INTERNATIONAL JOURNAL OF MEDICAL AND APPLIED SCIENCES
Earthjournals Publisher
E-ISSN:2320-3137
www.earthjournals.org

Review Article

ADVERSE DRUG EFFECTS IN MOUTH

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Abstract :

Drugs are double edged swords. They come with a potential of life saving miracles to acting as an equivalent potential weapon resulting in adverse, even fatal consequences. This is especially a concern due to the irrational prescription of drugs so common now a days. Medications play their part in harming oral mucosa not always by direct contact but also via entry through oral vascular supply. The knowledge about drug induced oral adverse effects helps health professionals to better diagnose oral diseases, administer drugs, improve patient's compliance during drug therapy and may influence a more rationale use of drugs. This review provides an update of various drug induced oral reactions, so that dentists and oral health professionals increase their knowledge for a better diagnosis and therapy. This article will briefly describe the common presentations and mechanisms of oral drug reactions. An exhaustive description of every manifestation of pharmacological therapy is beyond the scope of this article, consequently only the most common lesions and reactions are described.

Key words : Adverse drug reactions, oral reactions, xerostomia, taste disorders, gingival hyperplasia.

INTRODUCTION

The drug produces desirable effect and undesirable effects in the body. The desirable effect is called therapeutic effect while undesirable effect is called adverse effect of a drug.[1] Although most of medications effects on oral tissues are adverse, a few are beneficial.[2] An adverse drug reaction is defined by WHO as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, therapy of disease or for the modification of physiological functions.[3] Drug induced side effects are frequent occurrence. Oral drug reactions are often non-specific, but they mimic specific disease states.[4] Oral mucosa is particularly susceptible to the effect of medications on its structure and appearance. Medications can exert their effects in many ways in oral cavity. Localized as well as generalized reactions can occur.[5] Every drug can produce untoward consequences even when used according to standard or recommended methods of administration. ADR's can involve every organ and system of body and are frequently mistaken for signs of underlying diseases. The mouth and associated structures can also be affected by many drugs and chemicals.[6] Considering the ageing of the population and

widespread and increased use of prescriptions, over the counter drugs and herbal medications, dentists can expect to encounter oral side effects among their patients due to usage of these medications. Dentists should take a thorough medical history and be aware of medication related problems and their potential effects on diagnosis and treatment planning.[3]

Etiology and pathogenesis

Pathogenesis of drug reactions may be related to immunologic or non- immunologic mechanisms. Most adverse reactions to drugs are mediated by the immune system and are drug allergies. The diagnosis requires a high index of suspicion and careful history taking. Recent use of drug is important. Withdrawal of suspected drug should result in improvement and reinstitution of drug should exacerbate the patient's condition.[7]

Stomatitis medicament/ Fixed drug eruption

It is localized hypersensitivity reaction that reoccur in the same site each time causative agent is ingested.[6]The lesions may be localized to the mouth or can be associated with lesions at other mucocutaneous sites.[8] They appear as a well demarcated, round erythematous plaque with or without vesiculation and necrosis. The lesions may be asymptomatic or associated with burning and pain.[4] Lesions usually appear within 24 hours post- ingestion of drug.[6] Drugs commonly associated with fixed drug eruptions include ***ampicillin, barbiturates, chlorhexidine, dapsone, gold, ibuprofen, indomethacin, lidocaine, Nsaids, salicylates, suphonamides, tetracyclines.***

Contact stomatitis/Stomatitis venenata

It is inflammation or pain of oral mucosa caused by external substances. These substances act either as irritant or allergic contactants.[9] It may result from contact with **dental materials, oral hygiene products or foods, dental restorative materials, cinnamon containing tooth pastes, topical anesthetics, steroids, chewing gum, antiseptic lozenges, iodine**[10],[7] and establishment of infection control procedures that mandate the wearing of latex gloves for dental treatment procedures.[6] It presents as a localized stomatitis with a variable clinical picture varying from mild erythema to vesiculation and necrosis.[4] Some practitioners use patch tests to confirm the diagnosis.[11] (Figure 1).

Chemical burn and oral ulceration

Oral desquamation or ulceration may follow burns from the accidental ingestion of caustics from local application of drugs like ***aspirin, potassium tablets, hydrogen peroxide, phenol***. Affected mucosa appears whitish and corrugated with erosion and ulceration of more severely damaged areas.[3](Figure 2).

Mucositis

It is a common toxicity associated with both head and neck radiation and chemotherapy.[6] Widespread sloughing and ulceration arise within days of commencement of therapy often requiring opioid therapy or cessation of chemotherapy.[3] The risk of developing mucosal injury increases with the number of chemotherapy cycles and previous episodes of chemotherapy induced mucositis.[12] The combining of different chemotherapeutic drugs further increases the possibility of mucositis from 40% of patients treated with standard chemotherapy regimens to 70% of patients treated with a combination of chemotherapeutic drugs.[6]

Recurrent apthous stomattitis

It is one of the most common painful oral mucosal conditions, presenting as recurrent, multiple, small, round or ovoid ulcers with circumscribed margins having yellow or gray floors, surrounded by erythematous haloes.[13] Among its predisposing factors like genetics, trauma, tobacco, hematinic deficiency, gluten sensitive enteropathy, celiac disease, inflammatory bowel disease, hormonal changes, stress, oral streptococci, H. pylori[14] and drugs like ***Nsaids, nicorandil, alendronate, beta blockers, cyclosporine, indinavir, losartan, sertaline*** can cause RAS.[13] Oral apthous like ulceration is also seen with ***tiotropium bromide.***[15]

Burning mouth syndrome

It is characterized by burning sensation in oral mucosa in the absence of clinically apparent mucosal alterations.[16] BMS is a diagnosis of exclusion.[17] It is characterized by an intense burning preferably in tongue.[18] Etiology could be peripheral and central neuropathological factors, local, systemic and psychological factors[16] like Hematinic deficiency states, undiagnosed maturity onset diabetes mellitus, oral candidal infection, xerostomia, denture design faults, parafunctional habits, cancerophobia, allergy to dental materials, psychological states (chronic anxiety, depression).[19] Drug induced like antihypertensive drugs are most often associated with appearance of symptoms compatible with BMS, particularly ***ACE inhibitors (enalapril, captopril), Angiotensin converting enzyme inhibitors (candesartan),*** others include ***antiretroviral (efavirenz), anxiolytic (clonazepam), antidepressants (fluoxetine, sertaline venelaflexine)***. [20]

Erythema multiforme

Erythema multiforme is an uncommon, acute inflammatory disorder, which affects the skin and/or mucous membranes. It is a reactive mucocutaneous disorder.[21] Oral mucous membrane is considered as a third category of erythema multiforme other than its minor and major. Patients present with oral and lip ulceration typical of erythema multiforme but without any skin target lesion. It has been reported that primary attack is confined to oral mucosa but the subsequent attacks can produce more severe forms involving skin.[22] Lesions typically affect oral mucosa, lips and bulbar conjunctiva. A wide range of drugs can cause erythema multiforme especially ***sulphonamides, tetracyclines, oral hypoglycemic, albendazole, antimalarials, NSAIDs(diclofenac), barbiturates, captopril, carbamezipine, cephalosporins, cocaine, codeine, cotrimazole, diltiazem, estrogens, progesterons, ketoconazole,protease inhibitors, valproic acid.***[6] ***Even herbal products can induce a hypersensitivity reaction in erythema*** **multiforme**.[23] Only 4% of reactions are caused by drugs, 80% of cases are found with **steven Johnson syndrome.**[6] (Figure 3).

Toxic epidermal necrolysis is clinically characterized by extensive mucocutaneous epidermolysis preceded by maculo papular exanthema and enthema. It may be associated with ***sulphonamides, phenazones, anti epileptics, rifampicin, vancomycin.***[8]

Lichenoid eruption

Lichen planus is a chronic inflammatory disease that affects the skin and mucous membrane.[24] Oral Lichenoid lesions refers to lesions histologically and clinically similar to oral lichen planus but with an underlying identifiable cause.[25] Some drugs can induce oral disorders resembling OLP and are Said to be oral Lichenoid drug reactions These are uncommon and these reactions disappear after drug withdrawal. A characteristic white lace pattern may be seen.[3] These changes are most often associated with long term exposure of

oral mucosa to ***dental metals, acrylates, composites, additives*** leading to delayed hypersensitivity reaction.[26] Most commonly implicated drugs include ***Nsaids, ACE inhibitors,***[25] ***HIV protease inhibitors, tetracyclines, antimalarials, sulphonamides, diuretics, carbamezipine, penicillins, gold, metronidazole*.**[8]

Color changes of oral mucosa and teeth

Oral pigmentation may be exogenous or endogenous in origin.[27] Increased levels of heavy metals (***lead, bismuth, mercury, silver, arsenic, gold***) in blood represent a known cause of oral mucosal discolouration.[27] The pathogenesis of drug induced pigmentation varies depending on causative drug. It can involve deposits of drug metabolites, synthesis of pigments under the influence of drug or deposition of iron after damage to blood vessels. ***Chloroquine, antiarrythmic drugs*** causes blue- grey or blue- black discoloration of hard palate.[27] In HIV, diffuse macular pigmentation may develop following use of ***clofazimine, zidovudine, ketoconazole therapy, amiodarone*** may cause grey orofacial and oral mucosal discolouration.[4] Pigmented lesions of tongue (dark macular patches) are reported to occur in ***heroin*** addicts inhaling smoke.[3] Other drugs causing mucosal pigmentation are ***oral contraceptives, chlorhexidine, gold, methyldopa, phenothiazines.***[28]

Tooth discoloration

Extrinsic discoloration of teeth may occur due to ***chlorhexidine, essential oils and co amoxiclav***. Intrinsic discoloration is associated with ***fluorides, tetracyclines, minocyclines, ciprofloxacin*.**[29] Systemic administration of tetracycline and minocyclines during development is associated with deposition within bone and dental hard tissues.[30] The cervical 3rd is most affected and staining is directly proportional to the age at drug exposure, dosage and duration of therapy. Minocycline staining occurs after teeth are fully developed and erupted as it easily penetrates into both soft and calcified tissues.[3] Tetracycline is able to cross placental barrier and so should be avoided from 29 weeks in utero until full term. Since permanent teeth continue to develop in infant and young child until 2 years of age, tetracycline administration should be avoided in children below this age and in breast feeding and expectant mothers. Chlortetracycline produces a slate grey color, oxytetracycline causes a creamy discoloration. Since tetracycline fluorescence under U.V light, so do as affected teeth giving off a bright yellow discolouration.[30] Stains are due to formation of tetracycline-calcium orthophosphate complexes deposited in dentin and enamel and darkens upon exposure to light.[31] Metals such as ***lead or mercury or drugs such as gold salts, silver nitrate, potassium permagnate*** produce pigmentation along gingival margin.[3] Reversible staining of teeth is due to liquid iron preparation as reported in literature. ***Iron treatment*** during pregnancy is very important. Teeth and nail discoloration can be a complication of iron supplement.[29](Figure 4).

Gingival hyperplasia

Drug induced gingival enlargement can be localized or generalized and varies with degree of severity.[3] The enlarged gingiva appears fibrotic and patient often develops an overlying inflammation as hyperplastic tissues are difficult to keep clean.[3] Most frequently occur on labial gingiva and anterior maxilla.[5] It produces esthetic changes and clinical symptoms including pain, tenderness, speech disturbance, abnormal tooth movement, dental occlusion problems, enhancement of caries development, periodontal disease.[32] It is a well described oral side effect of drug therapy. The drugs most commonly implicated are ***phenytoin, cyclosporine, calcium- channel blockers specifically nifedipine, diltiazem verapamil.*** It develops few months of commencement of drug therapy.[8] Potential risk factors

include poor oral hygiene, periodontal disease, degree of microbial plaque accumulation, duration and dose of drugs.[33] It responds variably to improve plaque control or withdrawal or reduction of drug therapy.[8] Although mechanism of action may be different, clinical and microscopic appearance of enlargement is same with any drug. One property common to 3 classes of drugs is that they directly affect cellular calcium metabolism, as cellular production of collagenase is modulated by calcium influx, these drugs may produce an inactive form of collagenase from fibroblasts, responsible for increase in extracellular matrix.[32] Prevalence of phenytoin induced gingival enlargement is 15-50%, with cyclosporine in transplant recipients is 27%, with calcium channel blockers is 10-20%.[33] Other drugs occasionally reported to cause gingival hyperplasia include ***oral contraceptives, erythromycin, sertalin, ketoconazole*** etc.[8] Considerations should be 1st given to discontinue the medication, drug substitution is 2nd alternative.[6] (Figure 5).

Salivary glands

Dryness of mouth or xerostomia results from diminished secretions of saliva and a decrease in salivary calcium phosphate concentration.[3] Patients with xerostomia often complains of dry cotton mouth, difficulty in speech and mastication, altered taste, poor denture fit, parasthesia, burning mouth syndrome. Examination reveals a dry, erythematous oral mucosa.[4] Common oral manifestations include increased dental caries, fungal and bacterial infection, apthous lesions and dysphagia.[3]. Fluoride rinses should be used to manage the detrimental effects of xerostomia on teeth.[5] Drugs are the most common cause of xerostomia.[8] More than 250 medications claim xerostomia as a side effect.[3] It was significantly age related and there was a strong co- morbidity between reported prevalence of xerostomia and ongoing pharmacotherapy.[8] The synergistic effects of medications have been recognized and are increasingly common elderly patients taking multiple medications. The principle mechanism of drug induced xerostomia is an anticholinergic or symapthomimetic action.[34] Even in elderly patients with advanced cancer, xerostomia is 4th most common symptom but the usual cause is drug treatment.[35] Following drugs have xerostomia as most common adverse effect ***antidepressants, antipsychotics, antihistaminic, muscarinic receptor blockers, alpha receptor anatagonists, diuretics, beta blockers, ganglion blockers, appetite suppressants (sibutramine, fenfluramine), decongestants (pseudoephedrine), bronchodilators (tiotropium), skeletal muscle relaxant (tizanidine), antimigraine drugs (rizatriptan), opioids, benzodiazepines, hypnotics, atropine, H2 receptor antagonist, proton pump inhibitors, anti HIV drugs (protease inhibitors), alpha interferon.*** [6],[7],[34],[35]

Drug induced sialorrhea or ptyalism is less frequent than xerostomia, more often it is due to abnormalities in swallowing resulting in drooling rather than actual overproduction of saliva.[4] Major medications group associated are ***antipsychotics(clozapine), cholinergic agonists for treatment of dementia and alzheimer's and myasthenia gravis, heavy metal toxins (mercury and thallium) from exposure to irreversible acetyl cholinesterase inhibitors (insecticides).***[6] **Discoloration of saliva** (red or orange) may be seen in patients treated with ***clofazimine, levodopa, rifampicin.***[8]

Taste disorders

Individuals taking any variety of medication may present with subjective complaints of taste changes. Taste alterations may manifests as hypoguesia, dysguesia, parageusia, ageusia.[3] A wide range of drugs give rise to taste alterations either by interfering with chemical composition, flow of saliva or by affecting either taste receptor functions or signal transduction.[6] Medicines are most common cause of taste disturbance.[36] ***Sulphahydryl***

compounds are a common cause, ***penicillamine*** causes partial or total loss of taste, impaired salty taste is a frequent complaint associated with ***captopril. Sytemic greisofulvin*** can render certain foods profoundly tasteless.[6] Bitter taste is a frequent side effect of ***dorzolamide, metronidazole, iron preparations.***[36]. Diminished taste acuity may also increase preference for salt or sugar, complicating treatment of conditions like diabetes and hypertension.[37] Understanding the potential taste related adverse effects of a given medication is of practical importance, as it allows medical practitioner to more accurately council the patient thereby ensuring better compliance and allaying future. Fears about its use or simply stopping a medication is not always easy decision, when particularly dealing with life threatening conditions like seizures.[38] Other major class of drugs most strongly implicated in altering taste function include ***antiviral, chemotherapeutic agents, antithyroid drugs, ACE inhibitors, angiotensin receptor antagonists, calcium channel blockers, hypolipidemic drugs, corticosteroids, anti depressants, anti psychotics, anticonvulsants, amphetamines, zolpidem.***[38]

Angioedema

It is a sudden occurrence of sub cutaneous or sub mucosal swelling. Majority of cases are due to allergic reactions. It is an established and potentially life threatening side effects of ***ACE inhibitors***, occurring following onset of use of ACE inhibitors, and reverses within hours of terminating the use of drug. The incidence of ACE inhibitors induced angioedema is 0.4%-0.7%, mortality worldwide is 0.1%.[6] ***Topical anesthetics, local anesthetics*** are associated with type I hypersensitivity reactions.[3] Drug induced mucosa swelling predominantly affects lips, tongue rarely isolated uvula swelling occurs.[4]Hypersensitivity to ***latex*** is an increasing problem in oral health care with rapid onset of angioedema in susceptible patients, also associated with use of ***penicillamine. ACE inhibitors, aspirin, barbiturates, ibuprofen etc.***[8](Figure 6).

Drug related physical damage to tooth

Any sugar containing medication has the potential to cause an increased incidence of caries. Drugs with potential to cause GERD (like ***theophylline, anticholinergics, progestin's***, ***calcium channel blockers, anti asthmatics, aspirin***) causes tooth erosion. ***H_2O_2, and carbamide peroxide*** causes tooth sensitivity when used for bleaching. In childhood cancer, chemotherapy drugs in children below 5 years of age exhibit abnormal dental development. Severity of dentofacial developmental and tooth related abnormalities secondary to therapy depends on age of child, duration and dosage of treatment.[39]

Drug induced osteonecrosis of jaw/ alveolar ostetitis

Biphospanate associated osteonecrosis of jaw is a serious oral complications of biphosphanate treatment involving exposure of necrotic maxillary or mandibular bone. It is dependent on dose, duration of drug therapy, estimated incidence is 1-12%.[40] dental.

Oral contraceptives are the only medication associated with developing alveolar ostetitis, estrogen has been proposed to play a significant role in fibrinolytic process.[41]

Drug related lupus like reactions

Systemic lupus erythematosus is associated with over 80 drugs. 10% of cases are drug induced.[42] The most commonly implicated agents are ***procanamide and hydralazine.***[8]

Drugs definitely capable of inducing lupus include ***isoniazid, methyldopa, quinidine, minocycline.*** Drugs possibly inducing lupus include ***sulphasalazine, anticonvulsants, antithyroids, beta blockers, statins, interferons.*** Drugs suggestive to induce lupus include ***gold, streptomycin, tetracycline, estrogen, oral contraceptives, calcium channel blockers, captopril.*** Drugs recently reported to induce lupus includes ***clobazam, clozapine, zafirlukast.***[42]

Drug related pemphigoid like lesions

At least 30 days can give rise to conditions resembling bullous or mucous membrane pemphigoid. The oral mucosa is frequently involved, particularly with ***penicillamine***. It can be only affected mucosa although patients often also have cutaneous lesions.[8] It erupts involving the mucous membrane immediately after taking the offending drug which includes ***atenelol, NSAIDs, antimicrobials*** etc.[43]

Drug related pemphigus

Drugs capable of inducing pemphigus are divided into 2 main groups according to their chemical structure thiol ***and non thiol drugs***. Pemphigus vulgaris is occasionally associated with active thiol group drugs like ***ampicillin, diclofenac, cephalexin, captopril, phenylbutazone***.[8]

Fungal infections

Candiasis is most common opportunistic infection seen in dental practice.[3] Pharmacological action of these drugs may have a suppressive effect on normal oral bacterial flora that normally keeps the candidal population at check. ***Steroid inhalers, intraoral topical steroid preparations, azathioprine*** results in candidal infections.[44],[45] Drugs with xerostomic effect ***(anti cholinergic, anti depressants, anti psychotics, anti histaminics, anti hypertensives***) often cause oral candiasis.[44] Erythematous candiasis is often associated with use of ***broad spectrum antibiotics and corticosteroids***.[45]

Oral motor disorders

Some drugs can induce oral motor hyperactivity like dystonic reactions akathisia reactions parkinsonism. Drug induced extra pyramidal reaction involves muscles of head, face and jaws producing spasm, grimacing, tics or trismus. ***Antipsychotics, antiemetics, prochlormazine, promethazine, metochlorproamide, fluoxetine, sertaline, amphetamines***.[6]

CONCLUSION

A wide spectrum of drugs can give rise to numerous adverse orofacial manifestations. The most common reactions are dry mouth, taste disturbance and gingival overgrowth.[8 Since many patients take multiple medications, dentists must be aware of the issues related to drug use including indications, interactions and side effects. The ability to evaluate these issues it is necessary to accurately assess patient's status and prevent situations that compromise client safety. Rapid progress in pharmacotherapeutics requires clinician to constantly update their knowledge of drugs used by their patients.[6]

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Earthjournals Publisher
E-ISSN:2320-3137
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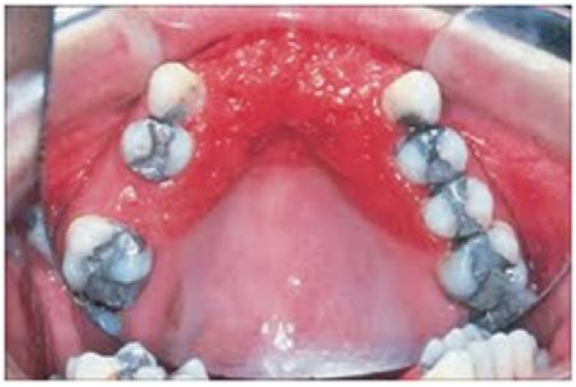

Figure 1: Contact Stomatitis

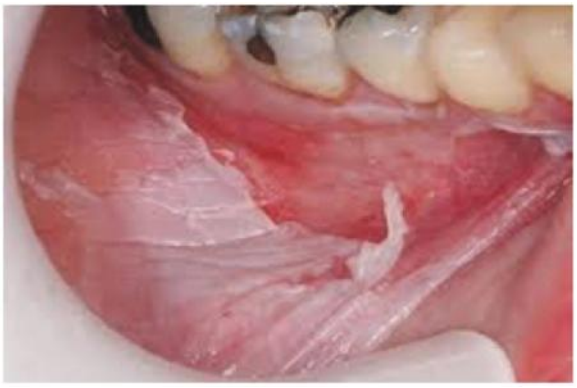

Figure 2: Aspirin induced chemical Burn

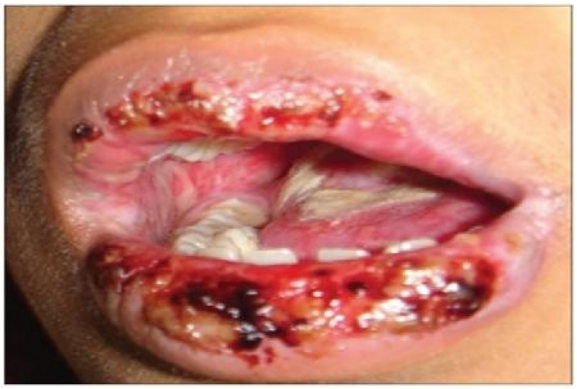

Figure 3: Drug induced erythema Multiforme

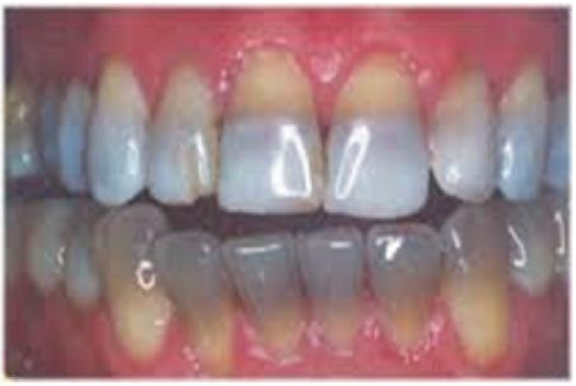

Figure 4: Tetracycline staining

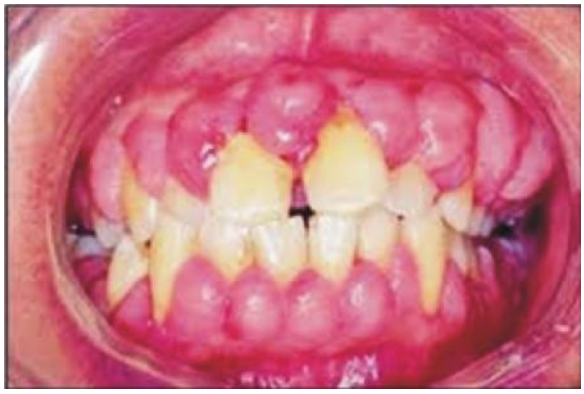

Figure 5: Drug induced gingival enlargement

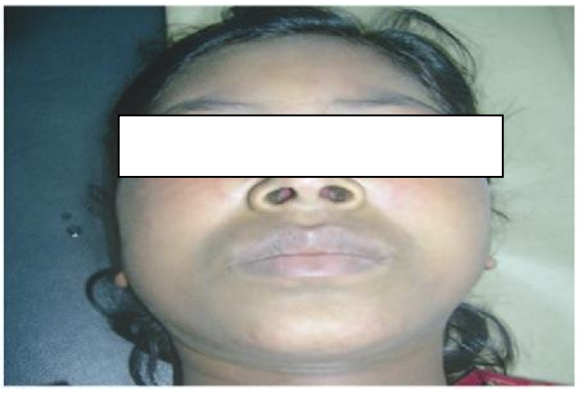

Figure 5: Drug induced angioedema

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