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Evaluation of Antihypertensive Drugs in relation to oral ulceration (Literature Review)

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Abstract

Ulcers are normal oral cavity symptoms, and some ulcerations are caused by drug interactions. When ulcers present with traditional clinical results, differential diagnosis is always simple, but assessing the precise diagnosis is more difficult. We looked at the various types of oral ulcerative diseases, the clinical characteristics of drug-induced oral ulcers, and the medications that cause oral ulcers. a ton of different kinds. Non-steroidal anti-inflammatory drugs (NSAIDs) and especially anti-hypertensive drugs are among the most well-known. Several recent studies, however, have linked oral ulceration to relatively new drugs used to treat chronic conditions like diabetes, angina pectoris, rheumatoid arthritis, and osteoporosis. These new medications were discussed, as well as typical cases of drug-induced oral ulcers. The aim of this article to discuss the relation between the oral ulcer and multi-causes that induce this oral symptom that effect movingly on the patient comforts and This paper focuses on ulcers erosions in the oral cavity induced by pharmacotherapy, with an emphasis on new drugs and approaches for the treatment of this chronic symptom.

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Key words: - Oral ulceration, Non-steroidal anti-inflammatory drugs, Anti-hypertensive drugs, Differential diagnosis.

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1. Introduction:

Many kinds of adverse reactions induced by drug medications in the oral cavity are now well recognized [1, 2, 3]. Among these, the most frequent are dry mouth (hyposalivation), dysgeusia, and stomatitis. Stomatitis is a general term for disturbance of oral epithelial cells and covers several types of oral mucosal symptoms. Oral mucosal symptoms caused by drugs can be further divided as follows:

(1) lichenoid reaction/lichen planus
(2) ulcers
(3) erythema multiforme
(4) pigmentation
(5) autoimmune vesiculo-bullous disease
(6) infections
(7) tumors (fibrovascular hyperplasia)
(8) swellings (angioedema)
(9) keratosis [1].

1.1. Oral ulcers:

Oral ulcers are common symptoms observed in the oral cavity and include traumatic, infective, aphthous, ulceration related to dermatoses, drug-induced, ulceration as a manifestation of systemic disease, and ulceration due to malignancy (Table 1) [4, 5, 6]. When ulcers show typical clinical findings, differential diagnosis may be easy; however, the exact diagnosis is difficult in most cases, and histopathological diagnosis may be needed.

Table 1. Reported Chronic oral ulcers [5] :-

Diagnosis	Clinical features
Drug-induced ulcers	Single, isolated ulcers, located on the side of the tongue, surrounded by an erythematous halo and resistant to usual treatments
Erosive lichen planus	Areas of atrophy, erosions or painful ulcers, generally resistant to conventional treatments
Pemphigus vulgaris	Bullae appear in oral cavity (posterior region), foming painful ulcers with necrotic fundus and erythematous halo
Mucous membrane pemphigoid	Spontaneous onset of bulla e that readily rupture, giving rise to a highly painful ulcerated area (most common areas are palate and gingiva)
Lupus erythematosus	Erythema and oral ulcers, without induration andaccompanied by whitish strias and a tendency to bleeding
Reiter's syndrome	Arthritis, urethritis, conjunctivitis and oral ulcers similar to those of recurrent aphtous stomatitis
Tuberculosis	Primary tuberculosis: deep, irregular, persistent and painful ulcer on the tongue, with rolled border and granulation tissue in the fundus Secondary tuberculosis: chronic ulcer, painful and indurated
Mycosis	Mycoses give rise to chronic ulcers on the oral mucosa, most commonly in immunocompromised patients
Other bacterial and parasitic diseases	Klebsiella and Leishmania spp.can produce chronic oral ulcers in HIV-infected patients
Eosinophilic ulcer	Large ulcer, generally in the tongue, with raised, indurated borders and white-yellowish fundus that may resemble a malignant lesion. Persists for weeks or months
Oral squamous cell carcinoma	Can produce ulcers (exophytic endophytic or mixed). Metastatic lesion can appear as ulcers in the oral cavity

1.1.1 Differential diagnosis:

The most significant factor in determining a provisional diagnosis is a thorough review of the oral mucosa. The word stomatitis is often misunderstood by patients, and the exact nature of the complaint should be verified. The patient's

age, sex, dental and medical history can be useful, as well as the number, shape, scale, and position of lesions, which must be carefully examined [7, 8.].

Mechanical, thermal, or chemical irritants cause traumatic ulceration [Figure 1]. Ill-fitting dentures, sharp-edged crowns or bridges, and tooth decay are the most common causes. The ulcer floor is normally clear, and the ulcer margins do not usually display induration when palpated, but bleeding, granulation, or induration that resembles a malignant tumor may occur. Multiple small aphthous ulcerations are often associated with viral infection. Fluid-filled vesicles appear first, but they quickly degrade into thin, round, painful ulcers with ragged margins, which often merge to form large, irregular ulcers. Herpes simplex virus (HSV)-1, varicella-zoster virus (VZV), and coxsackie virus (CVV) are the most common viral infections in the oral cavity [7].

Figure 1: Traumatic Ulceration

The most common form of oral ulcer is aphthous ulceration [Figure 2], which heals in 10–14 days [8]. The lesions typically appear as thin, circular or oval ulcers covered in pseudomembrane and surrounded by an erythematous halo in non-keratinizing epithelium. Related lesions have been identified in patients with Behçet's disease, Crohn's disease, celiac disease, and ulcerative colitis [9,10].

Figure 2: aphthous ulceration

The clinical presence of lichen planus varies [Figure 3]. Oral lichen planus (OLP) is characterized by bilateral and symmetrical white lace-like patterns [11] of buccal mucosa, but ulceration is common in the condition [12, 13]. Fine reticular white lines radiating from the ulceration's boundary are normally present. Another type of ulceration is when atypia coexists with focal red granular areas [13].

Figure 3: Lichen Planus

Autoantibodies against desmosome-related proteins desmoglein 1 and/or 3 [14, 15] cause pemphigus vulgaris [Figure 4], an autoimmune bullous disease. Oral lesions appear in around 70% of cases, with oral lesions being the first symptom in more than half of those. A common symptom is painful, shallow, irregular ulcers with friable adjacent mucosa, which can be caused by lateral

shearing force on the mucosa[16]. Intraepithelial acantholysis is characteristic histologically. Autoantibodies against desmoglein 1 and 3 can be identified in the blood using an enzyme-linked immunosorbent assay and immunofluorescence [15].

Figure 4: Pemphigus Vulgaris

Bullous pemphigoid [Figure 5] is also an autoimmune disease caused by autoantibodies to BP180NC16a, a hemidesmosome portion The key cutaneous symptom is the development of firm blisters against an erythematous backdrop. Multiple well-defined or diffuse ulcers can be found in the oral cavity. Subepithelial blistering with multiple eosinophils is seen histopathologically. The presence of BP180 antibodies correlates with the presence of BP180 antibodies [17].

Figure 5: Bullous Pemphigoid

On the oral mucosa, mucous membrane pemphigoid induces redness with erosions, gray-white vesicles, or blisters. Gingival desquamation is a common symptom of this disease. Immunofluorescence microscopy shows a linear arrangement of immunoglobulin (Ig)G, C3, and sometimes IgA along the basement membrane region [18, 19].

Oral mucosal lesions, also known as erythema exudative multiforme [firuge 6], occur a few days after symmetrical target skin lesions [20]. There are serious, widespread painful erosions with a gray-white pseudomembrane, as well as ocular and genital lesions. A characteristic symptom of pharmacotherapy or viral infection is erosive and hemorrhagic cheilitis with bleeding crusts [21].

Figure 6: Erythema Exudative Multiforme

Radiation causes widespread mucosal erythema, atrophy, ulceration, and pseudomembrane formation in the oral cavity. The degradation of the germinative layers of the oral mucosal epithelium causes these pathologies, which are exacerbated by intraoral bacterial infection. The most common malignancy of the oral mucosa is squamous cell carcinoma. White or red-white focal surface lesions are seen in the early stages, while ulceration with induration and elevated margins is seen in the later stages. The surface appears granular and/or necrotic, and bleeding is quick

1.1.2 Clinical features of drug-induced oral ulceration:

Typical oral ulcers due to drugs are clinically classified into two types; -

1- The first is widespread mucositis and ulceration, which is caused predominantly by cytotoxic anti-tumor chemotherapy drugs. Sloughing and ulceration appear within days of starting treatment, and the discomfort frequently necessitates the use of opioids and the modification or termination of chemotherapy. 5-fluorouracil, methotrexate, bleomycin, and cisplatin are examples of cytotoxic drugs. Immunosuppressive drugs can also lead to oral ulcers by causing opportunistic secondary infections with Gram-negative bacteria and fungi.
2- The second form is known as a fixed drug eruption, which is characterized by the development of treatment-resistant ulcers on a regular basis. On any site of the oral mucosa, single or multiple large ulcerations can be seen [22].

The ulceration is typically greater than aphthous ulceration, with a smooth surface that appears slightly white. The ulcer margin is transparent and sometimes slightly raised; however, there is no induration associated with the ulcers. They mimic traumatic and decubital ulcers, but there are no irritant factors in the region. A form of aphthous ulceration known as multiple aphthous ulceration has also been identified [8].

1.2 Antihypertensive drugs:

Antihypertensive drugs are a category of compounds that have the therapeutic goal of preventing, controlling, or treating high blood pressure. Antihypertensive drug groups vary structurally and functionally [Table 2]. They are important in anesthetic practice because they are widely administered to the

general public, with hypertension accounting for 31% of anaesthesia patients in the United Kingdom.

[a measurement of 140/90 mm Hg or higher in clinic, followed by ambulatory or home measurements of 135/85 mm Hg or higher, as specified by the National Institute for Health and Care Excellence (NICE)] -blockers in thyrotoxicosis and anxiety, or angiotensin-converting enzyme inhibitors (ACEIs) in heart failure, are examples of antihypertensive medications that are commonly used in unrelated conditions [23].

Table 2: Classes and subclasses of antihypertensive medications with common examples:

Antihypertensive Agents

1	ACE inhibitors (*Angiotensin converting enzyme inhibitors*)	Enalapril, Lisinopril, Ramipril, Captopril
2	ARBs (*Angiotensin receptor blockers*)	Telmisartan, Olmesartan, Losartan, Candesartan, Valsartan
3	Calcium channel blockers	Amlodipine, Felodipine, Nimodipine, Nifedipine, Isradipine, Verapamil, Diltiazem
4	Beta blockers	Atenolol, Metoprolol, Bisoprolol, Labetolol, Propranolol,
5	Diuretics	Hydrochlorthiazide, Chlorthiazide, Chlorthalidone, Spironolactone, Furosemide
6	Direct Vasodilators	Hydralazine, Minoxidil, Sodium Nitropruside, Diazoxide
7	Alpha blockers	Terazosin, Doxazosin, Prazosin
8	Central Alpha 2 Agonists	Clonidine, Methyldopa

1.3 Pathogenesis:

Hypertensive Drug-induced oral ulcerations, erosions, or necrosis of oral mucous membrane tissue can be triggered by systemic or locally delivered

medications. Pathogenic mechanisms include focal irritation due to low pH, allergic hypersensitivity, and cytotoxicity.

Hypertensive medications with strong evidence for injury of oral mucosal epithelium include chemotherapeutic agents. Hypertensive medication mediated the oral ulceration resulting in an ulcerative lichenoid reaction in the buccal or lingual mucosa.

Ulceration reaction is a delayed hypersensitivity reaction to a drug. Clinically, this condition is often confused with lichen planus, an autoimmune disease. Patients may or may not be symptomatic. Clinicians should assess a "new" presentation of ulceration and correlate onset with the timing of the introduction of a antihypertensive medication since the last dental visit. Although many other drugs have also been implicated, common medications associated with lichenoid drug reaction include nonsteroidal anti-inflammatory drugs [24,25].

2. Treatment:

- Saline mouthwash

Salt water mouthwash, prepared by dissolving half a teaspoon of salt in glass of warm water, should be used as a rinse at frequent intervals until the discomfort and swelling subsides.

-Antiseptic mouthwash or spray

Chlorhexidine gluconate 2mg/mL (0.2%) mouthwash or spray (sugar-free) used twice daily as instructed (10mL for one minute). It should not be used within 30 minutes of using toothpaste, owing to possible interaction (and it can cause an unpleasant taste in the mouth).

-Non-steroidal anti-inflammatory mouthwash or spray

Benzydamine hydrochloride 1.5mg/mL (0.15%) as mouthwash or spray (sugar-free) used four times daily as instructed (15mL as rinse or four sprays every 1.5 hours as required).

-Steroid aerosol inhalation or tablet

Beclometasone diproprionate aerosol inhalation, 50 micrograms/metered inhalation. Used as instructed (1–2 puffs directed on to ulcers twice daily). The use of this is unlicensed in oral ulceration [26,27].

Referral to a dental practitioner is required when an ulcer is thought to be traumatic owing to contact with teeth or other structures in the mouth. If there is a suspicion of mouth cancer or atypical oral ulceration, patients should visit their dental practitioner or GP. Patients with RAS who also report abdominal symptoms or possible blood loss should be referred to their GP, as should patients with severe HSV-1 infection. Any cases where the onset of ulceration coincides with the initiation of a new systemic medicine should be reported as suspected adverse drug event and referral to a GP.

3. Results:

Oral ulceration was the most common oral painful oral symptom, and the most reported culprit drugs were antihypertensive medications followed by cardiovascular drugs as the second culprit agents for ulceration. NSAIDs and β-blockers were the most common drugs responsible for oral ulceration. Antihypertensive drug were the most reported culprit agents for induction of oral ulcerative and vesiculo-bullous lesions followed by methotrexate. One not widely known detrimental effect of bisphosphonates is mucosal ulcerations, which can lead to intense pain causing severe morbidity.

4. Conclusion:

Oral ulcers are a common symptom of the oral cavity, and several different medications have been reported to cause them. Once drug-induced oral ulcers are antihypertensive medication after thorough clinical evaluation and prescription tests, the prescribing medical doctor should be consulted to discuss the possibility of substitute medications or dose reduction. Diagnosis of oral ulceration can be challenging and requires careful clinical examination and history taking. It is important to understand that oral manifestations may represent part of a larger problem. Biopsy may be indicated to ascertain a true diagnosis. Any unexplained ulcer found in the oral cavity that does not resolve in 2 weeks should be evaluated microscopically.

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