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PISMO UREDNIKU
LETTER TO EDITOR

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Povezanost atenolola i oralnog karcinoma?

Atenolol Associated With Oral Cancer?

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Sažetak
Opisano je da antihipertenzivni lijekovi mogu uzrokovati neželjene rekacije na oralnoj mukozi. Istaknute su aftozne ulceracije, kserostomija, lihenoidna reakcija, vezikuloerozivne lezije, pemfigoidne lezije, crn dlakav jezik, poremećaj okusa, lezije slične lupusu, gingivalna hiperplazija te ostalo. Pedesetjednogodišnjem Tajlanđaninu godine 2001. dijagnosticirana je hipertenzija te je dvije godine liječen atenololom (Prenolol®) u kombinaciji s diuretikom. Godine 2003., dvije godine nakon što se počeo liječiti atenololom, dobio je ulceraciju u desnom retromolarnom području. U ovom je pismu prikazana klinička slika pacijenta, tijek liječenja te moguća povezanost antihipertenziva s oralnim karcinomom.

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Ključne riječi
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Uvod

Atenolol je uobičajen lijek koji se koristi u liječenju pacijenata s hipertenzijom i anginom pektoris. Razvijen je iz propanolola godine 1976. te klasificiran u skupinu beta-blokatora. Kemijska struktura mu je $C_{14}H_{22}N_2O_3$, a kemijsko ime *(RS)-4-(2-hidroksi-3-izopropilaminopropoks) fenilacetamid*.

Iako propanolol može prijeći moždano-krvnu granicu te ući u mozak uzrokujući popratne pojave kao što su depresija i noćne more, atenolol je ne prelazi te kod njega nisu opisane takve pojave. Atenolol ima niz drugih prolaznih popratnih pojava, kao što su abdominalni grčevi, proljev, krvna diskrazija, crvenilo kože, konstipacija, umor, nesanica, mučnina, depresija, gubitak pamćenja, vrućica, impotencija, niska frekvencija srca, nizak tlak, obamrlost,

Introduction

Atenolol is a drug commonly used in the treatment of patients with hypertension and angina pectoris. It was developed from Propanolol in 1976 and was classified as beta blockers group. Atenolol's chemical structure is $C_{14}H_{22}N_2O_3$ and its chemical name is *(RS)-4-(2-hydroxy-3-isopropylaminopropox) phenylacetamide*.

Though Propanolol could cross the blood-brain barrier and pass into the brain, causing side effects such as depression and nightmares, Atenolol does not pass through the blood-brain barrier and hence those side effects are not encountered. Atenolol has a range of transient side effects including abdominal cramps, diarrhea, blood dyscrasia, skin rashes, constipation, fatigue, insomnia, nausea, depression,

peckanje, hladni ekstremiteti, grlobolja, gubitak daha ili produljeni ekspirij. Nadalje, atenolol može usporiti rast fetusa uzima li ga majka tijekom trudnoće. Nedavno su opisane nove popratne pojave kod žena – to su bolovi u prsima, natečenost i osjetljivost (1).

No, opisane pojave su minimalne, a oralni skvamozni karcinom nikada nije opisan kao jedna od njih. Svrha ovoga kratkog pisma jest upozoriti na mogućnost da taj antihipertenzivni lijek može biti povezan s karcinomom oralnih skvamoznih stanica, ako ga pacijenti duže dobivaju.

Prikaz slučaja

Pedesetjednogodišnjem Tajlanđaninu godine 2001. dijagnosticirana je hipertenzija te je dvije godine liječen atenololom (Prenolol®) u kombinaciji s diuretikom. Godine 2003., dvije godine nakon što se počeo liječiti atenololom, dobio je ulceraciju u desnom retromolarnom području (distalno od zuba 47). Područje je bilo blago bolno dva tjedna tijekom uzimanja hrane, ulkus nije cijelio te je potražio pomoć stomatologa. Njegov stomatolog liječio ga je 0,1%-tnim triamcinolon acetonidom u orabazi (Kenalog®) te antibiotikom. Nakon dvotjedne terapije nije bilo poboljšanja. Zbog ozbiljnosti ulceracije, došao je na Kliniku za oralnu medicinu Stomatološkog fakulteta Sveučilišta Chulalongkorna u prosincu 2003.

Anamnezom je utvrđeno da nije uživao ni duhan ni alkohol, da je imao dobru oralnu higijenu te da je zaposlen kao bankovni činovnik. Pregledom nije ustanovljena limfoadenopatija, a pregledom usne šupljine utvrđene su keratotične bijele strije s nekoliko keratotičnih plakova veličine 3x4 mm^2 s hiperpigmentacijom na sluznici desnog obraza. Bijeli hiperpigmentirani plakovi širili su se do ulceracije desno retromolarno od 47 s induriranim rubom, veličine 2x1,5 cm^2 (Slike 1. i 2.). Na sluznici desnog obraza bilo je i bijelih plakova i eritematoznih područja. Dijagnosticirani su pigmentirani i lihenoidni plakovi i/ili lihenoidna reakcija na atenolol te nespecifična ulceracija desno retromolarno. Incizijska biopsija obavljena je desno retromolarno te je obuhvatila ulkus i bukalnu mukozu.

Histopatološki su ustanovljene invazivne tumorozne stanice poredane u slojeve i mreže. Te maligne stanice bile su poligonalne, sa žarišnom keratinizacijom. Jezgre su bile blago do umjereno pleomorfne

memory loss, fever, impotence, slow heart rate, low blood pressure, numbness, tingling, cold extremities, sore throat, and shortness of breath or wheezing. Furthermore, Atenolol may cause growth retardation in fetus when given to women in pregnancy. Recently, it has been reported to cause a new adverse reaction in women of breast pain, swelling, and sensitiveness (1).

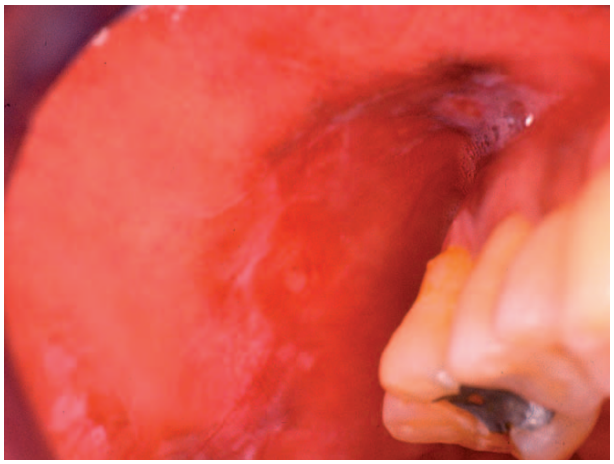
Atenolol has been reported to result in minimal adverse reactions. Oral squamous cell carcinoma has never been documented as one of its adverse reactions. The purpose of this communication is to raise awareness that the antihypertensive drug- Atenolol may be related to oral squamous cell carcinoma in patients receiving this medication as long term treatment.

Case report

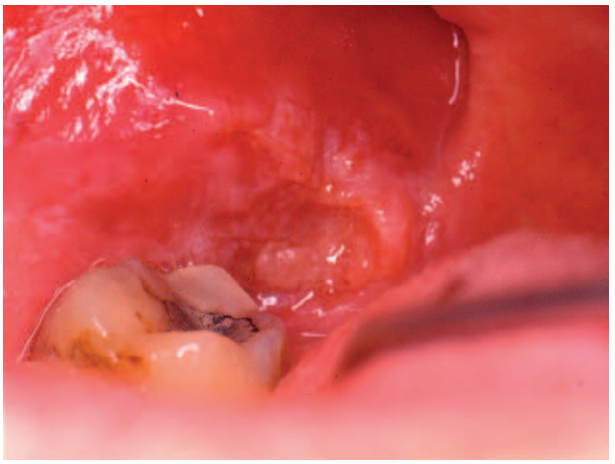
A Thai 51-year-old male patient was diagnosed with hypertension by his physician in 2001 and was treated with Atenolol (Prenolol®) combined with a diuretic drug for 2 years. In 2003, two years after administration with Atenolol, the patient developed oral ulceration on the right retromolar of area 47. He had slight pain in this region when eating for 2 weeks and the ulcer did not heal. Because of persisted ulceration, he sought dental advice. His dentist treated him with 0.1% triamcinolone acetonide in orabase (Kenalog®) and an antibiotic. After taking treatment for 2 weeks, the lesion did not show any improvement. Due to the serious nature of his oral ulceration, he presented at the Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University in December 2003.

Social history suggested he was not tobacco and alcohol user and had a good oral hygiene, and was employed as a bank officer. Family history of oral cancer was unknown. Physical examination revealed no lymphadenopathy. Oral presentation revealed keratototic white striae and several white keratotic plaques size 3x4 mm^2 with hyperpigmentation on the right buccal mucosa. White plaques with hyperpigmentation extended to the area of ulceration of the right retromolar area of 47 with indurated margin, size 2x1.5 cm^2 (Figs. 1 and 2). On the left buccal mucosa, the white plaques and erythematous areas were also found. Pigmented and plaque types of lichen planus and/or lichenoid drug reaction from Atenolol and non specific ulceration on the right retromolar were diagnosed. An incision biopsy was performed on the right retromolar area of the ulcer that extended to the buccal mucosa.

Histopathology revealed invasive tumor cells arranged in sheets and nests. These malignant cells



Slika 1. Bijeli plakovi s hiperpigmentacijom na sluznici desnog obraza - dosižu ulceraciju u području zuba 47.
Figure 1 White plaques with hyperpigmentation on the right buccal mucosa extended to the ulceration of area 47



Slika 2. Ulceracija desno retromolarno od zuba 47 s induriranim rubom.
Figure 2 Ulceration on the right retromolar area of 47 with indurated margin

te je postavljena dijagnoza dobro do umjereno diferenciranog karcinoma skvamoznih stanica. Tumor je graduiran kao T2NoMX.

Nakon operacije uklonjeno je 11 velikih uzoraka, rubovi su označeni te je provjereno da je imao potpunu eksciziju desnog submandibularnog, submentalog i jugulogastričnog limfnog čvora, mišića, gornjeg ruba intraoralnog periosta, fascije temporalisa, posteriorne oralne mukoze, posteriornog dijela primarne lezije te desne submandibularne žlijezde i primarne lezije. Mikroskopski pregled primarne lezije na bukalnoj mukozi otkrio je maligne stanice iz površinskog epitela s umjereno pleomorfnim jezgrama. Stanice tumora bile su u slojevima i jasno razgraničene. Neoplazma je dosezala gotovo do posteriornih rubova. Mala jezgra tumorskih stanica opažena je na anteriornom dijelu dvaju limfnih čvorova. Svi ostali resecirani limfni čvorovi bili su negativni. Uzorkovanje mišićnog, periostalnog, fascijalnog, mukoznog te tkiva submandibularne žlijezde, bilo je negativno na maligne stanice.

Tri tjedna nakon operacije širokom ekscizijom (SOHND, engl. supraomohyoid neck dissection, supramiohioidna disekcija vrata) obavljena je rekonstrukcija radijalnim miokutanim režnjem s područja podlaktice. Cijeljenje je bilo normalno, bez infekcije. Provedeno je i poslijeoperativno zračenje.

Pacijen je praćen 1, 2, 3 i 5 mjeseci nakon operacije i zračenja, a žalio se na suha usta. Oralnim pregledom ustanovljena je kserostomija i generalizirani mukozitis zbog zračenja te je liječen benzidamin-hidrokloridom kao tekućinom za ispiranje usta (Difflam®), adhezivnom pastom (Sol-

displayed polygonal shaped features with focal keratinization. The nuclei were mild to moderately pleomorphic. The pathology diagnosis was well to moderately differentiated squamous cell carcinoma. The tumor was graded T2NoMX.

After operation, the 11 gross specimens were removed and the margins labelled and checked for complete excision of right submandibular lymph node, submental lymph node, jugulodigastric node, muscle, upper margin of intraoral, periosteum, fascia of temporalis, posterior oral mucosa, posterior of primary lesion and the right submandibular gland and primary lesion respectively. The microscopic examination of the primary lesion at the buccal mucosa revealed malignant cells arising from the surface epithelium which possess moderately pleomorphic nuclei. The tumor cells were arranged in sheets and they showed distinct cells borders. The neoplasm extended close to the posterior margins. A small focus of tumor cells was seen in the shave margin at anterior of two lymph nodes. Other resected lymph nodes were all negative. The sampling tissues from muscle, upper margin of intraoral, periosteum, fascia of temporalis, posterior oral mucosa, posterior of primary lesion and completed excision of right submandibular gland were negative for malignant cells.

Three weeks after surgery by wide excision, SOHND (supraomohyoid neck dissection) reconstruction with radial forearm myocutaneous free flap showed normal wound healing, and no signs of infection. Post-operative radiation was arranged.

Patient was followed up at 1, 2, 3 and 5 months after surgery and radiotherapy. He complained of

coseryl®) te glicerin-boratom za smanjenje simptoma.

Nažalost, u lipnju 2004. SCC je pokazao ponovnu ulceraciju na spoju tvrdog i mekog nepca preko središnje linije, dimenzija 3x3 cm^2 i egzofitičnom masom gnjecavog tkiva veličine 1,5 cm. Pacijent je umro ubrzo nakon što je došao sa sekundarnim lezijama.

Rasprava

Opisano je da antihipertenzivni lijekovi mogu uzrokovati neželjene rekacije na oralnoj mukozi. Istaknute su aftozne ulceracije, kserostomija, lihenoidna reakcija, vezikuloerozivne lezije, pemfigoidne lezije, crn dlakav jezik, poremećaj okusa, lezije slične lupusu, gingivalna hiperplazija te ostalo (2-7). Beta-blokatori induciraju kserostomiju vjerojatno aktivacijom CNS-a i salivarnih alfa-2 adrenergičnih receptora. (8). Također su opisane aftozne ulceracije uzrokovane labetalolom (9).

Prenolol® ili atenolol jedan je od beta-adrenergičnih blokatorskih lijekova koji imaju opisane egzantematozne, ekcematozne, psorijaziformne osipe, eksfolijativni dermatitis, oklulo-mukokutane reakcije, fibrozirajući poliseritis te lezije slične sistemskom eritematoznom lupusu (10). Zanimljivo je da je dokumentirana i lihenoidna reakcija na lijek u mukokutanom području penisa nakon primjene propranolola (11). Iako je patogeneza odgovorna za te reakcije još nejasna, promjena bi mogla biti prouzročena više blokadom beta-receptora epidermalnih stanica i T-limfocita, nego izravnim imunološkim, alergijskim ili toksičkim mehanizmima (12).

Novija istraživanja pokazala su da je oralna lihenoidna reakcija povezana s malignom transformacijom (13-16). Potencijalno maligne lezije su one koje se pojavljuju u morfološki promijenjenim tkivima pa, ako je lihenoidna displazija i otkrivena, ona već u tom trenutku može prolaziti kroz inicijalnu fazu karcinogeneze (17).

Oralni karcinom šesti je najčešći oblik ljudskog karcinoma, a skvamozni je najčešći oralni karcinom. Prije mnogih oralnih karcinoma, ponajprije skvamoznih, moguća je maligna lezija koja se može manifestirati kao bijela ili crvena mrlja na oralnoj mukozi. U nedostatku potvrđenih molekularnih markera, histološko stupnjevanje epitelnih displazija preostaje kao jedini temeljni znak za određivanje potencijalnih malignih promjena. Oralne epitelne displazijske lezije mogu ima-

dry mouth. Oral examination revealed xerostomia and generalized mucositis due to radiation, he was treated with Benzydamine hydrochloride (Difflam®) mouthwash, Solcoseryl® Dental adhesive paste and Glycerine borax for relief of symptoms.

Unfortunately in June 2004, SCC showed recurrence of ulceration at the junction of hard and soft palate cross midline size 3x3 cm^2 and the exophytic mass with slough tissue covered size 1.5 cm. The patient died soon after presenting with secondary lesions.

Discussion

Antihypertensive drugs have been reported to cause adverse reactions to the oral mucosa such as aphthous ulceration, xerostomia, lichenoid reaction, vesiculoerosive lesions, pemphigus-like lesions, black hairy tongue, taste disturbance, lupus-like lesions, gingival hyperplasia and others (2-7). Beta blockers have been reported to induce xerostomia possibly by the activation of CNS and salivary gland alpha 2-adrenergic receptors (8). Aphthous-like ulceration by labetalol has also been reported (9).

Prenolol® or Atenolol is one of beta-adrenergic blocking drugs which has been reported with exanthematous, eczematous, psoriasiform rashes, exfoliative dermatitis, oculo-muco-cutaneous reactions, fibrosing polyseritis and systemic lupus erythematosus like lesions (10). Interestingly, lichenoid drug eruption on the mucocutaneous area of penis secondary to propranolol therapy has been documented (11). Although the pathogenesis responsible for this adverse reaction is still unclear, this change might be caused by blockade of the epidermal cells and T-lymphocytes beta-receptors more than by direct immunologic, allergic or toxic mechanisms (12).

Recent studies have shown that the oral lichenoid lesion IS associated with malignant transformation (13-16). Potentially malignant lesions are those occurring in morphologically altered tissues. Thus when lichenoid dysplasia was detected, it may be already undergoing this initial phase of carcinogenesis (17).

Oral cancer is the 6^{th} most common type of human cancer in the world. Among them, oral squamous cell carcinoma occurs at highest frequency. Many oral cancers, especially oral squamous cell carcinomas, are preceded by potentially malignant lesions, which may appear as white or red patches on the oral mucosa. In the absence of validated molecular markers, the histological grading of the epithelial dysplasia remains the hallmark for determining any potential malignant change. Oral ep-

ti različite stupnjeve progresije - od normalnog do malignog tkiva. Epitelna displazija klasificirana je prema predloženoj klasifikaciji Svjetske zdravstvene organizacije iz godine 2003. kao hiperplazija, blaga, umjerena i jaka, ili karcinoma in situ, ovisno o prisutnosti i jačini celularne atipije i građevnih karakteristika temeljenih na debljini displastičnih slojeva u usporedbi s ukupnom visinom epitela (18). Razvoj oralne leukoplakije znatno je povezan s egzogenom izloženosti karcinogenima, uglavnom pušenju i žvakanju duhana te betelova lišća (19). Uživanje duhana je najvažnije, prisutno je u 80% leukoplakija (20) i epitelnih displazija (21). Oralna leukoplakija ima predilekciju od 70% kod muškaraca starijih od 40 godina, a može se pojaviti i kao multiple lezije (22).

Kod toga pacijenta nije bilo predisponirajućih čimbenika za malignu transformaciju, osim uzimanja Prenolola® tijekom dvije godine. Oralne lezije u prvom su posjetu nalikovale na lezije oralnog liheна-planusa, pigmentirane lezije ili lezije uzrokovane lijekovima s ulceracijama. Mnogi antihipertenzivni lijekovi uzrokuju lihenoidne reakcije, ali nema ranijih potvrda o oralnom karcinomu skvamoznih stanica potaknutom Prenololom®. Oralni karcinom skvamoznih stanica toga pacijenta možda je nastao iz oralne lihenoidne lezije prouzročene lijekom koja se maligno transformirala. Neželjena reakcija na Prenolol® u ovom bi slučaju trebala privući posebnu pozornost.

Iako je atenolol koristan i učinkovit lijek u terapiji kardiovaskularnih bolesti, opisani slučaj pokazuje da se iz oralne lihenoidne lezije uzrokovane tim lijekom može razviti oralni karcinom skvamoznih stanica. Unatoč naprednom liječenju kirurškim tehnikama i adjuvantnom terapijom, pacijent je umro ubrzo nakon dijagnoze. Zato ovaj prikaz može biti koristan doktorima medicine i doktorima stomatologije u razmišljanju o liječenju hipertenzivnih pacijenata atenololom. Oni pacijenti koji se liječe antihipertenzivima moraju se pratiti zbog lihenoidne reakcije. Ako se one otkriju, predlaže se odmah prekinuti terapiju kako bi se spriječila maligna alteracija. Ipak, potrebni su daljnji dokazi koji će potvrditi povezanost atenolola i oralnih malignosti.

Zahvala

Željeli bismo zahvaliti prof. Samanu Warnakulasuriyji (Department of Oral and Maxillofacial Medicine and Pathology, King's College, University of London) za njegove vrijedne savjete.

ithelial dysplasia lesions may have different steps in the progression from normal to malignant tissue. Epithelial dysplasia was classified by the proposed WHO classification in 2003 as hyperplasia, mild, moderate, severe, or carcinoma in situ according to the presence and severity of the cellular atypia and to architectural features based on the thickness of dysplastic layers compared with the total epithelial height (18). The development of oral leukoplakia is strongly associated with exogenous exposure to carcinogens, mainly smoking, chewing tobacco and betal nut (19). The use of tobacco is the most important, present in 80% of leukoplakia (20) and epithelial dysplasia (21). Oral leukoplakia shows predilection for man, in general in 70% of men over 40 years old, and may occur as multiple lesions (22).

In this patient, there were no predisposing factors for malignant transformation except taking medication Prenolol® for 2 years. At the first visit, oral lesions resembled oral lichen planus plaque and pigmented types or drug-induced lichenoid lesion with ulceration. Many of antihypertensive drugs have been known to induce to oral lichenoid reactions, but there are no previous reports of Prenolol®- induced oral squamous cell carcinoma. This patient's oral squamous cell carcinoma might have arisen from drug- induced oral lichenoid lesion that underwent malignant transformation. The adverse drug reactions of Prenolol® in this case should receive attention.

Although Atenolol has been found to be useful and effective in the treatment of cardiovascular diseases, this case demonstrated that oral squamous call carcinoma might develop from drug- induced oral lichenoid lesion. Despite advanced treatment by surgical techniques and adjuvant for therapies, the patient died soon after diagnosis. Therefore, this report may be useful for the physicians for consideration in the treatment of hypertensive patients with Atenolol in the future. Those receiving antihypertensives may need monitoring for oral lichenoid reactions. If this is detected, early discontinuation of this drug may be recommended to prevent malignant transformation. However, further evidence with similar cases would be needed to support and confirm the relationship between Atenolol and oral malignancy.

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Abstract
Antihypertensive drugs have been reported to cause adverse reactions to the oral mucosa such as aphthous ulceration, xerostomia, lichenoid reaction, vesiculoerosive lesions, pemphigus-like lesions, black hairy tongue, taste disturbance, lupus-like lesions, gingival hyperplasia and others. A Thai 51-year-old male patient was diagnosed with hypertension by his physician in 2001 and was treated with Atenolol (Prenolol®) combined with a diuretic drug for 2 years. In 2003, two years after administration with Atenolol, the patient developed oral ulceration on the right retromolar. This letter shows clinical picture, treatment and the possibilities of the connection between antihypertensive drugs with oral cancer.

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Key words
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References

1. Kelleher JA. Atenolol-induced breast pain in a woman with hypertension. Ann Pharmacother. 2006;40(5):990-2.
2. Castells X, Rodoreda I, Pedros C, Cereza G, Laporte JR. Drug points: Dysgeusia and burning mouth syndrome by eprosartan. BMJ. 2002;325(7375):1277.
3. Scully C, Bagan JV. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med. 2004;15(4):221-39.
4. Eggerath J, English H, Leichter JW. Drug-associated gingival enlargement: case report and review of aetiology, management and evidence-based outcomes of treatment. J N Z Soc Periodontol. 2005;88:7-14.
5. Tsuruoka S, Wakaumi M, Ioka T, Yamamoto H, Ando H, Sugimoto K, Fujimura A. Angiotensin II receptor blocker-induces blunted taste sensitivity: comparison of candesartan and valsartan. Br J Clin Pharmacol. 2005;60(2):204-7.
6. Tsuruoka S, Wakaumi M, Araki N, Ioka T, Sugimoto K, Fujimura A. Comparative study of taste disturbance by losartan and perindopril in healthy volunteers. J Clin Pharmacol. 2005;45(11):1319-23.
7. Boulinguez S, Reix S, Bedane C, Debrock C, Bouyssou-Gauthier ML, Sparsa A et al. Role of drug exposure in aphthous ulcers: a case-control study. Br J Dermatol. 2000; 143(6):1261-5.
8. Nederfors T. Xerostomia: prevalence and pharmacotherapy. With special reference to beta- adrenoceptor antagonists. Swed Dent J Suppl. 1996;116:1-70.
9. Pradalier A, Dry J, Baron JF. Aphthoid stomatitis induced by labetalol. Therapie. 1982;37(6):695-7.
10. McGuiness M, Frye RA, Deng JS. Atenolol-induced lupus erythematosus. J Am Acad Dermatol. 1997;37(2 Pt 2):298-9.
11. Massa MC, Jason SM, Gradini R, Welykyj S. Lichenoid drug eruption secondary to propranolol. Cutis. 1991;48(1):41-3.
12. Faure M, Hermier C, Perrot H. Cutaneous reactions to propranolol. Ann Dermatol Venereol. 1979;106(2):161-5.
13. Reichart PA. Oral precancerous conditions-an overview. Mund Kiefer Gesichtschir. 2003;7(4):201-7.
14. van der Meij EH, Schepman KP, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(2):164-71.
15. Acay RR, Felizzola CR, de Araujo N, de Sousa SO. Evaluation of proliferative potential in oral lichen planus and oral lichenoid lesions using immunohistochemical expression of p53 and Ki67. Oral Oncol. 2006;42(5):475-80.
16. Larsson A, Warfvinge G. Oral lichenoid contact reactions may occasionally transform into malignancy. Eur J Cancer Prev. 2005;14(6):525-9.
17. Fatahzadeh M, Rinaggio J, Chiodo T. Squamous cell carcinoma arising in an oral lichenoid lesion. J Am Dent Assoc. 2004;135(6):754-9.
18. Pindborg JJ, Reichart PA, Smith CJ, van der Waal I. Histological Typing of Cancer and Precancer of the Oral Mucosa. World Health Organization International Histological Classification of Tumours. 2 nd ed. Berlin: Springer-Verlag Berlin Heidelberg; 1997.
19. Johnson NW, Warnakulasuriya S, Tavassoli M. Hereditary and environmental risk factors; clinical and laboratory risk matters for head and neck, especially oral, cancer and precancer. Eur J Cancer Prev. 1996;5(1):5-17.
20. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin. 2002; 52(4):195-215.
21. Jaber MA, Porter SR, Scully C, Gilthorpe MS, Bedi R.The role of alcohol in non-smokers and tobacco in non-drinkers in the aetiology of oral epithelial dysplasia. Int J Cancer. 1998;77(3):333-6.
22. van der Waal I, Axell T. Oral leukoplakia : a proposal for uniform reporting. Oral Oncol. 2002;38(6):521-6.