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Drug-induced Salivary Gland Disorders: A Review Article

Abstract:
Every drug can produce unexpected side effects even when used according to the standard dose. Adverse drug reactions can involve any organ and system of the body and are commonly mistaken for signs of underlying disease. The oral cavity can also manifest drug-induced reactions. An optimum salivary function is very crucial in maintaining oral health. The number of drugs and chemicals that can produce adverse reactions in the oral cavity is on the rise. A detailed history of the medication that the patient is taking should be asked as many patients take prescription and non-prescription drugs daily. A clinician should keep themselves updated with the list of offending drugs for proper management of these drug-induced lesions. This will help them in identifying the toxic and unwanted effects of the drugs that can be easily mistaken for symptoms of a common disease.

Key-words: Drug-induced, Adverse drug reaction, Salivary gland, Xerostomia, Ptyalism.

Introduction:

An adverse drug reaction is defined by the World Health Organization as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function".[1] Adverse drug reactions can involve any organ and system of the body and are commonly mistaken for signs of underlying disease. As newer therapeutic agents are approved, these reactions are on the rise and can cause serious health problems with effects also commonly seen in the oral cavity.[2,3] Drug therapy-induced complications are the major cause of patient morbidity and account for a significant number of patient deaths.[4]

The most frequent side effects of drugs affecting the oral cavity are reported to be xerostomia, dysgeusia, and stomatitis.[5] Saliva is an exocrine secretion product that flows into the oral cavity from three pairs of major salivary glands (parotid, submandibular, and sublingual) and minor salivary glands (or accessory glands) that are disseminated in the oral mucosa. Saliva plays an important role in food swallowing, digestion, protection against tooth decay, phonation, immune defences of the body etc.[6]

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Salivary gland secretion from the major and minor glands is mainly under neural control influenced by the autonomic nervous system. Hormones may also modulate the composition of saliva. Parasympathetic (cholinergic) stimulation of cranial nerves V, VII, and IX increases salivation, while sympathetic (adrenergic) stimulation through the cervical carotid centres- upper, middle, and lower

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centres produces more viscous saliva giving the appearance of depressed salivation.[7,8] Salivary gland function can be affected by a variety of drugs that can produce xerostomia or ptyalism.[7] Salivary glands can secrete the molecules that degrade medications and produce substances that can alter the physicochemical composition of saliva. This can cause taste alteration.[9]

A. Xerostomia

Mechanism:

Drug-induced xerostomia can result from several mechanisms.[9]

1. A dysfunction in the nervous control of salivation: sympathomimetic drugs (ephedrine, amphetamines, central antihypertensive), anti-cholinergic drugs (atropine, antispasmodic, tricyclic antidepressants, antiparkinsonian, antihistaminic, muscle relaxants).
2. Direct damage of the salivary glands (anticancer immunotherapies).
3. Medication-induced dehydration (increased urine flow with diuretics).

Several different mechanisms are responsible for drug-related salivary gland hypofunction or dry mouth, but an anticholinergic action is the most common underlying mechanism. The M3- muscarinic receptors (M3R) mediate parasympathetic cholinergic neurotransmission to salivary and lacrimal glands. Other receptors may also be involved.[10]

Cause:

There are a variety of possible causes responsible for dry mouth. Common habits such as tobacco smoking, alcohol, use of mouthwashes with alcohol, and the consumption of caffeinated beverages can cause some oral dryness but drugs are the most common cause of reduced salivation.[10,11] Xerostomia may be due to both the reduced salivary flow rate and due to a decrease in salivary calcium and phosphate concentration caused by drugs such as amphetamines.[7]

Xerostomia is commonly seen in patients who have received radiotherapy for head and neck cancer. In a study done by Chakrabarti et al, the incidence of severe xerostomia in patients receiving concurrent chemotherapy and radiotherapy was significantly higher as compared to patients receiving only radiation.[12] Dry mouth is a common complaint in patients treated for hypertension, psychiatric or urinary problems. It is also commonly seen in the elderly because of the large number of drugs used.[10]A study by Shetty et al observed synergistic effects of xerostomia-inducing medications in elderly patients taking multiple medications.[13]. In these patients, the intensity of xerostomia can be reduced by the substitution of drugs, by a change in the way they are taken, or by stopping or reducing the selected drug. Findings of the meta-analyses by Tan et al. confirmed that specific drugs used for urinary incontinence followed by antidepressants, and psycholeptics are significantly associated with xerostomia.[14]

The underlying condition for which the drug is being taken is also important. Patients with anxiety or depressive conditions may complain of dry mouth even in the absence of drug therapy or evidence of reduced salivary flow. Therefore, in some patients complaining of a drug-related dry mouth with no evidence of a reduced salivary flow or a salivary gland disorder, there may be apsychogenic reason for the complaint.[10] [Table- 1]

Clinical Presentation:

Common oral manifestations resulting from decreased salivary flow include increased dental caries, fungal infections, bacterial infections, aphthous lesions, and speech disorders. Patients may also complain of a burning sensation in the mouth, increased thirst, difficulty in chewing and swallowing, dry cracked lips, and tongue.[9,3,15]. The loss of lubrication also results in erythema and makes the mucosa more susceptible to frictional trauma against teeth causing profound discomfort to the patient.[3] Therefore, the knowledge of the medication that the patient is taking is crucial to prevent xerostomia by substituting, reducing, or suppressing the medication.[16]

Management:

The clinician should look for functional signs like difficulties in swallowing, chewing, speaking, and increased thirst. Also, clinical signs like saliva with whitish deposits, viscous saliva, sticky mucous tissues, absence of salivary film, absence of saliva at the ostium of the main salivary glands (after palpation), cervical caries, and mucosal atrophy should be noted. A sugar test and salivary flow measurement at rest and after stimulation can help with the diagnosis. Mouth breathing should also be ruled out.[17] The use of pilocarpine and bethanechol has been suggested to be useful in the management of drug-induced xerostomia.[18]. The use of malic acid non-alcoholic mouthwashes and saliva substitutes also are useful in drug-induced xerostomia.[15] Electro stimulation is a new management technique that may be helpful.[15]

B. Ptyalism or Sialorrhoea:

Sialorrhoea or ptyalism is the condition of increased salivary flow. It is relatively uncommon as compared to xerostomia. Increased salivary secretion can be seen during tooth eruption, local irritation, inflammation, gastroesophageal reflux disease, menstruation, down syndrome, cerebral palsy, Parkinsonism, etc.[9]

Mechanism:

Ptyalism is caused by drugs that have a cholinergic effect. The drugs either act directly on parasympathetic receptors (ex: pilocarpine) or act as cholinesterase inhibitors and thus prevent the destruction of acetylcholine by cholinesterase (ex: neostigmine).[18]

Cause:

Salivary hypersecretion or sialorrhea is usually caused by physiological factors such as menstruation or early pregnancy, local factors such as teething, oral inflammatory lesions, food, medications, or by nasogastric intubation.[19] [Table-2]

Management:

The treatment of drug-induced sialorrhoea is only symptomatic and to decrease the saliva to amounts that can be swallowed. Atropine-related oral anticholinergics are given systemically, or sublingual ipratropium spray is given locally.[7] The other mode of action is by increasing adrenergictone using a clonidine patch. To treat refractory cases, botulinum injections into the parotid gland have been used successfully.[7,9]

C. Pain and swelling of salivary glands:

Antihypertensives, chlorhexidine, anti-thyroidagents, cytotoxins, iodides, ganglion-blocking agents, phenothiazines, and sulphonamides may cause salivary gland pain. The drugs causing dry mouth may also cause pain in the salivary glands (Glass, 1989).[10]

Administration of either inorganic or organic iodine occasionally results in the bilateral swelling of the salivary glands known as iodine mumps. According to Carter this condition probably represents an iodine idiosyncrasy reaction. The studies of Shafer and Muhler have shown a close relationship between the thyroid and the salivary glands.[11]. [Table-3]

Painless, usually bilateral, salivary gland enlargement may be an occasional side-effect of oxyphenbutazone, phenylbutazone, or chlorhexidine. Clozapine, an antipsychotic agent, may cause transient salivary gland swelling as well as sialorrhea.[10]

D. Discoloration of Saliva:

Some medications are known to cause discoloration of saliva and other body fluids such as clofazimine, levodopa, rifampin, and rifabutin.[9]

Table 1: Drugs implicated in xerostomia:[7,10,15]

➢ Alizapride	➢ Glycopyrrolate	➢ Peginterferon alfa-2a
➢ Alpha 1 antagonist (e.g. terazosin,prazosin,alfuzosin)	➢ Guanabenz	➢ Phenothiazines
➢ Alpha 2 antagonist (e.g. clonidine, lofexidine)	➢ Guanfacine	➢ Phenylpropanolamine
➢ Ambroxol	➢ Hyoscine	➢ Posaconazole
➢ Amphetamines	➢ Insulin	➢ Pregabalin
➢ Antihistamines	➢ Ipratropium	➢ Propantheline
➢ Anti-HIV protease inhibitors	➢ Isotretinoin	➢ Proton pump inhibitors (e.g. omeprazole)
➢ Antimigraine agents	➢ Ketanserin	➢ Radioiodine
➢ Antineoplastics	➢ Ketotifen	➢ Rasagiline
➢ Antiparkinson drugs	➢ L-dopa	➢ Risedronate
➢ Atropine	➢ Lead	➢ Rotigotine
➢ Benzodiazepines	➢ Lithium	➢ Selective serotonin reuptake inhibitors
➢ Beta-blockers (e.g. atenolol, propranolol)	➢ Lubiprostone	➢ Solifenacin
➢ Belladonna alkaloids	➢ Mazindol	➢ Somlol
➢ Botulinum toxin type-A	➢ Methdilazine	➢ Spiramycin
➢ Bupropion	➢ Modafinil	➢ Tadalafil
➢ Cadmium	➢ Molindone	➢ Terodiline
➢ Calcium channel blockers	➢ Monoamine oxidase inhibitors	➢ Thiabendazole
➢ Ciprofloxacin	➢ Nabilone	➢ Thioridazine
➢ Cliclinium	➢ Nefazodone	➢ Tiamenidine
➢ Clozapine	➢ Nefopam	➢ Tizanidine
➢ Cyclobenzaprine	➢ Nicotine	➢ Trazodone
➢ Cyclopentolate	➢ Nitric oxide inhibitors	➢ Tricyclic antidepressants
➢ Cyclosporine	➢ Ofloxacin	➢ Tropicamide
➢ Cytokines	➢ Olanzapine	➢ Venlafaxine
➢ Dexmedetomidine	➢ Ondansetron	➢ Varenicline
➢ Ephedrine	➢ Opioids	➢ Vigabatrin
➢ Fenfluramine	➢ Orphenadrine	➢ Vorinostat
➢ Gentamycin	➢ Oxybutynin	➢ Zuclopenthixol
	➢ Paliperidone	
	➢ Paricalcitol	

Table 2: Drugs that can cause sialorrhea:[7,10]

➢ Alprazolam	➢ Iodides kanamycin	➢ Organophosphates
➢ Ambroxol	➢ Ketamine	➢ Pentoxifylline
➢ Amiodarone	➢ Lamotrigine	➢ Physostigmine
➢ Bethanechol	➢ Levodopa	➢ Pilocarpine
➢ Buspirone	➢ Lithium	➢ Risperidone
➢ Clozapine	➢ Mianserin	➢ Rivastigmine
➢ Desflurane	➢ Mefenamic acid	➢ Sildenafil
		succinylcholine
➢ Diazoxide	➢ Mercurial salts	➢ Tacrine
➢ Digoxin	➢ Modafinil	➢ Theophylline
➢ Edrophonium	➢ Neostigmine	➢ Tobramycin
➢ Galantamine	➢ Nifedipine	➢ Venlafaxine
➢ Gentamycin	➢ Niridazole	➢ Zaleplon
➢ Guanethidine	➢ Nitrazepam	➢ Zonisamide
➢ Imipenemcilastatin	➢ Olanzapine	

Table 3: Drugs that have the potential to cause pain and swelling in the salivary gland:[7,10,21]

➢ Bretylium	➢ Famotidine	➢ Phenytoin
➢ Catecholamine Inhalation	➢ Iodine	➢ Ranitidine
➢ Chlorhexidine	➢ Methyldopa	➢ Ritodrine
➢ Cimetidine	➢ Naproxen	➢ Sulphonamides
➢ Clonidine	➢ Nifedipine	➢ Trimipramine
➢ Clozapine	➢ Nitrofurantoin	➢ Warfarin
➢ Doxycycline		

Conclusion:

Drug-induced lesions can be caused by a wide range of medications. Most of the drug-induced oral reactions are moderate in severity. However, severe reactions need rapid withdrawal of the suspected drug. Delayed allergic reactions to commercially available drugs are the most common hypersensitivity reactions. In most cases, the oral reaction will be resolved by symptomatic treatment. The difficulty in obtaining a reliable clinical history makes arriving at an accurate diagnosis difficult. Also, the low sensitivity of skin tests and in vitro tests adds to the inability to diagnose drug-induced reactions accurately. Thus, the potential of a drug to cause allergy should be evaluated, to prevent the complications from drug therapy. This will in turn help in reducing patient morbidity and mortality.

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