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Systemic Medication- It's Effects on Oral Health

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Abstract: *Present days, the life expectancy has increased because of increased awareness about self care and improved medical facilities including use of various medications for prophylaxis and treatment purpose. Medications benefit our general health but they also carry some adverse effects and can be harmful to oral health also. This can vary from single hyper pigmented spot to marked destruction of both soft and hard tissue in oral cavity. As uses of various medications are unavoidable these days their adverse effects on oral environment are very common and often un/underdiagnosed or less cared by patient and the treating person. These events will likely increase as newer medicines are getting approved for various therapeutic and prophylactic indications and on the other hand various drugs are used non judicially. Health care providers should familiarise themselves with such adverse events of various medicines in the oral cavity. This article reviews the role of drugs as causal factors in oral health, diseases and disorders.*
Keywords: *Angioedema, gingival hypertrophy, oral pigmentation, xerostomia, myelosuppression, radionecrosis of jaw.*

I. Introduction

The ever growing understanding of disease processes, advanced research and use of various medications has increased the life expectancy. Drugs have been found to be effective in treatment and prophylaxis of diseases but are associated with some adverse effects. The deleterious effects are broadly classified as:-

First classification:-

- Predictable (Type- A or augmented) reactions : mechanism based adverse reactions
- Unpredictable (Type-Bor bizarre) reactions: patient based reactions i.e. allergy and idiosyncrasy.

Second classification

Effects of medications on periodontal tissues in health and disease[1]

1. An adverse effect on the periodontal tissues;
2. Affording some degree of protection against periodontal breakdown;
3. Causing an increased risk of periodontal breakdown;

1. An Adverse Effect on The Periodontal Tissue

Drug induced gingival hypertrophy is the commonest oral manifestation of various drugs. The three main drugs causative for gingival enlargement are phenytoin, cyclosporine and calcium channel blockers. Some case reports have implicated other drugs (e.g. Sodium valproate) but these are rare incidents.

Prevalence: 50% of dentate patients on phenytoin experience gingival changes, whereas the figures for cyclosporine and the calcium channel blockers are 30% and 10%, respectively.[4]

Risk factors: Major risk factors are age and other demographic variables, drug variables, concomitant medication, periodontal variables, and genetic factors. Children and teenagers are more susceptible to phenytoin and cyclosporine-induced gingival overgrowth. Adolescents will have higher levels of circulating androgens which could stimulate further gingival fibroblast to increase collagen synthesis or decrease collagenase activity.

Gender: Gender seems to be relevant in cyclosporine and nifedipine cases (more in males as compared to females) while not in Phenytoin induced cases.

Drug variables : A range of pharmacokinetic variables have been studied and include peak and trough serum concentration, drug dosage, drug concentration in saliva and gingival crevicular fluid. Most workers concur that some baseline or threshold concentration of the drug is required to induce the gingival changes.

Concomitant medications: Prednisolone and azathioprine appear to afford some degree of protection against the development of gingival overgrowth which may arise from their anti-inflammatory action on plaque-induced gingival inflammation in adult transplant patients. Other anti-epileptics can affect the hepatic metabolism of phenytoin, which in turn can impact upon the gingival tissue response. Phenobarbitone **,** primidone and carbamazepine induce the hepatic enzyme p450. The latter has a greater stimulatory effect on the gingival

fibroblast, which may explain the increased prevalence of gingival overgrowth in patients receiving multiple anti-epileptic therapy.

Periodontal variables: Patient's oral hygiene is contributory to development or progression of over growth is still controversial. Of particular concern is the extent of inflammation present in the gingival tissue prior to the dosing.

Genetic factors: Drug metabolizing enzymes - Phenytoin, cyclosporine and nifedipine are all metabolized by the hepatic cytochrome P450 enzymes. Other genes associated with cyclosporine and phenytoin are P-glycoprotein drug-transporter MDR1 gene polymorphism and CYP2C polymorphism respectively. There is evidence that patients who express HLA-DR1 are afforded some degree of protection against the development of drug-induced gingival overgrowth, whereas those who express HLA-DR2 may be more susceptible to this unwanted effect.

Pathogenesis of drug-induced gingival overgrowth: It is thought to be multifactorial. The main histo-pathological feature of drug-induced gingival overgrowth is a fibrotic or expanded connective tissue with various levels of inflammation and an enlarged gingival epithelium. Many investigations have also considered roles of a variety of inflammatory cytokines and growth factors on the effect of the drug on gingival fibroblast.

Treatment of drug-induced gingival overgrowth : First line of treatment is drug substitution.

Drug	Substitution
Nifedipine	Esmolol
Cyclosporine	Tacrolimus
Phenytoin	Valproate

Table 1: list of drugs used for substitution

Oral treatment includes oral prophylaxis as first line of treatment to control local factors followed by surgery if required for cosmetic reasons. Surgical approach can be either by 45^0 gingivectomy (using blade) or by lasers. Post surgery antibiotics and regular oral hygiene maintenance should be advocated.

Figure 1: Drug induced gingival enlargement associated with local factors also. Patient was taking Amlodepine for systemic hypertension.(Image Courtesy:- Dr. Meghna Sharma, PG student,Deptt. Of Periodontics, JDC, Jaipur)

2. Affording The Patient Some Degree Of Protection Against Periodontal Breakdown : Activation of the host's inflammatory and immune responses are pivotal in the pathogenesis of periodontal breakdown. Systemic medication affecting these processes are of special interest to periodontist.This interest is twofold. Firstly, these drugs can be used as tools to identify the particular roles of immune and inflammatory responses in the periodontal breakdown process. Secondly, the drugs may have an additional therapeutic role in the management of periodontal disease. These include- Immunosuppressants, corticosteroids and nonsteroid anti-inflammatory drugs:

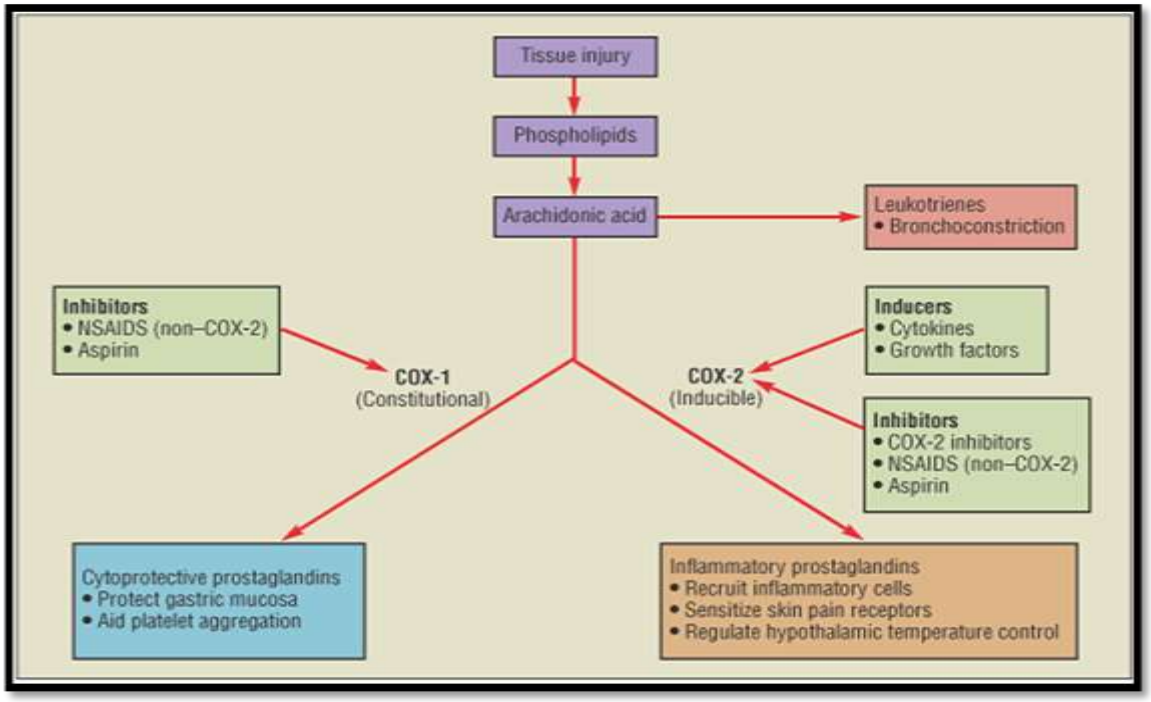

Figure 2:- algorithm of the biochemical pathway shows that the formation of prostaglandins occurs via both cyclo-oxygenase enzymes (COX-1 and COX-2)

The new COX-2 inhibitors have all the attributes of NSAIDs with a reduced risk of unwanted effects. These drugs have been evaluated as an adjunct to root surface instrumentation in patients with chronic periodontitis . The results showed little clinical benefit of COX-2 inhibitors in the management of such patients, but significant reductions in gingival tissue levels of PGE2 and PGF2.

3. Drugs Which Can Increase The Expression Of Periodontal Diseases

Sex hormones: The effects of sex hormones on the gingival tissues are well established and distinct changes in relation to puberty and pregnancy are well documented .Such changes are brought about by increased levels of circulating estrogen and progesterone. Observed periodontal changes are –

- an increased tendency for gingivitis
- increased probing depths ,
- Increased susceptibility to infection ,
- decreased neutrophil chemotaxis and
- an increased number of periodontopathogens
- Hormone replacement therapy- protective effect of estrogen possibly medicated by the prevention of osteoporosis.

Drug induced desquamative gingivitis : Several drugs can cause oral lichenoid reactions that can present as desquamative gingivitis. Drugs most commonly implicated include beta-adrenoceptor blockers (e.g. propranolol, atenolol), antidiabetic drugs (e.g. chlorpropamide and tolbutamide), gold salts and nonsteroidal anti-inflammatory drugs.

Drug induced depression of bone marrow: It is the most serious and potentially life-threatening adverse effect of systemic medications like antipsychotic agents (especially phenothiazines), antithyroid agents, phenacetin, methimazole, cefmetazole, sulphur derivatives and anti-inflammatory agents such as indomethacin.. It can result in aplastic anaemia, agranulocytosis and thrombocytopenia. Drug induced depression of bone marrow will also affect the periodontal tissues. There may be a rapid increase in the rate of periodontal destruction following a reduction in white blood cell numbers or activity. Thrombocytopenia will manifest in the gingival tissues, especially if these are inflamed. Excessive bleeding on probing and prolonged bleeding may be secondary to a drug-induced thrombocytopenia.

Bisphosphonates induced osteonecrosis of jaw : Bisphosphonate medications are primarily used to treat cancer (intravenous administration) and osteoporosis (oral administration). They act by inhibiting osteoclastic activity, which leads to less bone resorption, less bone remodeling, and less bone turnover. Osteonecrosis of the jaw associated with bisphosphonates was first reported in 2003 by Marx in a report of 36 cases of patients with avascular necrosis of the jaws who were treated with IV bisphosphonate for malignant tumors. Various terms have been used to describe this type of osteonecrosis of the jaw, including avascular necrosis, bisphosphonate-related or -associated ONJ (BRONJ), and bisphosphonate-induced ONJ (BIONJ).Clinically, BIONJ presents as exposed alveolar bone occurring spontaneously or after a dental procedure. The sites may be painful with surrounding soft tissue induration and inflammation. Infection with drainage may be present.
Radiographically, lesions appear radiolucent with sclerosis of lamina dura, loss of lamina dura, or widening of periodontal ligament in areas where teeth are present.
Histologically, bone appears necrotic with empty lacunae demonstrating a lack of living osteocytes. In advanced cases, pathologic fracture may be present through the area of exposed/necrotic bone.

Agents that alter oral tissue pigmentation:

- Antimalarials - chloroquine ,hydroxychloroquine ,
- Quinidine
- Zidovudine (AZT)
- Tetracycline
- Minocycline
- Chlorpromazine
- Oral contraceptives (OCP)
- Clofazimine
- Ketoconazole
- Amiodarone
- Methyl-dopa
- Chlorhexidine
- Anti cancer drugs - busalfan, doxorubicin, bleomycin,.cyclophosphamide.

Mechanism of pigmentation:

- Drug or drug metabolite deposition in dermis or epidermis
- Enhanced melanin production with or without an increase in the number of active melanocytes.
- Drug induced post-inflammatory changes to skin

Drug	Mechanism of action
Antimalarial drugs	Stimulate melanocyte activity
Tetracyclines and minocycline	Calcium ortho-phosphate complex formation
Oral contaceptives	Increased ACTH → increased MSH
zidovudine	↑ release of α- melanocyte stimulating hormone (MSH) due to deregulation of cytokines
clofazimine	Red colour of metabolized drug
chlorhexidine	(Erikson et al. 1985, Addy & Moran 1995, Watts & Addy 2001) 1. degradation of chlorhexidine molecule to release parachloraniline 2. catalysis of Maillard reactions 3. protein denaturation with metal sulphide formation 4. precipitation of anionic dietary chromogens
Miscellaneous drugs	Ketoconazole- ACTH pathway Methyldopa-melanin production to DOPA metabolism

Table 2: List of drugs with their mechanism of action of pigmentation

Agents that affect salivary flow andpH of oral cavity :

Xerostomia or dry mouth is caused because of decreased salivary flow. Causative medications can be diuretics, antihypertensives, antihistamines, antidepressants, antipsychotics, anticholinergics, antineoplastics and drugs of abuse such as opiates, amphetamines, barbiturates, hallucinogens, cannabis and alcohol**.** Use of agents such as mouth rinses containing alcohol or astringents may also contribute to oral dryness. Xerostomia has been associated with an increased susceptibility to root caries, dental erosion and hypersensitivity, chronic mucositis, trauma to soft tissues and oral candidiasis. Recent evidence suggests that the incidence and severity of periodontitis also increases in xerostomic individuals when compared with age- and sex matched controls.

Category	Example

Tricyclic antidepressants	Amitryptyline
Muscarinic receptor antagonist	Oxybutynin
Alpha receptor antagonist	Terazosin
Antipsychotics	Phenothiazine , lithium
Diuretics	Furosemide
Histamine H1- receptor blockers	Chlorpheneramine
Histamine H2- receptor blockers	Cimetidine
Central anti-hypertensives	Moxonidine
Angiotensin-converting enzyme inhibitors	Lisinopril
Bronchodilators	Tiotropium
Opioids	Morphine
Proton pump inhibitors	Omeprazole
Anti- human immunodeficiency virus (HIV) drugs inhibitors	Didanosine and HIV protease

Table 3: Categories of drugs and examles that can cause xerostomia

Management of drug induced Xerostomia: Local measures such as frequent sips of water or sugar-free chewing gum may help to alleviate some of the problems. Fluoride containing toothpastes would be beneficial in reducing the risk of root caries. Many of these agents are now available as an aerosol spray, which facilitates usage.e.g.-Pilocarpine 5 mg (an M3 muscarinic antagonist)

Drug induced Sialorrhea: The drug most frequently associated with sialorrhea is the antipsychotic agent, clozapine. Other agents that have been implicated include heavy metal compounds and irreversible anticholinesterase inhibitors (insecticides and nerve agents).

Management: The central anticholinergic drug clonidine[8] and botulinum toxin injection into the parotid glands are used in the management of clozapine induced sialorrhea.

Drugs That Alter Host Resistance: Alteration can occur with use of immunosuppressive agents such as azathioprine, cyclophosphamide and corticosteroids, while the inflammatory response may be simultaneously suppressed, masking the usual signs and symptoms of oral disease. Patients receiving immunosuppressive drugs may be at greater risk of developing oral viral or fungal infections such as primary or recurrent herpes simplex or candidiasis.

Drugswith Direct Effects On Oral Tissue: Long term use of aspirin can cause chemical burns. In dentistry, the use of phenolic compounds, silver nitrate, sodium perborate, hydrogen peroxide, carbamide peroxide, etching acids, volatile oils (cloves, wintergreen and eucalyptus oil), topical anaesthetics, fluoride compounds and astringents in retraction cords have been reported to elicit irritant reactions on occasion.Alcohol containing mouthwashes – intraoral burning and xerostomiaoccasionally.Hydrogen peroxide used in conjunction with sodium chloride and sodium bicarbonate powders for tooth cleansing may induce gingival abrasion and ulcerations.

Drug-induced taste disturbance: Many drugs induce abnormalities of taste either via reducing serum zinc levels or by a direct interaction with proteins or taste bud receptors. Drugs that contain a sulphydryl group (e.g. Penicillamine and captopril) are common causes of taste disturbances. The sulphydryl group binds with proteins on taste buds and reduces taste acuity. In addition, penicillamine-induced taste disturbance is dose related and may be enhanced by a drug-induced copper depletion. Loop diuretics (e.g. Furosemide) and to a lesser extent thiazide diuretics (e.g.Bendroflumethazide) are a cause of taste disturbance.

Both categories of diuretics deplete the body of a variety of metallic salts, including zinc (hypozincemia). Zinc is essential for taste acuity and mineral supplements containing zinc may be of help to such patients. Of concern to the dentist is the relationship between chlorhexidinemouthrinse and taste disturbance. This unwanted effect can persist for 60– 110 minutes following a single application.The precise mechanism for chlorhexidine-induceddysgeusia is uncertain, but may be related to chlorhexidines affinity for binding with protein sites of taste bud receptors.

Acetylsalicylic acid	Digitalis	Mesterolone	Streptomycin
Allopurinol	Diltiazem	Minoxidil	Salindac
Amlodipine	Ethambutol	Nifedipine	Sulphasalazine
Arsenic	Ethyl alcohol	Omeprazole	Tenoxicam
Atropine	Fluconazole	Oxyphenbutazone	Tolbutamide
Bsisulphan	Fluorozacil	Penicillin derivatives	Theophylline
Carbamazepine	Furosemide	Phenolphhthalein	Tocainide
Chloral hydrate	Gold	Phenylbutazone	Tolbutamide
Chloramphenicol	Griseofulvin	Phenytoin	Trimethadione
Chlorpropamide	Hydantoin	Piroxicam	Vancomycin
Clindamycin	Hydrochlorothiazide	Progesterone	Verapamil

Codeine	Indapamide	Pyrazolone derivatives	Zidovudine
Co trimoxazole	Measles/mumps/rubella vaccine	Quinine	
Diclofenac	Meclofenamic acid	Retinol	
Difluunisal	Mercury	Rifampicin	

Table 4: Drugs that have been implicated in causing erythema multiforme, Steven-Johnson syndrome and toxic epidermal necrolysis.

Angioedema: The most plausible explanation for the development of angioedema relates to the pharmacodynamics of angiotensin converting enzyme inhibitors. Angiotensin-converting enzyme, also known as kinase II, is responsible for converting angiotensin I to the more powerful vasoconstrictor angiotensin II. In addition, the enzyme is also responsible for the metabolism of the peptide bradykinin. This peptide is an important endogenous mediator of inflammation, causing vasodilatation and increased vascular permeability.
Following the administration of an angiotensin-converting enzyme inhibitor, bradykinin levels are raised and its action is prolonged. This may account for the troublesome cough that many patients experience while on these drugs.The prime concern in the management of edema is protection of the airway mainly non-surgically.

Behavioural Alteration: Patients with behavioural disorders being uncaring about their oral hygiene practices and, therefore, have a tendency towards increased plaque formation.Drugs acting as directly mood-altering drugs; alprazolam and fluoxetine hydrochloride may make patients more amenable to oral hygiene improvement. Since drowsiness is a side effect of these medications, motivation may still be problematic. Two other drugs alter mood as a side effect of their antihypertensive action; i.e., enalaprilmaleate and Captopril. These two medications may make patients less amenable to oral hygiene procedures since the medications tend to be depressive in nature.

II. Conclusion

It is evident that periodontal tissue is susceptible to a range of systemic medications. In today's world it is impossible for anyone to avoid any medications but such drug therapy can produce unwanted effects (e.g. gingival overgrowth), and reduce or increase the expression of periodontal disease. The periodontium may also be the target of adverse reactions of these drugs. This emphasises the importance of regular medical and drug histories and thorough oral and periodontal screening for all patients, especially the elderly and early diagnosis of these oral complications with proper treatment.

References

[1] Robin A. Seymour, Effects of medications on the periodontal tissues in health and disease, Periodontology 2000, Vol. 40, 2006, 120–129.
[2] Terry D. Rees, Drugs and oral disorders,Periodontology 2000, Vol. 18, 1998, 21-36.
[3] Sebastian G. Ciancio, Gingival Hyperplasia and Diphenylhydantoin, JPeriodontol 1996; 67:1055-1059.
[4] Iva Stamatova & Jukka H. Meurman,Probiotics and periodontal disease, Periodontology 2000, Vol. 51, 2009, 141–151.
[5] Louis F. Rose,periodontics medicine, surgery, and implants.
[6] Rosaiak K, Aruna K , NandiniTN,Nutritionalrequirmens of periodontal patient, Indian J Stomatol 2011;2(3): 175-78
[7] Carranza's clinical periodontology,11th edition.
[8] Terry D . Rees,Drugs and oral disorders,Periodontology2000, Vol. 18, 1998, 21-36.
[9] Shamimumal Hasan et al, drugs causing orofacialpigmentation : an overview of literature, Int. Res. J. pharm.2013,4(5).
[10] Antonio Bascones-Martinez, RiikkaMattila, Rafael Gomez-Font, and Jukka H. Meurman,Immunomodulatory drugs: Oral and systemic adverse effects,Med Oral Patol Oral Cir Bucal. 2014 Jan; 19(1): 24–31.
[11] Philippe P. Hujoel, Joana Cunha-Cruz, Gerardo Maupome,and Barry Saver, Long-Term Use of Medications and Destructive Periodontal Disease ,Journal of Periodontology August 2008, Vol. 79, No. 8, Pages 1330-1338 , JOP.2008.070648..
[12] TrophimusGnanabagyanJayakaran, The Effect of Drugs in the Oral Cavity - A Review,J. Pharm. Sci. & Res. Vol. 6(2), 2014, 89-96.
[13] Sebastian G. Ciancio, Medications as Risk Factors for Periodontal Disease,JOP 1996.67.1
[14] Wong W, Hodge MG, Lewis A, Sharpstone P, Kingswood JC.Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. Lancet 1994: 343: 986.
[15] Paik JW, Kim CS, Cho KS, Chai JK, Kim CK, Choi SH.Inhibition of cyclosporin A-induced gingival overgrowth by azithromycin through phagocytosis: an in vivo and in vitro study. J Periodontol 2004: 75: 380–387.