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EFIKASNOST GALIJUMA U PREVENCIJI GUBITKA ZUBA

EFFICACY OF GALLIUM IN TOOTH LOSS PREVENTION

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Sažetak

***Uvod**: Jedinjenja galijuma su u poslednje tri decenije dobila značajnu ulogu u medicini. Radioaktivni galijum i stabilni galijum nitrat koriste se kao dijagnostički i terapeutski agensi kod kancera, poremećaja kalcijuma i metaboličkih oboljenja kostiju. Pored toga, ova jedinjenja pokazala su antiinflamatornu i imunosupresivnu aktivnost u animalnim modelima humanih bolesti. Nedavno je takođe pokazano da galijum može da funkcioniše i kao antimikrobni agens.*
U ovom preglednom radu diskutovaće se o potencijalnoj aplikaciji galijuma u budućoj terapiji parodontopatije i prevenciji gubitka zuba. Karakteristična obeležja parodontalne bolesti su inflamacija gingive, bakterijska infekcija, destrukcija alveolarne kosti i posledični gubitak zuba. U terapiji parodontopatije trenutno se koriste hirurške tehnike, mehanički debridman ogoljene površine korena zuba i lokalna ili sistemska aplikacija antimikrobnih agenasa. Razvoj antibiotske rezistencije kod bakterija izazvao je potrebu za novim, alternativnim metodama lečenja infekcije.
***Zaključak**: Potencijalna korist galijuma u terapiji parodontopatije povezana je sa iskorenjivanjem infekcije uzrokovane bakterijskim biofilmom, povećanom depozicijom kosti i supresijom neželjenih imunskih odgovora. Adjuvanta terapija laserom na bazi galijuma mehaničkom instrumentacijom i korišćenjem gingivalnih gelova, paste za zube i rastvora za ispiranje usta koji sadrže galijum mogla bi da predstavlja krajnje rešenje za prevenciju gubitka zuba.*

***Ključne reči:** galijum, efikasnost, prevencija, gubitak zuba*

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Abstract

***Introduction**: Over the past three decades, gallium compounds have gained importance in medicine. Radioactive gallium and stable gallium nitrate are used as diagnostic and therapeutic agents in cancer and disorders of calcium and bone metabolism. In addition, gallium compounds have displayed anti inflammatory and immunosuppressive activity in animal models of human diseases. More recent studies have shown that gallium compounds may also function as antimicrobial agents.*
In the review, the potential application of gallium in the future treatment of periodontitis and prevention of tooth loss will be discussed. Gingival inflammation, bacterial infection, alveolar bone destruction and subsequent tooth loss are characteristic features of periodontal disease. Surgical techniques, mechanical debridement of the denuded root surface, and local or systemic application of antimicrobial agents are currently used treatments for periodontitis. However, the development of antibiotic resistance in bacteria has prompted a great need for new and alternative treatment methods for infection.
***Conclusion**: The potential anti-periodontitis benefits of gallium are related to eradicating infection due to bacterial biofilms, increasing bone deposition and downregulating unwanted immune responses. Adjunctive use of gallium laser therapy with mechanical instrumentation in combination with gallium-containing gingival gels, toothpastes and mouth rinses may represent the final solutions for tooth loss prevention.*

***Key words:** gallium, efficacy, prevention, tooth loss*

Uvod

Terapijska dejstva galijuma

Galijum (Ga) je trovalentni semimetalni element koji ispoljava brojne terapijski korisne biološke aktivnosti. Mnoge od ovih aktivnosti potiču od sposobnosti galijuma da deluje slično gvožđu (Fe). Dobro je poznato da je većini patogenih bakterija gvožđe potrebno za rast. Galijum (Ga3+) je strukturno sličan gvožđu (Fe3+), osim što ne može da se redukuje u fiziološkim uslovima. Dok je Ga3+ ireducibilan u fiziološkim uslovima, Fe3+ učestvuje u redoks reakcijama u kojima se odmah redukuje u dvovalentni jon (Fe2+). Tako, zamenom Fe3+, Ga3+ ometa sintezu bakterijske DNK i blokira redoks reakcije, od kojih zavisi elektronsko naelektrisanje gvožđa[1]. Sposobnost galijuma da kompetitivno deluje sa drugim esencijalnim metalima, naročito cinkom, verovatno je odgovorna za neke od njegovih bioloških aktivnosti. Tako je uočeno da jonski galijum dozno-zavisno inhibira aktivnost matriks metaloproteinaza. Pretpostavljeno je da je ovaj efekat uzrokovan zamenom galijuma za cink u ovim proteinima (cink-proteazama)[2,3].

Poznata terapijska dejstva u kojima galijum može da ima glavnu ulogu:

1) Aktivnost protiv određenih patogenih mikroorganizama, uključujući *Pseudomonas aeruginosa* i neke intracelularne bakterije[4,5].

2) Antiinflamatorna i imunomodulatorna dejstva. Antiinflamatorno dejstvo galijuma obuhvata supresiju inflamatornih T limfocita i makrofaga, kao i moguće posredovanje sa matriks metalo-proteinazama[6].

3) Anti-koštano resorptivno i anti-hiperkalcemijsko dejstvo, kao i moguće anaboličke aktivnosti. Galijum redukuje nivo kalcijuma u plazmi inhibicijom resorpcije kosti, prevashodno selektivnim dejtvom na osteoklaste[7]. Pored direktnog dejstva na osteoklaste, galijum može, na osnovu značajnih eksperimentalnih dokaza, da stimuliše formiranje kosti dejstvom na osteoblaste (ćelije koje formiraju kost)[8-10].

4) Aktivnost protiv patološke hiperproliferacije, naročito kod agresivnih tumora. Galijum ometa preuzimanje i upotrebu gvožđa od strane tumorskih ćelija. Pored toga, ima direktno inhibitorno dejstvo na ribonukleotidnu reduktazu[1].

Introduction

Gallium`s therapeutic activities

Gallium (Ga) is a trivalent semi-metallic element that exerts a variety of therapeutically useful biological activities. Many of these activities derive from gallium's ability to act as an ferric iron ($Fe3^+$) analog. It is well known that most pathogenic bacteria require $Fe3^+$ to grow. $Ga3^+$ is structurally similar to $Fe3^+$, except that it cannot be reduced under physiological conditions. While $Ga3^+$ is irreducible under physiological conditions, $Fe3^+$ participates in redox reactions, in which it is readily reduced to $Fe2^+$. Thus, by replacing $Fe3^+$, $Ga3^+$ interferes with bacterial DNA synthesis and blocks the redox reactions that depend on iron electron aquisition[1]. Gallium`s ability to compete with other essential metals, particularly zinc, is likely to be responsible for some of its other biological activities. Ionic gallium is observed to dose-dependently inhibit matrix metaloproteinase activity. This effect is hypothesized to be caused by substitution of gallium for zinc in these proteins (zink-bearing proteases)[2,3].

The known therapeutic activities in which gallium may play a major role include:

1) Activity against some pathogenic microbes, including *Pseudomonas aeruginosa* and some intracellular bacteria[4,5].

2) Anti-inflammatory and immunomodulatory activities. The anti-inflammatory action of gallium involves downregulation of inflammatory T cells and macrophages, as well as possible interference with matrix metalloproteinases[6].

3) Anti-bone resorptive and antihypercalcemic activities, as well as possible anabolic activities. Gallium reduces plasma calcium by inhibiting bone resorption, predominately through selective actions on osteoclasts[7]. In addition to acting directly on osteoclasts, gallium can, based on considerable experimental evidence, stimulate bone formation through action on osteoblasts (bone forming cells)[8-10].

4) Activity against pathological hyperproliferation, particularly against some aggressive cancers. Gallium interferes with the uptake and utilization of iron by cancer cells. In addition, it has direct inhibitory activity on ribonucleotide reductase[1].

5) Moguće analgetsko dejstvo. Analgetski efekat verovatno je povezan sa dejstvom protiv tumora, resorpcije kosti i pridružene inflamacije[11,12].

Jedinjenja galijuma kao dijagnostički i terapijski agensi u medicini

Aplikacija jedinjenja galijuma kao dijagnostičkih i terapijskih agenasa u medicini pokrenula je pitanja o farmakologiji, kliničkoj efikasnosti i potencijalnim neželjenim dejstvima. Jedinjenja galijuma mogu da prođu različite stepene metaboličkih izmena u telu u zavisnosti od načina njihove administracije i hemijske prirode. Rastvor citratnog galijum nitrata (CGN) za injekciju trenutno je odobren u Sjedinjenim Američkim Državama za terapiju hiperkalcemije uzrokovane tumorom. Kako bi se izbegla renalna toksičnost CGN mora da se primenjuje kao spora infuzija u toku nekoliko dana[13]. Otkriće anti-tumorskih dejstava galijuma poklapa se sa uvođenjem Ga-skenera u dijagnostici i lokalizaciji naročito raznih tumora u telu. Ga-skeneri su senzitivni na limfome, određene sarkome i koštane tumore[14].

Kako bi se izbegla neugodna primena i renalna toksičnost intravenskog galijum-nitrata, razvijen je galijummaltolat (GaM)kao oralno aktivno jedinjenje galijuma. Galijum se veoma slabo resorbuje na konoralne administracije u obliku nitrata, što je delimično uslovljeno hidrolizom, u toku koje u gastro-intestinalnim fluidima nastaju polimerizovani hidroksidi galijumoksidanske solubilnosti. GaM obezbeđuje nekoliko puta veću oralnu arsorbciju galijuma u poređenju sa galijum-nitratom. Pored toga, GaM je solubilniji u lipidima u poređenju sa galijum-nitratom i ne izaziva neželjene efekte. GaM zbog lipidne solubilnosti ima bolju bakterijsku penetraciju i ispoljava superiorniju antimikrobnu aktivnost[15,16]. Galijum 8-kvinolinolat i galijum-hlorid takođe su razvijeni kao oralno aktivne forme galijuma[3,17]. Testiranje oralnih formulacija galijuma kod čoveka pokazala su aktivnost protiv određenih tumora, kao i anti-koštanu resorptivnu aktivnost. Jedinjenja galijuma su naročito efektna kada se lokalno aplikuju na kožu imukozne membrane, gde mogu brzo da dostignu visoke koncentracije i preveniraju ili tretiraju biofilm[18,19]. Dermalna kozmetička krema Gallixa uspešno tretira inflamaciju i bol bez ikakvog neželjenog dejstva.

5) Possible analgesic activity. The analgesic effect may have been due to the activity of gallium against cancer, bone resorption and associated inflammation[11,12].

Gallium compounds as diagnostic and therapeutic agents in medicine

The application of gallium compounds as diagnostic and therapeutic agents in medicine raises some questions about the pharmacology, clinical efficacy and potential side-effects. Gallium compounds can undergo various degrees of metabolic alteration in the body depending on their route of administration and chemical nature. A citrated gallium nitrate (CGN) solution for injection is presently approved in the United States for the treatment of human cancer-related hypercalcemia. CGN must be administered as a slow infusion over several days to avoid renal toxicity[13]. The discovery of gallium`s anticancer activity coincided with the introduction of Ga-scans to diagnose and locate a variety of cancers in the body. Ga-scans were found to be particularly sensitive to lymphomas, some sarcomas and bone tumors[14].

To avoid the inconvenience and renal toxicity of intravenous gallium nitrate, gallium maltolate (GaM) was developed as an orally active gallium compound. Gallium is absorbed very poorly when orally administered as nitrate, in part due to hydrolysis that produces low-solubility polymerized gallium oxide hydroxides in the gastrointestinal fluids. GaM is found to provide oral gallium absorption at least several times higher than from gallium nitrate. In addition, GaM is more lipid soluble compared to gallium nitrate and it is not known to cause adverse effects. Because of its lipid solubility GaM has better bacterial penetration and shows superior antimicrobial activity[15,16]. Gallium 8-quinolinolate and gallium chloride have also being developed as orally active forms of gallium[3,17]. Testing of gallium oral formulations in humans have shown activity against some cancers, as well as anti-bone resorpting activity.

Gallium compounds may be particularly effective when locally applied to the skin and mucous membranes, where they

Izgleda da je galijum obećavajući terapijski agens u oblasti tumora, koštanih oboljenja, infektivnih i autoimunskih bolesti.

Potencijalna aplikacija galijuma u prevenciji gubitka zuba

Parodontopatija je infektivna bolest usne duplje u kojoj oralni biofilm ima uzročnu ulogu. Oralni biofilm je trodimenzionalna struktura udruženih bakterija pričvršćenih za solidnu površinu, kao što je gleđ zuba, gingivalna površina, periodontalni džep, površina korena ili endodontska površina[20]. Glavni patogeni koji prate ove biofilmove su *Porphyromonasgingivalis,Prevotellaintermedia,Treponemadenticola,Actinobacillusactinomycetemcomitansi Fusobacterium nucleatum*[21-23]. Karakteristična obeležja periodontalne bolesti su inflamacija gingive, destrukcija alveolarne kosti i posledični gubitak zuba[24]. U najizraženijoj formi, parodontopatija povećava rizik za nastanak ateroskleroze, dijabetesa i neželjenih ishoda trudnoće, i na taj način ispoljava uticaj na sistemsko zdravlje[25-28]. Stepen parodontopatije određen je abnormalnim odgovorom domaćina i povećanom produkcijom proinflamatornih citokina, kao što su Th1 (IFN-γ i IL-2), Th17 (IL-17, IL-21) i pro-resorptivni citokini kosti (IL-1, IL-6, IL-11, TNF-α). U terapiji parodontopatije trenutno se koriste hirurške tehnike, mehanički debridman ogoljene površine korena zuba i lokalna ili sistemska aplikacija antimikrobnih agenasa[29]. Međutim, postojeće terapije ne uspevaju da iskorene bolest. Razvoj antibiotske rezistencije kod bakterija izazvao je potrebu za novim, alternativnim metodama lečenja infekcije. U nedavno objavljenim studijama pokazano je da je terapija periodontalnih džepova laserom na bazi galijuma efikasna pomoć u skidanju zubnog plaka I planiranju korena u terapiji i nadzoru parodontopatije[30-32].

Potencijalna korist galijuma u terapiji parodontopatije povezana je sa iskorenjivanjem infekcije uzrokovane bakterijskim biofilmom, povećanom depozicijom kosti i supresijom neželjenih imunskih odgovora. Efikasnost galijuma u prevenciji formiranja biofilma i iskorenjivanju postojećih biofilmova pokazana je u brojnim studijama. Galijum-nitrat i galijum-transferin blokiraju gvožđe-zavisan rast kompleksa *Mycobacterium tuberculosisa i Mycobacterium aviuma*, kako ekstracelularno, tako i unutar humanih makrofaga. Galijum onemogućava da *Mycobacterium tuberculosis* preuzme gvožđe u fagozomima makrofaga, što rezultira baktericidnim dejstvom[33].

can rapidly achieve high concentrations and can prevent or treat biofilms[18,19]. A cosmetic skin cream Gallixa successfully treats inflammation and pain without a trace of any adverse effect.

Gallium appears to be a promising therapeutic agent in the areas of cancer, bone diseases, infectious and autoimmune diseases.

Potential application of gallium in tooth loss prevention

Periodontitis is an infectious disease of the oral cavity in which oral biofilms play a causative role. Oral biofilms are three-dimensional structured bacterial communities attached to a solid surface like the enamel of the teeth, the gingival surface, periodontal pocket, the surface of the root or endodontic surface[20]. The major pathogens accompanying these biofilms are *Porphyromonas gingivalis, Prevotel-la intermedia, Treponema denticola, Actinobacillus actinomycetemcomitans* and *Fusobacterium nucleatum*[21-23]. Gingival inflammation, bacterial infection, alveolar bone destruction and subsequent tooth loss are characteristic features of periodontal disease[24]. In its most severe form periodontitis can have an impact on systemic health, as it increases the risk of atherosclerosis, diabetes and adverse pregnancy outcomes[25-28]. The severity of periodontitis is thought to be determined by abnormal host response with increased pro-inflammatory cytokine production, such as Th1 (IFN-γ and IL-2) and Th17 derived cytokines (IL-17, IL-21) together with pro-resorptive cytokines (IL-1, IL-6, IL-11, TNF-α). Surgical techniques, mechanical debridement of the denuded root surface, and local or systemic application of antimicrobial agents are currently used treatments forperiodontitis[29]. However, the existing therapies do not eradicate the disease. The development of antibiotic resistance in bacteria has prompted a great need for new and alternative treatment methods for infection. Recent studies have been reported that gallium-containing laser therapy of diseased periodontal pockets seemed to be an effective adjuvant to scaling and root planning in the treatment and management of periodontitis[30-32].

The potential anti-periodontitis benefits of gallium are related to eradicating infection due to bacterial biofilms, increasing

U formi nitratne soli galijum ispoljava baktericidno dejstvo protiv plaktonskog i adherentnog *Pseudomonas aeruginosa-ei Burkhholderiacepacia-e in* vitro, dok se galijum-maltolat pokazao kao efikasan protiv *Pseudomonas aeruginosae i Staphylococcus aureusa* in vivo[34-36].

Kako je elementalni galijum snažan inhibitor resorpcije kosti, jedinjenja galijuma potencijalno su korisna u terapiji raznih bolesti koje karakteriše povećani gubitak kosti, kao što su parodontopatija, osteoporoza, koštane metastaze, multiplimijelom, Pedžetova bolest kostiju. Poznato je da osteoklasti imaju ključnu ulogu u resorpciji kosti, modelovanju i remodelovanju[37]. Galijum svojim dejstvom blokira aktivnost osteoklasta bez uticaja na vijabilnost ovih ćelija[38]. Pored toga, galijum se akumulira u metafizi i dijafizi kosti, na spoj u organskih (kolagen) i mineralnih komponenti, menja solubilnost kristala i čini kost rezistentnijom na resorpciju. Terapija galijumom značajno povećava sadržaj kalcijuma u kostima i čini kost manje podložnom resorpciji. Galijum je takođe efikasan u blokiranju koštane resorpcije indukovane određenim proresorptivnim citokinima, kao što je TNF-α. Ovi efekti javljaju se u koncentracijama koje nisu toksične za normalne koštane ćelije[6].

Nekoliko studija pokazalo je imuno supresivnu aktivnost galijuma u animalnim modelima autoimunskih bolesti. Galijum-nitrat suprimira eksperimentalni autoimunski encefalomijelitis i prevenira adjuvantni inflamatorni artritis supresijom funkcije makrofaga i T limfocita u modelima kod pacova[41,42]. Druge studije pokazale su da galijum-nitrat može da suprimira lupus i prevenira odbacivanje srčanog alografta u mišjim modelima[41,42]. Galijum-transferin i galijum-nitrat inhibiraju odgovor mešovitih limfocita u kulturi i prolongiraju preživljavanje miševa sa izraženom bolešću „kalem protiv domaćina“ u mišjem modelu transplantirane koštane srži[43]. I pored ovih zanimljivih zapažanja, imuno modulatorna i antiinflamatorna svojstva galijuma nisu ispitana u modelu parodontopatije. Buduća istraživanja trebalo bi da utvrde da li su rezultati ovih animalnih studija relevantni za periodontalnu bolest. Suprimiranje neželjenih imunskih odgovora bilo bi korisno za buduću terapiju parodontopatije i prevenciju gubitka zuba.

bone deposition and downregulating unwanted immune responses. The efficacy of gallium at preventing biofilm formation and eradicating established biofilms have been shown in numerous studies. Gallium nitrate and transferrin-gallium were shown to block iron dependent growth of *Mycobacterium tuberculosis* and *Mycobacterium avium* complex extracellularly as well as within human macrophages. Gallium interfered with iron acquisition by *Mycobacterium tuberculosis* within the macrophage phagosome resulting in a bactericidal action[33]. In the form of the nitrate salt, gallium demonstrated bactericidal activity against planktonic and adherent *Pseudomonas aeruginosa* and *Burkhholderia cepacia* in vitro, whereas gallium maltolate was effective in vivo against *Pseudomonas aeruginosa* and *Staphylococcus aureus*[34-36].

As elemental gallium is a potent inhibitor of bone resorption, gallium compounds are potentially useful treatments for a variety of diseases that are characterized by accelerated bone loss, including periodontitis, osteoporosis, bone metastases, multiple myeloma and Paget`s disease of the bone. It is well-known that osteoclasts play a critical role in bone resorption, modeling and remodeling[37]. Gallium acts by blocking osteoclasts activity without affecting the viability of these cells[38]. In addition, gallium accumulates in the metaphysis and diaphysis of bone at the interface of the organic (collagen) and the mineral components, thus altering crystal solubility and rendering bone more resistant to resorption. Significant increases in bone calcium content occur in gallium-treated bones which also make bones less likely to be resorbed. Gallium is also effective in blocking bone resorption induced by certain cytokines proresorptivnim, kaošto is TNF-α.These effects occur at concentrations that are not cytotoxic to normal bone cells[6].

Several studies have shown that gallium compounds have immunosuppressive activity in animal models of autoimmune disease. Gallium nitrate has been shown to suppress experimental autoimmune encephalomyelitis and prevent adjuvant inflammatory arthritis through suppression of macrophage function and T-cells in rat models[39,40]. Other studies showed that gallium nitrate can suppress lupus and prevent cardiac allograft rejection in murine models[41,42]. Transferrin-

Zaključak

Nakon skoro 135 godina od otkrića, galijum nastavlja da pokazuje potencijal u terapiji tumora, metaboličkih oboljenja kostiju, autoimunskih i infektivnih bolesti. Međutim, ovaj potencijal mora dalje da se ispita i jedinjenja galijuma novijeg datuma treba da se uvedu u kliničke studije nakon rigoroznog prekliničkog testiranja. Razvoj gingivalnih gelova, pasta za zube i rastvora za ispiranje usta sa dodatkom galijuma, kao i zaštitna upotreba terapije laserom na bazi galijuma sa mehaničkom instrumentacijom mogla bi da predstavlja krajnje rešenje za prevenciju gubitka zuba.

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gallium and gallium nitrate were shown to inhibit the mixed lymphocyte culture response and prolong the survival of mice with severe graft-versus host disease in a murine bone marrow transplant model[43]. Despite these interesting observations, the immunomodulatory and anti-inflammatory properties of gallium have not been investigated in periodontitis. Further investigations appear warranted to establish whether the results of these animal studies are relevant to periodontal disease. Suppressing the unwanted immune responses would be beneficial in the future treatment of periodontitis and prevention of tooth loss.

Conclusion

Almost 135 years after its discovery, gallium continues to show promise for the treatment of cancer, metabolic bone diseases, autoimmune and infectious diseases. However, this potential needs to be further explored and the newer gallium compounds being developed should be advanced to clinical trials after rigorous preclinical testing. Development of gallium-containing gingival gels, toothpastes and mouth rinses and adjunctive use laser based on gallium therapy to mechanical instrumentation may represent the final solutions for tooth loss prevention.

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