is obtained with doses as low as 1–2 mg twice daily (Jenkins et al. 1994). Topical applications of 0.2% solutions of CHX to the tooth surface only (spray), produced the same level of plaque inhibition as rinsing with the full dose of 20 mg CHX (Addy & Moran 1983; Jenkins et al. 1989; Kalaga et al. 1989a, b).

Toxicity and safety of CHX

Absorption

The cationic nature of CHX minimizes absorption through skin and mucosae including that of the gastrointestinal tract. Studies with radiolabelled CHX showed that when CHX is swallowed, the drug binds to the mucosal surfaces of the alimentary tract. The expired cells are desquamated and together with any onbound CHX are excreted in the feces. Thus, practically all CHX swallowed is excreted in the feces (Winrow 1973). The very small amount of CHX that may be absorbed is minimally metabolized in the liver and excreted in urine (Winrow 1973). No systemic toxicity even from long-term topical application and ingestion has been reported (Gjermo 1989). Intravenous infusion in animals is well tolerated and has even accidentally occurred in humans without serious consequences (Foulkes 1973; Denton 1991). When orally ingested, LD50 for CHX is 2,000 mg/kg body weight. This means that individuals with an average body weight of 70 kg would need to drink 70 liters of a 0.2% CHX solution at once in order to kill 50% of the test population. (As many CHX rinses contain alcohol, they would die from the ethyl alcohol content of such rinses long before reaching 70 liters!).

Teratogenic effects: Pregnancy category B

Reproduction studies have been performed in rats and rabbits at CHX gluconate doses up to 300 mg/kg/day and 40 mg/kg/day, respectively, and have not revealed evidence of harm to the fetus (Foulkes 1973). Adequate and well-controlled studies in pregnant women have, however, not been attempted.

Carcinogenesis, mutagenesis, and impairment of fertility

In a drinking water study in rats, carcinogenic effects were not observed at doses up to 38 mg/kg/day. Mutagenic effects were not observed in two mammalian in vivo mutagenesis studies with CHX gluconate. The highest doses of CHX used in a mouse dominant-lethal assay and a hamster cytogenetics test were 1,000 mg/kg/day and 250 mg/kg/day, respectively. No evidence of impaired fertility was observed in rats at doses up to 100 mg/kg/day (Foulkes 1973).

Neurosensory deafness

This can occur if CHX is introduced into the middle ear. The antiseptic should not be placed in the outer ear in case the ear drum is perforated.

Nursing mothers

It is not known whether CHX is excreted in human milk. Because many drugs are excreted in human milk, caution might be indicated when CHX is administered to a nursing woman. In parturition and lactation studies with rats, no evidence of impaired parturition or of toxic effects to suckling pups was observed when CHX gluconate was administered to dams at doses that were over three g per day.

Bacterial resistance

Resistance has not been reported even in long-term oral use. There is no evidence of superinfection by fungi, yeasts or viruses. Long-term oral use resulted in a small shift in the flora towards less sensitive organisms but the effect was rapidly reversible after discontinuation of use (Schiott et al. 1976).

Oral side effects of CHX

Staining

When used as a mouthrinse, CHX has a number of local oral side effects (Löe & Schiott 1970; Flotra et al. 1971). The most common is a brown discoloration of the teeth, some restorative materials, the mucosae and notably the dorsum of the tongue. Cosmetic problems associated with intraoral staining are a factor decreasing patient compliance. The amount of staining seems to be dependent on the mode of application, concentration, and presence of potential discoloring agents within the diet. The mechanisms at the origin of the CHX-staining are still debated (Eriksen et al. 1985, Addy & Moran 1995). The following explanations have been proposed:

– degradation of the CHX molecule to release parachloraniline,
– catalysis of Maillard reactions,
– protein denaturation with metal sulfide formation,
– precipitation of anionic dietary chromogens.

Release of parachloraniline, however, does not occur on storage or as a result of metabolic processes and Alexidine, a similar bisbiguanide, not having any parachloraniline groups, also causes staining identical to that of CHX (Roberts & Addy 1981). Non-enzymatic browning reactions (Maillard reactions) catalyzed by CHX are theoretically possible (Nordbø 1979), however, evidence is indirect, circumstantial or inconclusive (Eriksen et al. 1985). The same holds true for protein denaturation produced by CHX. Staining due to precipitation of anionic dietary chromogens by cationic antiseptics, including CHX and polyvalent metal ions, is supported by a number of controlled laboratory and clinical studies (for review see Addy & Moran 1995). Thus, the locally bound antiseptics or metal ions on the mucosa or on the teeth can react with polyphenols in dietary substances to produce staining. Beverages such as tea, coffee and red wine are particularly chromogenic. The stain is of extrinsic origin and easily removable from the tooth surfaces by professional oral hygiene measures.

Bitter taste/taste disturbance

Aqueous solutions of CHX have a very bitter taste which is difficult to mask in dental products. Objective testing of the taste sensation has also confirmed a transient effect on the perception of sweet and salt taste (Gjermo et al. 1974) with salt taste being preferencially affected (Lang et al. 1988). Similar impairments of taste perception occur with most strong cationic substances other than CHX (Gjermo et al. 1970, 1974).

Mucosal desquamation

Desquamation and soreness of the oral mucosa in connection with mouth rinses with bisbiguanides have been sporadically reported (Gjermo et al. 1970) and have been explained by precipitation of the mucin layer weakening its lubricating effect (Gjermo et al. 1974). This side effect is concentration dependent and usually can be controlled by double diluting rinses. To maintain the dose and thereby the effect, a double volume has to be rinsed.

In vitro studies with CHX showed that the total protein synthesis is reduced, cell division is suppressed, and wound contraction is affected (Pucher & Daniel 1992). The cytotoxicity observed in vitro is, however, not seen in vivo (Sanchez et al. 1988). Using an infected wound model, it was found that CHX accelerated the rate of healing compared with saline-treated models (Denton 1991). This effect might be ascribed to decreased microbial irritation eventually also masking some cytotoxicity.

Clinical studies with CHX-containing chewing gum

The use of CHX as an adjunct to or even as a short-term replacement for mechanical oral hygiene measures is well established. It is proven effective for treating gingivitis (Stiefel et al. 1995, Pernu et al. 1996; Valente et al. 1996; Bretz et al. 2000). Traditional methods of application of CHX, such as rinses or gels have, however, not proved acceptable in many special care patients (Francis et al. 1987; Clark et al. 1991; Burtner et al. 1996). Moreover, the above mentioned disadvantages – bitter taste, impairment of taste perception, reversible staining of teeth and tongue, and interaction with surface-active substances such as sodium lauryl sulfate, contained in most commercial toothpastes – led to a search for alternatives to the traditional galenic forms. Thus CHX-containing chewing gum has been explored for the treatment of gingivitis, periodontitis and infections in the oral cavity or throat.

The in vivo release of CHX acetate from chewing gum was 35% after 5 min and approximately 68% after 15 min of chewing (Ainamo & Etemadzadeh 1987). This finding promised a longer oral presence of CHX from chewing gum than after rinsing with a CHX mouthwash.

Several well controlled clinical studies in humans have since been performed with CHX-containing chewing gum. They are described in chronological order in the following.

The effect on plaque growth of a CHX-containing gum and of a placebo gum was assessed in a four-day double-blind, crossover clinical trial with 12 adult volunteers. During the trial no oral hygiene measures were allowed except for the chewing of two pieces of test gum at a time for 10 min five times daily. CHX gums contained 5 mg CHX acetate each (total daily CHX = 50 mg). At the beginning and at the end of the test period plaque was assessed using plaque index, plaque wet weight and area of plaque on the tooth surface. No increase in plaque index and plaque wet weight was found when CHX-containing gums were used (Ainamo & Etemadzadeh 1987).

A five-day crossover, investigator-blind clinical study was performed with six adult volunteers to compare the antiplaque effects of (i) daily chewing of 2×2 pieces of CHX gum (5 mg CHX per gum, total daily CHX = 20 mg), (ii) two daily rinses with 10 ml of Hibitane® mouthwash (0.2% CHX gluconate, total daily CHX = 40 mg), and (iii) chewing gum base with neither CHX nor any sweetening agent in the absence of oral hygiene. The CHX-containing chewing gums inhibited plaque growth (plaque index and area %) as effectively as did the Hibitane® rinses (Ainamo et al. 1990).

The same study design was used with eight adult volunteers for six days and using CHX-containing gums with 5, 4 and 3 mg of CHX acetate (total daily CHX = 20 mg, 16 mg and 12 mg). Also the lower doses inhibited plaque growth as well as the CHX rinses (Ainamo et al. 1990).

A six-day, double-blind, three-treatment, crossover clinical trial with 14 adult volunteers was made to compare dental plaque formation without mechanical oral hygiene when chewing five pieces per day of (i) CHX-containing gum (5 mg CHX acetate per gum, total daily CHX = 25 mg), (ii) xylitol gum (0.8 g xylitol per gum) and (iii) sorbitol gum (1.0 g sorbitol per gum). The gums were chewed for 20 min on each occasion. Chewing CHX-containing gum resulted in significantly reduced plaque values compared to the sorbitol- and xylitol-containing gums (Tellefsen et al. 1996).

The clinical effectiveness in controlling supragingival plaque and the stain-forming potential of CHX-containing gum was investigated in an eight-week, randomized, single-center, investigator-blind, parallel designed clinical trial employing three groups of 50 adult volunteers each (total n = 150). Group 1 chewed 2×2 pieces of CHX-containing gum for 10 min (5 mg CHX per gum, total daily CHX = 20 mg). Group 2 likewise chewed placebo gum and Group 3 rinsed twice daily with 10 ml of a 0.2% CHX aqueous solution for 1 min (total daily CHX = 40 mg). Plaque index, gingival index, gingival bleeding index and indices of stain intensity and stain extent were recorded at baseline, after four and after eight weeks. After eight weeks of use, plaque and bleeding scores in the CHX-chewing gum group were equal to those of the CHX-rinse group and significantly lower than those of the placebo group. Further, the staining intensity was significantly lower after eight weeks use of CHX-containing chewing gum than after eight weeks use of CHX-containing rinsing solution (Smith et al. 1996). The authors concluded that the CHX-containing gum used twice daily provided significant benefits to oral hygiene and gingival health.

The important finding of less CHX-staining in conjunction with chewing gum was somewhat corroborated in a six-week clinical trial that showed that the use of sugar-free chewing gum after rinsing with CHX did not diminish the therapeutic effect of the CHX, but controlled some of the staining effect (Yankell & Emling 1997).

In order to assess the efficacy of CHX-containing gum as an oral delivery system for antibacterial agents in elderly patients with salivary hypofunction and to monitor its acceptability among this population, a clinical trial was performed with 53 volunteers aged between 65 and 98 years (mean age 79.5 years) who had a minimum of six teeth and wore dentures. The study was a four-week, randomized, single-center, double-blind, parallel designed clinical trial with a test- (n = 26) and a placebo group (n = 27). While maintaining their normal mechanical oral hygiene, the test-group chewed two pieces of CHX-/xylitol-containing gum

twice a day for 10 min (5 mg CHX per gum, total daily CHX = 20 mg). The placebo group chewed equal amounts of a xylitol-/sorbitol-containing gum. Saliva samples were inoculated on selective media and colony forming units per ml saliva for *S.mutans,* yeasts and Lactobacilli were counted at baseline and after four weeks of gum use. Area and severity of stain as well as saliva flow rates were assessed. The attitudes of the subjects to gum chewing were evaluated by questionnaires. The CHX-/xylitol-gum significantly reduced the salivary levels of *S. mutans,* Lactobacilli and yeasts while the xylitol-placebo gum produced significant reductions in *S. mutans* only. The study population found chewing gum an acceptable method of receiving medication and improving oral health. The desire to continue gum use was significantly related to subjects'evaluation of oral dryness at baseline. Only those participants who had stained enamel at baseline exhibited increased enamel staining following CHX-/xylitol-gum use (Simons et al. 1997).

The effect of CHX-containing gum on plaque accumulation and gingival inflammation in the absence of all oral hygiene measures was assessed in a five-day, randomized, single-center, double-blind, crossover study with intermittent nine-day washout periods. Eight subjects with a mean age of 51.3 years participated. After a professional tooth cleaning they used in a random order (i) 2×2 pieces of a liquorice flavored CHX-/xylitol-containing chewing gum (5 mg CHX per gum, total daily CHX = 20 mg), (ii) 2×2 pieces of a chocolate mint flavored CHX-/xylitol-containing gum (5 mg CHX per gum, total daily CHX = 20 mg), (iii) 2×1 pieces of a liquorice flavored CHX-/xylitol-containing gum (5 mg CHX per gum, total daily CHX = 10 mg) and (iv) 2×2 pieces of a liquorice flavored xylitol-containing gum without CHX. The gum was chewed for 15 min at a time. Plaque index, gingival index and intensity and area of stain were recorded at baseline and after the five-day study period. Plaque indices when chewing 2×2 CHX-/xylitol gums (irrespective of flavor) were significantly lower than when chewing xylitol-containing gum. The gingival index was significantly higher after xylitol-containing gum than after the other chewing regimes. Stain indices demonstrated no differences for any of the gums chewed. The authors concluded that CHX-containing gum is useful to control dental plaque formation and to decrease gingival inflammation in the absence of mechanical hygiene routines (Simons et al. 1999a).

Oral health care, especially the prevention of stomatological problems, caries and periodontitis, is hampered among elderly occupants of residential homes. The main reasons are cost, low levels of perceived need by residents and staff, restricted mobility, diminished manual dexterity, impaired vision, physical limitations such as stroke and arthritis and the carers' lack of dental knowledge. Elderly occupants of residential homes are often dependent on their carers to perform all their daily care including the maintenance of good oral hygiene. This may place considerable burdens on the staff, and unfortunately residents rarely receive more than emergency treatment for dental pain and discomfort.

In order to investigate the attitudes of elderly residents to using an antimicrobial chewing gum as an aid to oral health, and to assess the opinion of their carers on such a procedure, a cross-sectional, multi-center survey using a structured interview/questionnaire was conducted with elderly residents and their carers in nine residential/nursing homes randomly chosen from the homes in West Hertfordshire, GB. 207 residents, aged between 53–100 years (mean age 82.2 years) were asked to chew two pieces of CHX-containing gum twice daily for seven days (5 mg CHX per gum, total daily CHX = 20 mg). 47 carers were involved in distributing and collecting the gum. 59% of the residents were edentulous and 41% were partially dentate. 35% of the residents found that chewing the gums was difficult with 18% of this group being unable to chew. 19% of the subjects disliked the flavor of the gum. Of the 170 persons who chewed the gum 57% found it reduced oral dryness and 45% reported it made their mouth feel healthy. 54% of the dentate and 41% of the edentate residents wished to keep using the gum. 75% of the carers found it easy to distribute the gum and 62% thought that chewing gum was an acceptable method of maintaining oral health for residents. The authors concluded that the antimicrobial gum was acceptable to many elderly occupants and their carers, and that it significantly improved the perceived oral health and oral dryness of residents (Simons et al. 1999b).

The long-term effect of CHX-containing chewing gum on plaque accumulation and gingival inflammation of elderly occupants in residential homes was assessed in a one-year, randomized, multi-center, double-blind, controlled clinical trial. 164 volunteers from 21 residential homes were involved. They were randomly assigned to three groups. Group 1 chewed 2×2 pieces of a CHX-/xylitol-containing gum (5 mg CHX per gum, total daily CHX = 20 mg). Group 2 likewise chewed 2×2 pieces of xylitol-containing gum (placebo) and Group 3 chewed no gum at all. Plaque and gingival indices were recorded at baseline, three, six, nine and 12 months. In the CHX-gum group, the plaque and gingival indices significantly decreased over the 12 months. In the xylitol-gum group, only the plaque score significantly decreased, and in the "no-gum" control group, both indices remained high. The acceptance of both chewing gums was high but more participants in the CHX-gum group felt that the gum kept their mouth healthy. The effect of the CHX-gum on plaque and gingival indices was significantly greater than for the xylitol gum. The authors concluded that the long-term use of a CHX acetate-/xylitol-containing chewing gum supported oral hygiene routines in this elderly dependent population (Simons et al. 2001).

The long-term effect of CHX-containing chewing gum on salivary flow rate, denture debris score, prevalence of angular cheilitis, denture stomatitis and salivary levels of caries associated microorganisms was assessed in elderly residents of residential homes in a one-year, randomized, multi-center, double-blind, controlled clinical trial. 111 volunteers from 16 residental homes were involved. They were randomly assigned to three groups. Group 1 chewed 2×2 pieces of a CHX-/xylitol-containing gum (5 mg CHX per gum, total daily CHX = 20 mg). Group 2 likewise chewed 2×2 pieces of xylitol-containing gum (placebo) and Group 3 chewed no gum at all. Paraffin stimulated whole saliva flow (ml/min), colony forming units per ml of saliva of *S. mutans,* yeasts and Lactobacilli (plate counting) and clinical examination were performed at baseline, three, six, nine and 12 months. The stimulated whole saliva flow rate increased significantly for the CHX-gum and the xylitol-gum groups over baseline and over the "no-gum" group levels. The levels of *S. mutans,* Lactobacilli and yeasts significantly increased in the xylitol-gum and the "no-gum" groups. Denture debris status was significantly lower in the CHX-gum and the xylitol-gum groups than at baseline or in the "no-gum" group. The reductions of 91% and 75% in denture stomatitis and angular cheilitis prevalence, respectively, that occurred in the CHX-gum group were significantly greater than the respective reductions in the xylitol-gum group. Prevalence of denture stomatitis and angular cheilitis were not significantly changed in the "no-gum" group. The authors concluded that the use of the medicated chewing gum significantly improved oral

health in older occupants of residential homes and that chewing gums should be considered as an adjunct to other oral hygiene procedures in older subjects (Simons et al. 2002).

Conclusions

Therapeutic activity

CHX is one of the most investigated antiseptic compounds in dental medicine and is used as a gold standard to which other antiplaque and antigingivitis agents are compared. Oral application of CHX in chewing gum has proven effective and convenient in adult and elderly people.

Indications for CHX-containing chewing gum

CHX-containing chewing gum as a means to fight plaque and gingivitis is a valid choice for persons with high caries activity in general and especially for oligosialic (hyposalivary) and xerostomic patients. It is further indicated to fight bad breath and before and after undergoing periodontal therapy as an adjunct to other oral hygiene measures. CHX-gum should also be chewed by all persons temporarily unable to perform mechanical oral hygiene for whatever reason. It is further indicated to help maintain the oral health in older dependent populations and other at-risk groups unable to perform adequate oral hygiene.

Dosage of CHX-containing chewing gum

According to the manufacturer, the release profile of CHX from the CHewX gum formulation is equal to the release profiles of the CHX-containing chewing gums used in the above mentioned clinical studies. These were (i) a chocolate/mint flavored gum (63098) in the cited studies by Tellefsen et al. (1996), Smith et al. (1996), Simons et al. (1997, 1999a), and (ii) a liquorice flavored gum (63145-1997) in the cited studies by Simons et al. (1999a, b, 2001, 2002).
The daily recommended use of CHewX-gum is four to six pieces, ideally twice or three times daily two pieces at a time chewed for 20 min. One piece of CHewX chewing gum contains 5 mg of CHX, thus the total daily dose is 20–30 mg of CHX.

Contraindications

CHewX should not be used by persons who are known to be hypersensitive to CHX diacetate or other gum formula ingredients.

Precautions

For patients having coexisting gingivitis and periodontitis, the presence or absence of gingival inflammation following treatment with CHX should not be used as a major indicator of underlying periodontitis.
While using CHX some patients may experience an alteration in taste perception which is reversible when the treatment is discontinued.

Advantages of chewing gum as a CHX delivery system

The advantages of chewing gum over traditional methods of application of CHX are obvious:
1. Ease of intake (without water, any time, everywhere)
2. Less pronounced bitter taste
3. Less impairment of taste sensitivity
4. Better oral distribution
5. Longer oral presence
6. Less staining
7. Less interference with surface active ingredients contained in toothpastes.

Benefit – risk

CHX-containing chewing gum can be used as an antiplaque and antigingivitis agent.
It is a valid adjunct to individual oral hygiene in persons with high caries activity, especially in oligosialic and xerostomic patients, in patients having undergone periodontal therapy and also in persons temporarily or permanently unable to perform oral hygiene. CHX-gum is effective against bad breath.
The main risk is the appearance of light brown discolorations of teeth, some restorative materials and the tongue. Staining is, however, easily removed by professional oral hygiene measures.

Zusammenfassung

Auf Grund der Markteinführung von CHewX®, einem Mundpflegekaugummi mit 5 mg Chlorhexidin, in der Schweiz wird eine klinische Dokumentation von Chlorhexidin-Kaugummi präsentiert. Nach einer Übersicht über funktionelle Kaugummis wird der Wirkungsmechanismus von Chlorhexidin (CHX), die Toxizität und Sicherheit besprochen und eine Literaturübersicht von klinischen Studien mit CHX-Kaugummi gegeben. Indikationen, Kontraindikationen, Dosierung, Anwendungseinschränkungen, unerwünschte Nebenwirkungen und die Vorteile der neuen Verabreichungsform von CHX werden besprochen.

Résumé

Après le lancement sur le marché suisse de CHewX®, un chewing gum contenant 5 mg de chlorexidine, une documentation clinique des chewing gum contentant de la chlorexidine est présentée. Après un survol des différents chewing gum «fonctionnels» existants, le mécanisme d'action de la chlorexidine, sa toxicité et sa sécurité d'emploi sont discutées et une revue d'études cliniques concernant les chewing gum à base de chlorexidine est présentée.
Les indications, contre-indications, dosages, effets secondaires, limitations d'emploi et avantages sont décrits.

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