

# Pripravci za higijenu usne šupljine i farmakoterapijski dodaci

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## Sažetak

*Preparati za higijenu usne šupljine s učinkovitim farmakoterapijskim dodacima idealan su način čuvanja oralnog zdravlja, te smanjenja karijesa i poboljšanja zdravlja usne šupljine u mnogim dijelovima svijeta. Glavni dodatak koji učinkovito smanjuje učestalost karijesa jesu fluoridi (monofluoridni fosfat, kositar fluorid, aminofluoridi, natrij fluorid). Danas ih mnogi istraživači smatraju odgovornim za smanjenje karijesa u mnogim razvijenim zemljama.*

*Ostali aktivni dodaci su oni za smanjenje zubnog kamenca (pirofosfati), za preosjetljiv dentin (stroncij klorid, kalij nitrat), za uklanjanje neugodnog zadaha iz ustiju (antimikrobni lijekovi) i dr. Važno je osigurati da ovi dodaci ne interferiraju s antikarijesnim učinkom fluorida.*

**Ključne riječi:** terapijske zubne paste, preparati za oralnu higijenu

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Pravilna i redovita higijena usne šupljine temeljni je čimbenik u održavanju zdravlja i prevenciji bolesti orodentalnoga sustava. Za nju su potrebne dobro odabране četkice za zube, te zubne paste i vode za ispiranje usta. Uloga je četkice za zube da mehanički čisti površinu zuba i masira desni. Masažom se povećava otpornost gingive na lokalne čimbenike, koji bi ju mogli oštetiti (bakterije i sl.) (1).

Uz četkice za zube rabe se zubne paste. One mogu biti u obliku gela ili pasta.

## 1. Zubne paste

Zubna pasta ima zadaću:

1. uklanjati zubni plak,
2. reducirati karijes,

3. prevenirati pojavu gingivitisa,
4. razvijati i druge učinke, poput desenzibilizacije osjetljivog dentina.

Četkanjem zuba zubnim pastama uklanja se zubi plak s pristupačnih površina.

Sastavni dijelovi zubne paste jesu:

1. abraziv
2. pjeneće sredstvo
3. sredstvo koje pasti daje okus i miris
4. ovlaživač
5. veziva
6. konzervans
7. boje

Osim navedenog u paste se mogu dodavati i farmakološki aktivni dodaci kako bi se pojačao antikarijesni učinak i terapijski djelovalo na zubni plak, zubni kamenac, preosjetljiv dentin i dr.

### 1.1. Abrazivi

Abrazivi, uz pjeneća sredstva, služe mehaničkom uklanjanju zubnoga plaka. Uz to abrazivi uklanjuju i obojenja s površina zuba. Moraju biti dovoljno tvrdi da uklone naslage, ali ne odviše tvrdi kako ne bi oštetili površinu cakline. Najviše rabljen abraziv (vrlo jeftin i izrazito bijel) bio je precipitirajući kalcij karbonat. Kako on veže fluor, koji se često dodaje zubnim pastama, i tako ga čini nadjelotvornim, danas su češći u zubnim pastama kao abrazivi nalaže dikalcij fosfat (također veže fluor), kalcij pirofosfat, titan dioksid te aluminij trihidrat i silikati, koji ne vežu fluor, te kemijski inertni polimeri organskih materijala poput polimetakrilata, polistirena i dr.

Čestice abraziva smiju biti veličine 3 do 12 $\mu\text{m}$  (veće čestice čine zubnu pastu "pjeskovitom" i ljudi ih zbog toga ne vole) i oblih rubova kako ne bi oštetile meka i tvrda tkiva usne šupljine.

### 1.2. Pjeneća sredstva

Sapuni ili detergenti dodaju se zubnim pastama kako bi snizili površinsku napetost, razvili pjenu koja pomaže mehaničkom čišćenju površine i djelovali antimikrobnog dejstva.

Prije su se rabili natrijevi sapuni, a danas anionski detergenti: natrij laurilsulfat i natrij dodecilbenzosulfat, koji imaju veliku moć pjenjenja, dobri su emulgatori i djelotvorni antiseptici (1).

### 1.3. Dodaci za okus i miris

Zubna pasta treba biti ugodna okusa i mirisa, te nakon uporabe stvoriti osježavajuću ugodu u ustima. Najčešći dodaci za ugodan okus i miris jesu pripravci dobiveni iz ulja paprene metvice *mentol* i *peppermint*, koji su lagano paprenastog hlađecog mirisnog okusa i svježeg mirisa po metvici.

*Spearmint*, koji se dobiva iz eteričnog ulja zelenе metvice, oštra je ugodna okusa, ne razvija osjećaj hlađenja i prodorna je mirisa, te *ulje cimeta*, gorkasta, malo paprenasta okusa, koji izaziva osjećaj topeline, specifična mirisa. Oni se dodaju zubnim pastama u količinama od nekoliko promila (cimet) do 2% (mentol).

Kao dodaci upotrebljavaju se i eterična ulja anisa, pimenta, eukaliptusa i limuna, a za djecu mješavine voćnih aroma (2).

Uz to zubnim pastama dodaju se i umjetna sladila: saharin i ciklamat.

### 1.4. Ovlaživači

Ovlaživači se dodaju zubnoj pasti kako bi joj se sačuvala vlažnost i postojanost te spriječilo da se susi i skrućuje. Čine i do 50% zubne paste. Najviše se rabe sorbitol, hidrogenirani škrobni hidrolizati i glicerin (1).

### 1.5. Veziva

Veziva se dodaju zubnim pastama kako bi se održala njihova stabilnost i spriječilo da se odvajaju vodenim od nevodenih sastavnih dijelova. Uz to daju pasti čvrstoću pri istiskivanju iz tube, povećavaju pjenu i osiguravaju glatkost paste. Moraju biti netoksični, inertni i nesenzibilirajući.

Najčešća su veziva: karboksimetilceluloza, anorganski silicijevi prašci ili gume prirodnoga podrijetla poput karagena (hidrokoloid iz crvenih morskih alga, koji se stavlja u gel paste s visokom vlažnošću) ili ksantan gume (ekstracelularni polisaharid koji proizvodi bakterija *Xanthomonas campesiris*) (1).

### 1.6. Konzervans

Kako bi se u pastama spriječio razvoj bakterija dodaju se konzervansi, najčešće netoksični natrij benzoat. Oni ne razvijaju antiseptički učinak na bakterije u usnoj šupljini.

### 1.7. Boje

Zubna pasta mora imati privlačnu boju, osobito ako je namijenjena djeci. Dobro odabrana boja ima jak subjektivni učinak na redovitu uporabu takve zubne paste. Zato na tržištu postoje i zubne paste obojene prugama raznih boja (2).

Boja mora imati vijek koliko i pasta. U zubne paste dodaju se boje koje se rabe i u prehrambenoj industriji.

### 1.8. Farmakološki aktivni dodaci zubnim pastama

#### 1.8.1. Fluoridi

Najčešći aktivni dodatci zubnoj pasti jesu fluoridi. Otkako je dokazano da fluoridi smanjuju nastanak zubnoga karijesa, i to ne samo pri endogenoj (resorptivnoj) primjeni, nego i topikalno primjenjeni na površinu zuba, počeli su se oni dodavati i zubnim pastama. Dentalno je zdravije odraz ravnoteže između kariogenih čimbenika (kao što su šećer u hrani i zubni plak) i poznatih preventivnih metoda (oralne higijene i provedbe fluoridacije). Za endogenu fluoridaciju (fluoridacija vode, kuhijske soli ili tableta) u mnogim je studijama potvrđeno da ima antikariogeni učinak (3) i ona se široko u svijetu provodila, osobito fluoridacija vode. No, oko godine 1970. u mnogim je gradovima prekinuta fluoridacija vode (4,5), a čestoča karijesa se ipak smanjivala, što se moglo objasniti samo individualnim preventivnim mjerama uporabom fluoriranih zubnih pasta. U Nizozemskoj je, primjerice u 1991., 97% zubnih pasta sadržavalo fluoride, a slično je u većini europskih zemalja (6, 7, 8). Kao jedna od djelotvornih endogenih metoda fluoridacije mnogo su se primjenjivale tablete fluora (9), ali zadnjih desetak godina rabe se znatno manje. Tablete je i inače uzmala razmjerno mala subpopulacija djece savjesnih i educiranih roditelja, pa se ni ta metoda fluoridacije ne može smatrati uzrokom za čak 80% smanjenju čestoču karijesa u ukupnoj dječjoj populaciji u Europi (8).

I topikalna fluoridacija (profesionalna), koju se drži potrebnom provoditi poglavito u djece s velikim rizikom od karijesa, ne provodi se dovoljno često (10) i njezina je uloga neznatna pri smanjenju prevalencije karijesa koja je u zadnjih 10 godina nađena u adolescenata. Zato je opće prihvaćeno mišljenje da na smanjenu čestoču karijesa utječu zubne paste s fluoridima, koje većina djece upotrebljava dva puta na dan (11).

Kako je u prehrani važan kariogeni čimbenik i šećer, neki su autori prepostavlјali da su promijenjene prehrambene navike možda razlogom pada čestoče karijesa u djece iz razvijenih zemalja Europe (12, 13), SAD (14), Novog Zelanda (5) i dr. No, potrošnja šećera u tim zemljama nije smanjena, a čestoča karijesa i dalje pada.

Zato König (6) zaključuje: "Stalno smanjenje čestoče karijesa u mnogim područjima Europe u kojima se voda ne fluorira gotovo je isključivo posljedica uporabe zubnih pasta s fluoridima i vjerojatno poboljšanih higijenskih mjeru".

Prema podatcima SZO iz godine 1994. oko 450 milijuna ljudi u svijetu upotrebljava zubne paste s fluoridima (15).

Jedna studija obavljena između godine 1971. i 1981. na britanskom otoku Lewisu (uz zapadnu obalu Škotske), na kojem je vrlo mala migracija stanovnika i gdje do 1971. na tržištu nije bilo fluorirane zubne paste, a niti su provedene druge metode fluoridacije, podkrepljuje tu tvrdnju. Od 1971. svi su stanovnici toga otoka počeli rabiti fluorirane zubne paste i čestoča zubnoga karijesa je nakon 10 godina pojedinih dobnih skupina **djece** bila više od 30% niža (16), Tablica 1.

Tablica 1. Postotak djece bez karijesa 1971. i 1981. na otoku Lewis

Table 1. Caries-free children 1971 and 1981 on the Isle of Lewis

| Dob djece<br>Nominal age   | 5 god.<br>5 years | 8 god.<br>8 years | 11 god.<br>11 years | 14 god.<br>14 years |
|--|-------------------|-------------------|---------------------|---------------------|
| Postotak djece bez karijesa<br>Percentage of children without caries |                   |                   |                     |                     |
| 1971.  | 7,0               | 10,3              | 0,0                 | 0,0                 |
| 1981.  | 21,3              | 40,9              | 9,4                 | 1,5                 |

Prema Hargraves JA, Caries Res 1983; 17:554. (16).  
According to Hargraves JA, Caries Res 1983; 17:554. (16).

Kako su ioni fluora vrlo reaktivni, sastavni dijelovi zubne paste moraju biti pomno odabrani, da ne bi ioni fluora reagirali sa sastojcima paste i postali nedjelotvornima.

Od fluorida u paste za zube dodaju se: natrij fluorid, kositar fluorid, natrij monofluoridni fosfat, te aminofluoridi. Međutim, najraširenija je upotreba monofluoridnog fosfata zbog njegove vrlo dobre kompatibilnosti sa sastojcima zubnih pasta. U Tablici 2. prikazane su kompatibilnosti pojedinih abraziva u zubnim pastama s dodanim fluoridima (19). Vidljivo je da monofluoridni fosfat s kovalentno vezanim fluoridima zadržava aktivnost s većinom abraziva, pa i s kalcij karbonatom, a ostali spojevi koji oslobađaju ionski fluor mogu zadržati djelotvornost s malim brojem abraziva.

Koncentracije fluorida u zubnim pastama najčešće su 0,1% F. Kako mala djeca gutaju veliki dio

Tablica 2. Pregled abraziva kompatibilnih s fluoridima  
Table 2. Abrasives compatible with fluoride

|  |   |
|--|---|
| Ionski fluor: NaF, SnF <sub>2</sub> , aminofluoridi<br>Ionic fluoride<br>NaF, SnF <sub>2</sub> , amine F | Kovalentno vezani, fluoridi monofluoridnog fosfata<br>Covalently bonded fluoride monofluorophosphate  |
| akrilni abraziv / Acrylic<br>(NaPO <sub>3</sub> ) <sub>x</sub><br>SiO <sub>2</sub>                       | akrilni abraziv / Acrylic<br>(NaPO <sub>3</sub> ) <sub>x</sub><br>SiO <sub>2</sub><br>CaHPO <sub>4</sub><br>CaCO <sub>3</sub><br>Al <sub>2</sub> O <sub>3</sub> |

paste, prosječni dnevni unos fluorida iz paste može iznositi 0,27 do 0,3 mg. Fluoridi iz zubnih pasta vrlo se brzo resorbiraju i razina fluorida u plazmi može se naglo povećati (20). Općenito se smatra da je "optimalna" dnevna doza fluorida u prevenciji karijesa 0,05-0,07 mgF/kg tjelesne težine (21), a prema Fejerskovu (22) unos fluorida veći od 0,1 mgF/kg tjelesne težine može izazvati fluorozu zuba. Zbog toga mogućeg utjecaja zubnih pasta na nastanak fluoroze zuba (23) ispitivana je djelotvornost zubnih pasta s nižim koncentracijama fluora (0,025% F, 0,04% F, 0,05% F) i rezultati su ohrabrujući (24) jer su nađeni učinkoviti karijesprotektivni učinci spojeva za topikalnu fluoridaciju s nižim koncentracijama fluora (24, 25, 26).

Mehanizam zaštitnoga djelovanja fluorida složena je interakcija s caklinom. Slobodni ion fluora iz zubne paste ili vode za usta ili bude ugrađen u kristalnu strukturu cakline za vrijeme procesa remineralizacije ili se adsorbira na kristale smanjujući brzinu njihova otapanja (27). Danas se postojanje fluorida u tekućoj fazi oko kristalića apatita smatra važnjim čimbenikom u redukciji demineralizacije od inkorporacije fluorida u kristale (28). I vrlo niske koncentracije fluorida uz nizak pH mogu gotovo potpuno zaustaviti otapanje kristala i/ili smanjiti brzinu demineralizacije (29,30). Nakon kratkoga izlaganja zubnim pastama ili vodama za usta, fluor se na zubima zadržava u obliku kalcij fluorida u plaku ili na površini cakline. Tijekom kariogenih zbijanja taj kalcij fluorid osigurava slobodne ione fluora koji se ugrađuju u caklinu kao hidroksilfluorapatit ili fluorapatit (31,32).

Klinička se djelotvornost pripravaka za higijenu usne šupljine u prevenciji karijesa se procjenju-

je temeljem postojanja tih dvaju čimbenika: dovoljnih količina fluorida u vrijeme moguće demineralizacije, kako bi ju zaustavili, i/ili trajnom nazočnošću malih količina fluorida kako bi ubrzali remineralizaciju (18).

Fluoridi u zubnoj pasti, osim što pospješuju remineralizaciju početnih caklinskih lezija, prije nastanka karijesnog kaviteta djeluju i baktericidno na bakterije u zubnome plaku. Fluoridi inhibiraju karbohidratni mehanizam acidogene mikroflore zubnoga plaka inhibicijom glikolitičkog enzima enolaze. Time je smanjen nastanak kiselina koje demineraliziraju caklinu (33).

Fluoridi mogu smanjiti i dentinsku preosjetljivost. Otopine fluorida sporo difundiraju u dentinske tubule, u kojima fluor ostaje ili kao slobodan ion ili vezan u precipitatu kalcij fluorida na površini peritubularnog dentina. Neki autori drže (34,35) da se sporom difuzijom fluoridi u intratubularnom dentinu vežu za hidroksilapatit. Hellwig (36) je pokazao da je odmah nakon topikalne primjene aminofluorida najveći dio fluora nakupljenog u dentinu bio topiv u alkalijama (KOH) i da se taj dio smanjuje tijekom nekoliko dana, a istodobno raste količina čvrsto vezanih fluorida. To su pokazali i drugi autori. Brz gubitak alkalno topivih fluorida vjerojatno je posljedica jednostavne re-difuzije slobodnog fluora iz dentinskih tubula u slinu ili u otapanju precipitata spoja poput kalcij fluorida i gubitka fluorida slinom.

### 1.8.2. Sredstva za prevenciju zubnoga kamenca

U prevenciji zubnoga kamenca - kalkulusa, koji nastaje kod 45-65% ljudi - rabe se pirofosfati. Njihova je uloga da inhibiraju rast jezgara mikroskopskih kristala kalcij fosfata, koji su nađeni u zubnome plaku, a da pri tome ne utječu na remineralizaciju ranih karijesnih lezija (19). Uz to oni vežu i slobodni kalcij iz sline i sprječavaju da se taloži na površini zuba. Redukcijom zubnoga kamenca lakše se održava higijena usne šupljine i lakše se smanjuje zubni plak, intenzitet kojega korelira s pojmom i jakosću gingivitisa i periodontitisa (37,38,39).

### 1.8.3. Antimikrobna sredstva

*Antiseptici*, kao antimikrobni dodaci, također postoje u zubnim pastama, a svrha im je reducirati mikroorganizme zubnoga plaka i smanjiti čestoću nastanka gingivitisa (40). Od antiseptičkih dodata-

ka zubnim se pastama dodaje *triklosan*, *sangvinarin*, te antiseptici iz eteričnih ulja koji sadrže fenol i dje luju na mikroorganizme kao protoplasmatski otrovi (41). Triklosan (kloksifenol) je klorirani bifenolni antiseptik djelotvoran protiv gram pozitivnih i većine gram negativnih bakterija, te protiv gljivica. Slabo djeluje na sojeve Pseudomonasa i često se dodaje sredstvima za higijenu usne šupljine (38, 39, 42, 43, 44, 45).

Sangvinarin je alkaloid dobiven iz podanka biljke *Sanguinaria canadensis* koji djeluje antimikrobi no i koji je u kliničkim pokušima u kombinaciji sa cink kloridom pokazao dobre učinke u redukciji plaka i u poboljšanju gingivitisa (46,47).

I fluoridi koji se dodaju zbog antikarijesnog učin ka djeluju kako je gore opisano baktericidno (33).

#### 1.8.4. Sredstva za smanjenje preosjetljivosti dentina

*Preosjetljivost dentina* vrlo je česta pojava. Ona može nastati na jednom ili na više zuba. Posljedica je ogoljenosti dentina zbog nedostatka dijela cakline ili cementa. Ti nedostaci mogu biti posljedica grješaka u embrionalnom razvoju u području caklin sko-cementnog spoja ili nastaju tijekom života kao posljedica abrazije, atricije ili erozije zuba zbog ne pravilnog četkanja zubnim četkicama ili zbog rece sije gingive nakon parodontnih zahvata (48). Mehanizam nastanka preosjetljivosti još se ne zna točno, premda postoji nekoliko teorija kojima se nastoji objasniti njezin nastanak:

- izravan podražaj živčanih završetaka u dentalnim tubulima;
- nazročnost limfe u dentinskim tubulima koja omogućuje da pri izlaganju dentina poraste koloidni tlak u tubulima čime se povećava pritisak na odontoblaste i njihove nastavke (Tomesovo vlakno) kojima se posredno prenesu impulsi do živčanih završetaka pulpe;
- hidrodinamsko gibanje tekućine u tubulima brzinom od 2-4 mm/sek koje podražuje mehanoreceptore i uzrokom je odašiljanja akcijskog potencijala u subodontoblastičnom živčanom pleksusu i pojave боли (49, 50, 51, 52).

Iako mehanizam još nije objašnjen, liječenje dentinske preosjetljivosti provodi se tako da se:

- zatvaraju dentinski tubuli,
- smanjuje osjetljivost živaca u pulpi.

Kalij nitrat, natrij citrat i stroncij klorid pokazali su se djelotvornima u kliničkim pokušima u smanjenju osjetljivosti zuba na mehaničke, termalne i druge podražaje.

Kalij nitrat ( $\text{KNO}_3$ ) se dodaje zubnim pastama u 5% koncentraciji. Čini se da je mehanizam njegova učinka u povećanoj koncentraciji kalijevih iona i produženoj hiperpolarizaciji živčanih vlakana.

Stroncij klorid dodan zubnoj pasti u 10% koncentraciji stvara, u kombinaciji s fosfatima iz dentinske tekućine i zamjenom kalcija iz hidroksilapatita, stroncij fosfat koji zatvara dentinske tubule (53).

Istim mehanizmom kako je naprijed opisano djeluju i fluoridi (36, 54, 55).

## 2. Vode za usta

Osim pasta za zube sve se češće u higijeni usne šupljine upotrebljavaju i vode za usta. One otplavljaju zubne naslage, osiguravaju ugodan okus i da te prikrivaju neugodan zadah iz usta. Ako takve vode sadržavaju antiseptike, moguće je sublingvalnom irigacijom ublažiti gingivitis i djelovati protuupalno. Od antimikrobnih lijekova vodama za usta dodaju se kationski detergenti, kvaterni amonijevi spojevi, poput cetilpiridina (u koncentraciji od 0,05%) i benzalkonij klorida (0,1-0,2%), zatim timol i sangvinarin (0,01%) (56, 57, 58). Mnoge vode za usta sadržavaju i natrij fluorid u koncentraciji od 0,02-0,05% koji također djeluje antibakterijski i pomaže u redukciji karijesa.

Neke vode za usta sadržavaju oksidacijske antiseptike, poput vodik peroksida (1-1,5%) ili natrij perborata, koji potpomažu mehanički uklanjanjati naslage oko zuba. No, dugotrajna uporaba takvih voda za usta može prouzročiti razvoj crnoga dlakavog jezika (58).

Sastavni dio pojedinih voda za usta jesu i etil alkohol u koncentraciji od 14 do 27%. O dodatku alkohola sredstvima za higijenu usne šupljine mišljenja su podijeljena, iako se etil alkohol pokazao dobrim u redukciji zubnoga plaka (58).

Za redukciju zubnoga kamenca vodama za usta dodaje se di-ili tetranatrij pirofosfat koji oslobađa 1% ionskog pirofosfata i reducira kamenac pri uporabi vode za usta dva puta na dan 35 do 40% (58).

Vode za usta služe i za uklanjanje neugodna zadaha iz usta. Neugodan zadah iz usta (halitosis ili

foetor ex ore) čest je u ljudi (59). Uzroci mu mogu biti sustavski i lokalni. Najčešći je razlog (u 80-90% slučajeva) nakupljanje plaka i ostataka hrane na tvrdim i mekim tkivima u usnoj šupljini. Bakterije iz zubnoga plaka na proteinima koji potječu iz oljuštenoga oralnog epitela, proteina iz sline, ostataka hrane i krvi razgrađuju mnoge spojeve, uključujući sulfide i mukoproteine. Od njih nastaju razgradni produkti metil merkaptan i vodik sulfid koji stvaraju neugodan zadah iz ustiju. Neugodan zadah prati lokalne promjene u usnoj šupljini: gingivitis, periodontitis, karijes, fistule i ulceracije sluznice usne šupljine, ali može biti posljedica i sustavnih bolesti, poput bolesti respiratornog ili gastrointestinalnog sustava, faringitisa i tonsilitisa, infekcija sinusa i dr. Terapija treba biti etiološka, a dok se ona provodi treba upotrebljavati vode za usta koje svojim antimikrobnim i dezodorantnim učikom kratko-trajno (oko 30 min) uklanjaju neugodan zadah.

### Zaključak

Redovito i pravilno održavana higijena usne šupljine osnovni je uvjet za čuvanje orodontalnoga zdravlja. U tome važnu ulogu imaju zubne paste i vode za usta s dodatcima koji mogu utjecati da se smanjuje karijes, gingivitis, zubni kamenac, neugodan zadah i dr. Zadaća je stomatologa da prema orodontalnom statusu pomogne svojem bolesniku izabrati zubnu pastu ili vodu za usta s farmakoterapijskim dodatcima koji će pomoći održavati zdravlje ili djelovati terapijski.

Od svih farmakoterapijskih dodataka zubnim pastama najvažniji su fluoridi. Velikom raširenosti uporabe pripravaka za higijenu usne šupljine s fluoridima čestoča zubnoga karijesa je, osobito u industrijski razvijenim zemljama, uvelike smanjena.

“Zdravim ustima” kao socijalno poželjnom čimbeniku, pogotovo u mladoj populaciji, pridonose i ostali farmakoterapijski dodaci pripravcima za higijenu usne šupljine: antiseptici, sredstva protiv zubnoga kamenca, lijekovi za desenzibilizaciju osjetljivog dentina i sredstva za uklanjanje neugodna zada.

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# Oral Hygiene Products and Pharmacotherapeutic Agents

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## Summary

*Oral hygiene products with effective pharmacotherapeutic agents are an ideal mode for maintenance of oral health, decline in caries and general improvement in oral health in many areas of the world.*

*The main agents are fluoride effective in reducing caries in humans (monofluorophosphate, stannous fluoride, amine fluoride, sodium fluoride). Today many researchers consider them, to be the major reason for the decline in dental caries in most developed countries. Other active agents are calculus control agents (pyrophosphate), ingredients for reducing dental hypersensitivity (strontium chloride, potassium nitrate) and halitosis (antimicrobials).*

*It is important to ensure that these agents do not interfere with the anti-caries activity of fluoride.*

Key words: therapeutic dentifrice, oral hygiene products

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Regular and correct care of oral hygiene is the basic measure for maintenance of oral health. For this interaction of toothbrush and dentifrice is needed and auxiliary agents like mouthrinses. The major function of the *toothbrush* is mechanical cleansing of the surfaces of teeth and the massage of gums. Massage increases the resistance of gingival tissue to local factors (such as bacterial attack) able to cause inflammation (1).

Toothbrushes are used with *dentifrices*. Dentifrices are available in the form of gels and pastes.

## 1. Dentifrices

The main value of dentifrices is their ability to:

1. facilitate the removal of plaque and stain,
2. reduce caries,
3. prevent gingivitis,

4. ensure other therapeutic effects like desensitization of dentinal hypersensitivity, anti-tartar or anti-plaque effects.

Toothbrushing with a dentifrice remove stain, debris and dental plaque from the accessible tooth surfaces.

The essential components of dentifrices are:

1. abrasive
2. foaming agents
3. flavoring agents
4. humectant
5. binders
6. preservatives
7. coloring agents

The dentifrices also contain pharmacotherapeutic agents in order to increase the anticaries effect, and to reduce dentinal hypersensitivity, calculus and plaque formation.

### 1.1. Abrasive

The abrasive component of dentifrice serves, with the foaming agents, to remove the mechanically stained pellicle from sites of the dentition that are accessible to the toothbrush bristle. They must be hard enough to remove the dental plaque but not too hard so that minimal tooth structure is removed when they are used. In the past the most common dentifrice abrasive was calcium carbonate. However, as it prevents the release of the fluoride ion from dentifrice, most dentifrice abrasives today are inorganic salts, that are relatively insoluble. They include a number of phosphate salts such as dicalcium phosphate, calcium pyrophosphate, calcium metaphosphate, hydrated aluminum oxides, silicates and silicagels.

The selection of an abrasive depends not only on its abrasiveness but also on its lack of interaction with other dentifrice components.

The size of the abrasive particle must be 3 to 12 µm and it must have a smooth and regular shape. An irregular shape can damage the soft and hard tissues of the oral cavity. Dentifrices with larger particles are highly abrasive, like sand, and people do not like them.

### 1.2. Foaming agents

Anionic surfactants are of importance in oral hygiene product formulation, because of their high foaming capacity. The foam helps the mechanical cleaning and acts as a antimicrobial. The two common foaming agents, lauril sulfate and sodium decilbenzoate, are used extensively today. They are used for their deteritive, emulsifying and antimicrobial properties (1).

### 1.3. Flavoring agents

The dentifrice must provide a pleasant refreshing sensation in the mouth. Flavor is the key to acceptability of dentifrices. Only a few compounds can provide the freshness characteristics essential to an oral product. These are mints (spearmint, peppermint) and cinnamon.

Peppermint oil is derived from the plant *Mentha piperita*. Peppermint oil has a fresh, minty odor and a sweet, balsamic taste and strong cooling effect.

Spearmint oil is derived from the plant *Mentha crispata* and *tenuis*. It provides a warm penetrating herbaceous odor and a sharp, but pleasant pungent taste. It lacks the cooling effect.

Cinnamon oil has a somewhat bitter flavor, is slightly pungent and quite "hot". These flavors are incorporated into dentifrices at a level of some % to 2% (menthol).

These flavoring agents are usually used in combination with any number of other flavoring compounds-fruit note, spice note like Anise oil, Eucalyptus oil, Lemon oil or for children fruit extracts (2).

Nonsucrose sweetening agents are also added to the dentifrice e.g. saccharin or cyclamate, which are noncariogenic.

### 1.4. Humectants

Humectants make a substantial contribution to the bulk properties of dentifrice by providing a vehicle into which additives can be incorporated (abrasive, drug, flavor) to produce a smooth, homogeneous mixture and maintaining an extrudable paste which resists "drying out" when the product is exposed to the atmosphere for prolonged periods of time. The humectant may account for 50% or more of the dentifrice. Humectants used in dentifrices today are sorbitol, glycerin and hydrogenated starch hydrolyzates (1).

### 1.5. Binders

Binders are the important parts of dentifrices. Their importance rest mainly in their role of structuring toothpastes and in stabilizing these products against separation of aqueous and nonaqueous component during storage and distribution. Their major functions are to help give the paste firmness along with extrudability, to provide a smooth, shiny dentifrice and make the dentifrice thixotropic. They must be nontoxic, physiologically inert, nonirritant and non-sensitizer.

The binders now in use are: the silicas, sodium carboxymethyl cellulose, and a few natural vegetable gums like carrageenan (hydrocolloid obtained by aqueous extraction of certain species of red seaweeds) which is a part of clear high-humectant content dentifrices or xanthan gum (an extracellular polysac-

charide produced by the bacterium *Xanthomonas campestris*) (1).

### **1.6. Preservative**

The preservative in the dentifrice must be an antimicrobial agent. The most common agent for the dentifrice is nontoxic sodium benzoate. It has antibacterial and antifungal properties, but not on the microorganisms in the oral cavity.

### **1.7. Coloring agents**

The color of the dentifrice subjectively influences the regular use of dentifrice especially by children. On the market there are dentifrices of different colors or color stripes (2).

The color must be as stable as the dentifrice itself. The colors in the dentifrices are the same as those used in the food industry.

### **1.8. Pharmacotherapeutical components in dentifrices**

#### **1.8.1. Fluoride**

The most important pharmacotherapeutic agents in dentifrices are fluorides. The absolute clinical relevance of fluoride applied systematically and topically was established long ago. The ability of fluoride-containing dentifrices to contribute to caries control has been more extensively documented than any other topical fluoride measure and their cariostatic benefits are widely used.

Dental health reflects equilibrium between cariogenic factors (such as sugar and plaque) and well known preventive factors (oral hygiene and fluoride in various forms).

The clinical relevance of the anticaries effect of endogenous fluoridation (fluoridation of drinking water, domestic salt or tablets) is unquestionable (3) and was widely administered. However, although in the 1970s water fluoridation was discontinued in many cities (4,5) the decline of caries prevalence continued.

Fluoride tablets are an important source of caries-preventive fluoride. The fluoride tablets which were in use in a number of European industrialized

countries had systemic as well as topical potential (6). However, sales have dropped considerably over the last 10 years. The tablets were always given to children in the rather small subpopulations of highly educated conscientious parents. Thus this source of fluoride cannot be the reason for the conspicuous caries reduction in 80% of the total child population (7). This can only be explained by individual preventive measures, and the increasing use of fluoride dentifrices.

In the Netherlands in 1991 97% of the total amount of dentifrices were fluoride dentifrices, in the USA more than 90%, and a similar situation exists in most developed countries of the world (8,9).

The topical (professional) application of fluoride, which should be regularly applied, especially in high-risk patients, does not take place often enough (10). Topical treatment could also have played a minor role in caries decline over the last 10 years. It has been suggested that the main reason for the decline of caries in adolescents is the greater availability of fluoride dentifrices adolescents. Most of them brush their teeth once or twice a day (11).

All fermentable carbohydrates, including sugar, contribute to development of dental decay. Some authors believe consider that decrease in sugar consumption could be the reason for the decrease in caries in children. However, in the developed countries of Europe (12,13), USA (14), New Zealand (5) sugar consumption has either remained roughly stable or has even increased, while the prevalence of caries has decreased consistently. The general conclusion of König (8) was: "The continuous decrease of caries in many nonfluoridated areas of Europe is nearly entirely due to fluoride contained in toothpastes and probably improved hygiene measures and cleanliness".

According to data by WHO in 1994 more than 450 million people throughout the world used fluoridated dentifrices (15).

The results of a study by Hargraves on the Isle of Lewis (Scotland) confirm this opinion (16). Prevalence data collected from a 1971 survey conducted on children aged 5, 8, 11 and 14 were compared ten years later with the data from the same age groups of children in this community. There was little change or movement of the population on this island and there was no fluoride in the drinking wa-

ter and no appreciable use of fluoride rinses or tablets in this community. However, the toothpaste market changed from zero fluoride in 1970 to virtually 100% in 1976. The results of this study confirmed a general decrease in dental caries (Table 1) by more than 30%.

Fluoride ions are very reactive. The fluoride in a dentifrice must be properly chosen and compatible with the type of abrasive in the toothpaste. The fluorides incorporated in dentifrices are: sodium fluoride, stannous fluoride, sodium monofluorophosphate and amine fluoride. Clinical caries trials have indicated that, with proper formulation, there is little or no difference in effectiveness among toothpastes prepared with these different fluoride agents. The main caries inhibition for all of them is about 20% (17,18). Most dentifrices world-wide contain monofluorophosphate which is compatible with a wide variety of abrasive systems (19). Table 2 lists fluoride abrasive combinations that are sufficiently compatible to be used in dentifrices. Sodium monofluorophosphate is listed separately because it is compatible with more abrasives than ionic fluoride.

Fluoride concentration in most dentifrices is 1%. After the use of fluoride dentifrices some fluoride is inadvertently swallowed. The amounts of fluoride ingested especially by small children following the use of fluoride-containing toothpastes can range from 0.27 to 0.3 mg of fluoride. The bioavailability of fluoride from toothpaste is almost 100%. That is, most of the ingested fluoride reaches the systemic circulation and the plasma fluoride level can elevate suddenly (20). The "optimal" daily dose of fluoride in caries prevention is 0.05-0.07 mgF/kg of body weight (21). The intake of more than 0.1 mgF/kg can cause dental fluorosis (22). There has been a trend in recent years to lower the F concentrations in dentifrices (0.025%F, 0.04%F, 0.05%F) in order to avoid dental fluorosis (23). The results of many studies with low fluoride preparations are quite promising (24,25,26).

The mechanism of anticaries effect of fluoride containing dentifrices is most likely a combination of various mechanisms. The free ionic fluoride from toothpastes can be incorporated into the crystal structure of enamel during remineralizing cycles or adsorbed into crystals thus reducing its rate of dissolution (27).

The availability of fluoride in the liquid phase around the apatite crystallites is today believed to

be more important in decreasing dissolution of crystallites than fluoride incorporation in the crystal lattice (28). Very low liquid fluoride concentration under low-pH conditions can block crystalline dissolution almost completely and/or reduce the rate of demineralization (29, 30). Fluoride which is retained on teeth after brief exposure to toothpastes is retained mainly as calcium fluoride. Calcium fluoride is most likely the provider of free fluoride ions during cariogenic challenges. These being subsequently incorporated into enamel as hydroxyfluorapatite or fluorapatite (31, 32).

The two most important factors in determining the clinical success of fluoride containing dentifrices are probably the presence of sufficient concentration of fluoride at critical times which inhibit the dissolution reaction and the continued presence of low concentrations which promote remineralization (18).

Beside its effects as a remineralizing agent as well as caries inhibitor, fluoride is also an antienzyme. It may inhibit enzymatic acid production by plaque bacteria. The fluoride induced reduction of acid production is due in part to the inhibition of the glycolitic enzyme-enolase (33).

Fluoride can also reduce dental hypersensitivity. Fluoride solutions can diffuse into the dentin tubules and this fluoride is present either as the simple fluoride ion or is bound as a CaF<sub>2</sub> precipitate on the surface of the peritubular dentin. There is evidence from the literature that the intertubular diffusion of fluoride in dentin is slower (34, 35). With this slower diffusion fluoride in intratubular dentin is bound as fluoridated hydroxyapatite. Hellwig's study shows that immediately after the topical application of aminefluoride, the main part of the accumulated fluoride in dentin was alkali soluble (KOH), which diminished within a few days. Simultaneously the amount of structurally bound fluoride increased (36). This is in accordance with the studies of other authors. The fast loss of alkali soluble fluoride may be due to simple rediffusion of free fluoride from the dentin tubules into saliva or to the dissolution of the CaF<sub>2</sub> like precipitate and to the subsequent loss of fluoride into saliva or both.

### 1.8.2. Calculus reducing agents

A number of oral products are available for reduction of supragingival calculus in dental patients. The incidence of calculus formation ranges from

45-65%. The pyrophosphates have calculus reducing properties. Their mechanism of action is related to their ability to inhibit crystal growth and interrupt the transformation of calcium phosphate into dental calculus (19). A decrease in calculus formation could make oral hygiene procedures easier. The reduction of plaque formation could well correlate with the reduction of gingivitis and periodontitis (37, 38, 39).

### 1.8.3. Antimicrobials

*Antiseptics* are also components of dentifrices. They can reduce the bacteria in dental plaque and frequencies of gingivitis (40). The most frequently used antiseptic dentifrice ingredients are triclosan, sanguinarine and antiseptics from aetherolea which have the phenol and act on microorganisms like a protoplasmic poison.

Triclosan (cloxifenol) is a chlorinated bisphenol antiseptic effective against gram positive and gram negative bacteria, but with variable or poor activity against *Pseudomonas*. It is also active against fungi (38,39,42,43,44,45).

Sanguinarine is an alkaloid (benzophenanthridine) derived from the bloodroot of plant *Sanguinaria canadensis*. The clinical studies of sanguinarine have shown that it can significantly reduce plaque and gingivitis (46,47).

The fluoride is also an antimicrobial (33).

### 1.8.4. Desensitizing agents

*Hypersensitive dentin* is a condition which occurs when the vital dentin is exposed to the environment of the oral cavity. Dental hypersensitivity can occur in singular or multiple sites. It may be the consequence of irregular embryonal development of teeth, improper teeth brushing (with toothbrushes) (48) or the recession of the gingive after periodontal instrumentation.

The cause of dentinal hypersensitivity remains unclear. Among the theories advanced are the following:

- Innervation of dental tubules permits transmission of impulse to the pulp.
- Lymph fluid is present in the dentinal tubules, so that exposure of the dentin results in increased colloidal pressure on the tubules, thereby increa-

sing pressure on the odontoblastic cells and their neurons.

- Hydrodynamic mechanism involves the movement of tubular fluid (at a rate of 2-4 mm/sec) in either direction. It starts the transmission of the nerve impulse in the subodontoblastic plexus and eliciting pain in the pulp (49, 50, 51, 52).

Although not one of these theories has been proved, there are two ways to relieve the pain:

- sealing the dentinal tubules,
- reducing the neuronal transmission of impulses.

Potassium nitrate, sodium citrate and strontium chloride are included in dentifrice formulations for use in the treatment of dentinal hypersensitivity. They can reduce sensitivity on mechanical, thermal and chemical stimulation.

Potassium nitrate ( $\text{KNO}_3$ ), in a concentration of 5% in the dentifrice can increase the concentration of potassium ions and prolong the neuronal hyperpolarization.

Strontium chloride in a concentration of 10% in the dentifrice, combined with phosphate ions from dentinal fluid, can seal the dentinal tubules and reduce the hypersensitivity (53).

The mechanism of fluoride as a desensitizing agent is similar (36, 54, 55).

## 2. Mouthrinses

Mouthrinses, along with dentifrices, are the most frequently used oral care products. They flush loose debris from the mouth, provide a pleasant taste and mask bad breath. It is possible that subgingival irrigation with antibacterial mouthrinses may result in a reduction of gingivitis and the control of inflammation.

The antimicrobial ingredients of mouthrinses are the quaternary ammonium disinfectants like benzalkonium chloride (0.1-0.2%) and cetylpyridinium chloride (0.05%), thymol (0.05%) and sanguinarine (0.01%) (56, 57).

Fluoride is also a very frequent ingredient of mouthrinses in a concentration of 0.02-0.05%. Its effect is antimicrobial and anticariogenic.

Some mouthrinses contain an oxygenating agent like hydrogen peroxide (1-15%) or sodium perbo-

rate, which mechanically removes loose debris around teeth releasing oxygen and associated effervescence. Long-term use of these agents has occasionally been associated with the development of a black, hairy tongue (58).

Several mouthwashes contain alcohol in a concentration of 14-27%. Although alcohol has the ability to reduce dental plaque, opinions on the alcohol content in mouthrinse products are controversial (58).

Disodium and tetrasodium pyrophosphate in a concentration of 1.6% in mouthrinses act against calculus formation. Calculus reduction has been reported to be 35-40% with twice a day rinsing (58).

Mouthrinses can mask bad breath. Bad breath (halitosis) may be caused by a variety of conditions (59). The most common source of halitosis is accumulation of plaque and food debris on the oral hard and soft tissue. Bacteria in these plaque accumulations develop on proteinaceous substances such as exfoliated oral epithelium, salivary proteins, food debris and blood odoriferous sulfate substances. It appears that oral malodor results from methyl mercaptan and hydrogen sulfide in the breath as a result of these degrading processes. Halitosis is particularly related to local factors: caries, gingivitis, periodontitis, fistulas, ulcerative lesions, but also to systemic factors like respiratory or gastrointestinal disorders, pharyngitis, tonsillitis, sinus infections etc.

Therapy should be directed toward removing the causative factors. Until such factors are removed a mouthwash may be recommended to mask the bad breath temporarily (30 min) with its antimicrobial and deodorant effect.

### Conclusion

Careful oral hygiene is the basic factor in maintaining oral health. Oral dental products: dentifrices and mouthrinses are the major contributors to optimal care. They can reduce or prevent caries, gingivitis, calculus formation, halitosis etc. The dental health professional, must help their patients choose the right dentifrice or mouthrinse, according to their oral status, which can help them maintain oral health or act therapeutically.

Fluoride is the most important pharmacotherapeutic agent in dentifrices. The widespread application of oral products with fluoride is the main reason for the dramatic decline in the prevalence of dental caries which is evident in many highly industrialized countries. Other therapeutic ingredients of oral products, besides fluoride can contribute: antimicrobials, to the "healthy mouth", a socially desirable factor, especially in the young population: desensitizing agents, and agents for reduction of calculus or halitosis.