

## **Drug-related oral complications.**

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Drug-induced side effects are a frequent occurrence. The oral drug reactions are often nonspecific, but they may mimic specific disease states.

Regarding different parts of the oral system, these reactions can be categorized to:

- oral mucosa and tongue,
- periodontal tissues,
- dental structures,
- salivary glands,
- cleft lip and palate,
- muscular and neurological disorders,
- taste disturbances,
- drug-induced oral infection,
- facial edema.

### **Oral drug-reaction patterns include:**

- **Aphthous stomatitis** (also termed recurrent aphthous stomatitis, recurring oral aphthae or recurrent aphthous ulceration). Is a common condition characterized by the repeated formation of benign and non-contagious mouth ulcers (aphthae), in otherwise healthy individuals.
  - **Burning mouth syndrome (BMS)** is a painful, frustrating condition often described as a scalding sensation in the tongue, lips, palate, or throughout the mouth. Signs and symptoms are: burning, scalding or tingling feeling on the tongue, lips, throat or palate, no specific lesion evident, with or without any sign of inflammation and discomfort usually worse at the end of the day.
    - **Glossitis** Glossitis is inflammation of the tongue. Signs and symptoms are: swollen intensely painful tongue, red and smooth tongue. Pain may be

referred to the ears and salivation, fever and enlarged lymph nodes may develop if infection is present.

- **Oral ulcerations (nonspecific ulceration and mucositis)**

They are clinically diverse, but usually appear as a single, painful ulcer with a smooth red or whitish-yellow surface and a thin erythematous halo. Oral drug reaction may be as small round /oval lesions/ with yellow or grey floor

- **Vesico-bullous lesions**

Oral drug reactions that bear striking clinical, histopathologic, and even immunopathologic resemblance to idiopathic Lichen planus, Erythema multiforme (EM), Pemphigoid, Pemphigus vulgaris, and Lupus erythematosus (LE) are well recognized

- **Lichen planus**

is a relatively common papulosquamous disorder involving the skin and mucous membranes. Often these lesions are asymptomatic.

- **Erythema multiforme (EM) – like – drug induced reaction**

Erythema multiforme is a syndrome consisting of symmetrical mucocutaneous lesions that have a predilection for the oral mucosa, hand, and feet. Initial bullae may rupture, giving rise to widespread superficial ulceration. A spectrum of disease can be seen ranging from a benign cutaneous eruption to a severe mucocutaneous eruption.

- **Pemphigoid – like – drug induced reaction**

Clinically, lesions appear as relatively sturdy vesicles or bullae that break down into shallow ulcerations. Generalized or multifocal involvement of the gingival tissues may be observed, with marked erythema and erosion of the superficial gingiva.

- **Pemphigus – like – drug induced reaction**

have been reported to have similar clinical, histologic, and immunofluorescent patterns as Pemphigus vulgaris. In drug-induced pemphigus vulgaris, the relatively fragile vesicles are rarely observed at clinical

examination, and most cases are characterized by irregular ulcerations with ragged borders that may coalesce to involve large areas of the mucosa.

- **Lupus erythematosus (LE) – like-drug-induced reaction**

Clinically, the oral lesions of drug-induced LE may simulate those of erosive lichen planus, with irregular areas of erythema or ulceration bordered by radiating keratotic striae.

- **Color changes of oral mucosa and teeth (Pigmentation)**

Pigmentation may be normal pigmentation which are a physiological finding, particularly in dark-skinned individuals because increased melanin production and deposition in the oral mucosa. Clinically, it appears as multiple brown pigmented areas, usually located on the anterior labial gingiva of the mandible. Teeth discoloration may be intrinsic or extrinsic.

- **Black hairy tongue (Lingua villosa, Lingua nigra)**

Hairy changes are on the upper side of the tongue (never on under side). Hairy tongue is a relatively common disorder that is due to marked accumulation of keratin on the filiform papillae of the tongue. Lingua is black but may also be brown, white, green or pink. Normally asymptomatic and may develop secondary fungal infection (Candidosis).

- **Drug induced gingival enlargement**

Gingival enlargement is seen in periodontitis, system disorders, and drug-induced states. The enlargement is usually generalized throughout the mouth but is more severe in maxillary and mandibular anterior regions. Clinically, both marginal gingiva and interdental papilla appear enlarged and firm.

- **Xerostomia or dry mouth**

Is the most common adverse drug-related effect in the oral cavity. Clinical signs and symptoms are: difficulty eating and swallowing, difficulty speaking and little saliva present in the mouth or may be thick stringy saliva

- **Swelling**

Several drugs can induce type I hypersensitivity reactions, or disease mediated by immunoglobulin E mast cells, that can range from isolated swelling of the oral tissues to full-blown anaphylaxis. Around the mouth, the lips are the most frequently involved site, followed by the tongue. The swelling is acute and is often transient. Lesions typically last for only several hours, but may last for days. Affected mucosa typically appears edematous and erythematous within minutes or hours after exposure to the offending drug.

- **Oral thrush — Oral candidosis**

The yeast, *Candida albicans* is the most common cause of infection of the oral cavity. Drug induced oral candidosis is usually asymptomatic, but it may have an associated erythematous, ulcerated base. Presents of creamy-white lesions on tongue, pain, slight bleeding if the lesions are rubbed or scraped, "cottony" feeling in the mouth, loss of taste (ageusia) and difficulty swallowing (if infection spreads to throat).

- **Taste disturbance (Ageusia, Dysgeusia)**

Numerous causes exist that can lead to a decreased ability to perceive taste or causing an unpleasant taste. The alteration in taste may be simply a blunting or decreased sensitivity in taste perception (hypogeusia), a total loss of the ability to taste (ageusia), or a distortion in perception of the correct taste of a substance, for example, sour for sweet (dysgeusia) total loss of ability to taste, complaints of metallic taste, impaired salty taste, reduced appetite and weight loss.

- **Stomatitis — Contact allergy**

Stomatitis or oral inflammation of the mouth is a nonspecific term that describes many oral drug reactions. This is a relatively common oral mucosal reaction to continuous contact of substances. The clinical symptoms may include: nonspecific generalized inflamed gums, palate, lips, tongue and buccal mucosa, bleeding, oral lesions as ulcerations and erosions, and breathing difficulties if severe

allergic reaction involving tongue. Lesions occur within 24 hours of ingesting the medication.

- **Angular cheilitis (AC), or perleche**

Is a common disorder of the angles of the mouth. This is soreness and cracks at the corners of the mouth. The condition is characterized by erythema, maceration, fissuring, erosion, and crusting at commissures. Remissions and exacerbations are common.

- **Osteonecrosis**

Is a disease resulting from the temporary or permanent loss of blood supply to the bones. Clinical symptoms are: swelling and loosening of teeth, altered local sensation, facial pain, toothache, loose teeth, exposed bone, recurrent infection and marked oral odour.

Salivary gland function can be affected by a variety of drugs that can by a variety of drugs that can produce

- **xerostomia or ptyalismus.**

It is suggested this is due to both the reduced salivary flow rate and to a decrease in salivary calcium and phosphate concentration.

Systemic drug therapy can also produce pain and swelling of the salivary glands. Salivary gland enlargement may be painless or associated with tenderness

- **Sialorrhoea, or excessive salivation**

is commonly associated with many systemic conditions. Clinical signs and symptoms are: increased salivary flow, drooling or dribbling and increased swallowing.

- **Halitosis**

is the offensive breath resulting from poor oral hygiene, dental or oral infections, ingestion of certain foods, use of tobacco, and some systemic diseases. Halitosis, or bad breath, with an abnormal taste in the mouth.

- **Bleeding**

#### **Drug-dependent effects in oral cavity – causes**

- Direct drug-dependent toxic effect
- Indirect drug-dependent effect
- Allergic reactions

#### **Oral complication of cancer chemotherapy:**

##### **Direct toxicities**

- oral mucosistis
- salivary gland dysfunction
- neurotoxicity (trigeminal nerve, taste dysfunction, dental hypersensitivity)
- temporomandibular joint dysfunction
- dental growth and development (abnormalities in dentition)

##### **Indirect toxicities**

- infection of mucosa (HSV, VZV, CMV, EBV, Candida, Aspergillus)
- dental caries
- pulpal infections
- periodontal infections
- vomiting (acidic damage to oral tissues)
- oral haemorrhage (trombocytopenia)

##### **Drug-related mucositis (oral ulcerations)**

- Cellular turnover rates in oral mucosa vary from 4-5 day for buccal and labial mucosa to as many as 14 days for hard palate
- The more rapid the cell division rate of the progenitor cells ⇒ the higher the susceptability to damage from chemotherapy
- The initial changes of oral mucositis become evident 3-6 days after the start of chemotherapy, damage peaks -7-11 days after the last dose, mucosal healing proceeds over the next 7-28 days.
- Bland rinses (normal saline, sodium bicarbonate solutions)
- Mucosal coating agents (antacid solution, kaolin solution)
- Water-soluble lubricating agents – artificial saliva
- Topical anaesthetics (lidocaine, benzocaine)
- Film-forming agents (hydroxypropyll cellulose)

## Dysbacteriosis

- Dry, red mucosa
- Tongue – smooth and red in the early phase of dysbacteriosis
- Tongue – with brown fur (advanced dysbacteriosis) - microorganisms accumulate on the tiny projections of the tongue — called papillae — and cause discoloration. Certain types of bacteria and yeast make red blood cell pigments (porphyrins), which can give the tongue a black appearance.

Antibiotics (especially wide-spectrum) – aminopenicillins, cephalosporins 3rd generation, tetracyclines

## Gingival hyperplasia

- Ca-channel antagonists, especially: nifedipine, nitrendipine, felodipine, amlodipine
- Hydantoin derivatives: phenytoin
- Calcineurin inhibitors: cyclosporin, tacrolimus – the severity of hyperplasia is correlated with drug concentration in blood; there is relation between gingival hyperplasia and parodontium status before therapy

Gingival hyperplasia is more frequently observed in young persons - ↑ sensitivity of younger cells to proliferative factors.

## Enamel discoloration

- Tetracyclines in children during tooth-bud formation (milk and permanent teeth) – from 4 mo of fetal life till 8-12 y
- Yellow or grey discoloration of enamel and dentine
- Hypoplasia of enamel
- ↑ susceptibility to caries in further life

## Taste dysfunction

- penicillamine
- griseofulvine
- metronidazole
- lithium
- Mostly persistent dysfunction

## Xerostomia

Antidepressants - tricyclic antidepressants

Antihistamines – cetirizine

Antipsychotics - phenothiazine derivatives - chlorpromazine

Muscarinic receptor antagonists used to treat overactive bladder - oxybutinine

Alpha receptor antagonists – alfuzosin

Antihypertensives – clonidine, methyl dopa, moxonidine

Opioids – codein

Benzodiazepines – diazepam

Antiparkinsonian cholinolytic agents - biperiden

Anti-HIV drugs – didanosine

Cytokines – interferon alpha

Xerostomia – mechanism not related to the ↓ saliva production

diuretics - ↓ body water volume

inhaled antiasthmatic agents – ipratropium

## Salivary glands enlargement – xerostomia

Painless, usually bilateral, salivary gland enlargement

- clonidine
- chlorhexidine
- clozapine
- naproxen
- nicardipine

Drug-related salivary gland pain

- Antihypertensives
- Anti-thyroid agents
- Chlorhexidine
- Cytotoxics
- Phenothiazines
- Sulfonamides

## Discoloration of saliva- red or orange saliva

- rifampicin, rifabutin
- clofazimine
- levodopa

### **Erythrema multiforme – affects skin and mucosa**

- Recurrences; round or oval lesions, well outlined
- Blisters in oral cavity – crack leaving scraps of epithelium
- TEN; Lyell syndrome - toxic epidermal necrolysis - extensive mucocutaneous epidermolysis.
- sulfonamides
- quinine, quinidine
- phenylbutazone
- salicylates
- fluconazole
- penicillins
- tetracyclines
- allopurinol

### **Quincke's edema – angioedema**

It is form of the urticaria (hives) with deeper localization.

Vasoactive mediators released from the cells act on postcapillaries and venules – induce cells shrinking and enlargement of the extracellular spaces, increase vascular permeability and edema development.

In the next step mediators penetrate to the skin and subcutaneous tissue.

- salicylates
- NSAIDs
- ACE inhibitors