A Summary of Common and Significant Adverse Effects of Drugs in Oral Region

Santosh R Patil¹, G Maragathavalli², DSV Ramesh³, MS Munisekhar⁴, Krishna A Rao⁵, Mohammad Khursheed Alam⁶

ABSTRACT

Background: Dental practitioners must regularly update their knowledge of medications used by their patients. Attention must be paid to their adverse effects which may mimic the features of common diseases. The aim of this article is to present a summary regarding various drug-induced oral reactions.

Material and methods: A comprehensive and extensive search of literature was carried out through the National library of medicine (PubMed), SCOPUS, EMBASE databases using different keywords. All the relevant articles were analyzed according to their importance and reviewed to evaluate the adverse effects of drugs in the mouth and associated structures.

Results: Most of the drugs produce untoward effects even when used according to standard prescriptions. Adverse drug reactions can manifest in the oral cavity in multiple forms affecting the oral mucosa, tongue, periodontal tissues, dental structures, etc.

Conclusion: Dental surgeons should be updated with the knowledge of adverse drug oral reactions and their presenting features for timely diagnosis and management of such conditions.

KEY WORDS

oral reactions, oral mucosa, adverse drug effects, xerostomia

INTRODUCTION

The oral cavity might be the objective organ for various different anomalies that manifest from adverse effects of medicines. Progressively, patients with complicated therapeutic issues reporting to the dental surgeon present with usage of various medications for the treatment of some or the other diseases¹. Many of these medications produce changes in oral cavity because of their toxic overdoses, side effects, allergic reactions or due to primary action of the drug. These changes include stomatitis, ulceration, vesiculo-bullous lesions, necrosis, opportunistic infections, hemorrhage, gingival hyperplasia, soft tissue pigmentation, teeth discoloration, altered taste sensation, altered salivary function and secretion². A patient who complains or presents with any of these signs and symptoms should be thoroughly questioned regarding medication. If an offending drug is identified, its alteration or elimination, in consultation with the prescribing clinician, often results in resolution of the clinical problem³. The pathogenesis of oral adverse effects identified with use of various medications is not clearly established to date. They are, in any case, regarded to be a moderately routine phenomenon, despite the fact that drug induced oral adverse effects are routinely regarded by the dental practitioners as inconsequential manifestations⁴,⁵. Table 1 summarizes the major adverse effects of drugs in the oral region.

Xerostomia

Age and medications are the major cause of hyposalivation. About 500 drugs have been reported to have some incidence of dry mouth as side effect, the majority being antihypertensives, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, antidepressants, sedatives, centrally acting analgesics, antiparkinsonism medication, anti-allergic medications, and antacids. These include ketorolac, tramadol, omeprazole, cetrizine, cyclopam, diazepam and furosemide etc⁶,⁷. In addition to causing xerostomia, these drugs can also indirectly cause or aggravate halitosis.

Ptyalism

Also known as Sialorrhea is a condition in which there is salivary
Aphthous-like Ulceration

Lesions typically appear as white striations (Wickham’s striae) on buccal mucosa, lateral borders of the tongue and may also exhibit as multiple aphthous ulcers. When associated with drugs, they usually have an onset from days to weeks after the patient begins taking the offending drug and resolve after discontinuation of the drug. Paracetamol, barbiturates, tetracyclines, sulfonylureas, and many antihypertensive drugs are common offenders. It is clinically difficult to differentiate between drug-induced erythema multiforme from disease due to other causes. The common causative drugs include barbiturates, cephalosporins, tetracyclines, penicillins, sodium perborate, sodium peroxide, streptomycin, sulfonamides, tetracycline, thiothixene, trifluoperazine, and tetracyclines. Drugs which are solitary initially, may become multiple with repeated exposure to the causative drug. Paracetamol, barbiturates, tetracyclines, sulfonamides, and rifampicin are commonly associated with this condition.

Mucositis

Oral mucositis is a common adverse effect of radiation therapy, chemotherapy, and certain drugs. It is characterized by inflammation, swelling, and pain in the oral mucosa. Drugs such as aspirin, diclofenac, mefenamic acid, piroxicam, fluconazole, phenytoin, aspirin, and nifedipine are known to cause oral mucositis. Clinically, TEN causes widespread ulceration of oral mucosa with extensive mucocutaneous erosion and hence a potential cause of septicemia. Sulfonylureas, phenytoin, piroxicam, fluconazole and rifampicin are commonly associated with this condition.

Fixed Drug Eruptions

These eruptions are usually confined to a single area of the body and recur in the same site upon reexposure to the causative drug. The common causative drugs include barbiturates, cephalosporins, tetracyclines, penicillins, sodium perborate, sodium peroxide, streptomycin, sulfonamides, tetracycline, thiothixene, trifluoperazine, and tetracyclines. Drugs which are solitary initially, may become multiple with repeated exposure to the causative drug. Paracetamol, barbiturates, tetracyclines, sulfonamides, and rifampicin are commonly associated with this condition.

Erythema Multiforme and Toxic Epidermal Necrolysis (TEN):

It is clinically difficult to differentiate between drug-induced erythema multiforme from disease due to other causes. The common causative drugs include barbiturates, cephalosporins, tetracyclines, penicillins, aspirin, diclofenac, mefenamic acid, piroxicam, fluconazole, phenytoin, verapamil, and nifedipine. Clinically, TEN causes widespread painful blistering and ulceration of oral mucosa with extensive mucocutaneous epidermolysis. Sulfonylureas, phenytoin, piroxicam, fluconazole and rifampicin are commonly associated with this condition.

Mucositis

Anti-cancer drugs like methotrexate, 5-fluorouracil, doxorubicin, melphalan, bleomycin cause ulcerations and wide spread sloughing of oral mucosa associated with pain, which may serve as portal of entry for infection and hence a potential cause of septicemia.

Oral Burns Secondary to Drugs

Accidental ingestion of caustics like lime, topical application of aspirin, potassium tablets and other aliments like hydrogen peroxide, sodium lauryl sulphate may cause desquamation of oral mucosa and ulceration of oral mucosa associated with pain, which may serve as portal of entry for infection and hence a potential cause of septicemia.

Fixed Drug Eruptions

Clinically this condition manifests as repeated ulceration at the same site, associated with vesicles, erythematous patches, erosions which are solitary initially, may become multiple with repeated exposure to the causative drug. Paracetamol, barbiturates, tetracyclines, sulfonamides, dentifrices and mouth washes are the main causative agents.

Oral Candidiasis

Various drugs such as broad spectrum antibiotics (tetracyclines), corticosteroids, and immunosuppressive agents like cyclosporine, cyto-
toxic agents and drugs causing xerostomia can lead to oral pseudomembranous candidiasis.\(^{\text{19}}\)

**Black Hairy Tongue**

Hypertrophy of filiform papillae on the surface of the tongue superimposed with proliferation of chromogenic microorganisms are seen in patients using long term corticosteroids, antibiotics like penicillin, cephalosporines, clarithromycin, streptomycin, sulfonamides, tetracycline, etc.

**Oral Tissue Pigmentation**

Minocycline (tetracycline agent), used to treat soft tissue infections can cause black pigmentation in the gingival tissue and underlying alveolar bone.\(^\text{20}\) Gingival pigmentation may also be seen secondary to metal alloys of crowns or to gold and amalgam restorations leading to localized areas of pigmentation.\(^\text{21}\)

**Teeth Discolorations**

Antimicrobial agents like tetracycline and minocycline can stain teeth especially in developing teeth and bones. Staining is directly proportional to the age at drug exposure, dosage and duration of therapy. Minocycline staining occurs after the teeth are fully developed and erupted as it can penetrate easily into both soft and calcified tissues and cause irreversible staining. Pigmentation is formed by integration of the drug from the pulp into the dentin and enamel. Oxidation from the saliva and gingival crevicular fluid produces a bluegray staining in the middle and incisal thirds of the teeth.

**Taste Disorders**

Drugs interfering the chemical composition, flow of saliva, affecting taste receptor function, can cause a loss of taste acuity, taste distortion or loss of taste sensation.\(^{\text{12}}\) Changes may range from bitter to metallic. Drugs prescribed by dentists that fall into this category are metronidazole, hydrocortisone, bactol and chlorhexidine. Other drugs causing taste disorders include aspirin, tetracycline, levamisole, methotrexate, phenytoin, ACE inhibitors and anti-thyroid.\(^\text{13}\)

Three possible mechanisms have been suggested that could cause dysgeusia.

a. The drug itself might be secreted in the saliva.
b. It could be interaction of drug metabolites with the taste buds.
c. Taste buds might be damaged by the drug.

**Bisphosphonate related osteonecrosis of jaws (ONJ)**

Bisphosphonate drugs are the treatment of choice in osteoporosis and other metabolic bone diseases and are also used in treatment of certain metastatic malignancies like multiple myeloma and carcinoma of breasts to decrease the local and metastatic spread of these lesions. The prolonged exposure of these derivatives of pyrophosphates decrease rate of bone turnover leading to suppressing the ability of jaw bones to undergo normal remodeling. In this scenario, due to the presence of diverse oral microbial flora the patients become more susceptible to the infections and necrosis of the jaws.

**Intraoral hemorrhage**

Intraoral hemorrhage may occur due to defective vascular integrity, a decrease in the platelet count (thrombocytopenia) or alterations in coagulation. Chronic use of certain drugs may cause intraoral hemorrhage by bringing one of the aforementioned causes.

Drugs such as sulfonamides, heparin, phenytoin, methylidopa, thiazide diuretics, quinine & quinidine, antineoplastic agents, digitalis, gold salts are known to cause thrombocytopenia resulting in hemorrhage intraorally.

Antibiotics such as tetracyclines, penicillin and cephalosporin have been known to cause intraoral hemorrhage by decreasing the ability of

**CONCLUSION**

Since many patients regularly take medications, both prescribed and non-prescribed, dentists always must take a thorough medical history so that they can be aware of medication-related problems and the impact of medications on diagnosis and treatment planning.

**REFERENCES**