Review

Side effects of drugs on the oral cavity

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A R T I C L E  I N F O

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A B S T R A C T

Although drugs are the most powerful therapeutic tools we have for improving the quality of life of the population, their use is not free of adverse effects. Today there are many polymedicated patients, and it is difficult to find the cause of their adverse effects that increase exponentially when more than 4 drugs are combined.

There are a large number of drugs that can result in numerous adverse effects in the oral cavity. The most common are xerostomia, altered taste, gingival enlargement and mucositis caused by cancer treatment. We also review other disorders of the salivary glands, oral mucosal changes, pigmentation, halitosis, osteonecrosis, opportunistic infections and bleeding diathesis.

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Reacciones adversas a medicamentos en la cavidad oral

R E S U M E N

A pesar de que los fármacos son la herramienta terapéutica más potente de la que disponemos para mejorar la calidad de vida de la población, su uso no está exento de efectos adversos. Hoy en día son muchos los pacientes polimedicatedados, siendo complicado encontrar la causa de los efectos adversos generados por la medicación y aumentando estos de manera exponencial cuando se combinan más de 4 fármacos.

Existe un amplio número de fármacos que pueden dar lugar a numerosos efectos adversos en la cavidad bucal. Los más frecuentes son la xerostomía, las alteraciones del gusto, el agrandamiento gingival y las mucositis producidas por el tratamiento oncológico. También se revisan otras alteraciones de las glándulas salivales, las alteraciones de la mucosa oral, las pigmentaciones, la halitosis, la osteonecrosis, las infecciones oportunistas y las diáfisis hemorrágicas.

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Introduction

When we talk about medications, “adverse reaction” or “adverse or undesirable event” is defined, according to the WHO, as an unexpected detrimental response that appears after the administration of a medication at the dosage normally used for the prophylaxis, diagnosis, and treatment of a disease or for the modification of a physiological function¹.

These adverse reactions can occur in many organs or systems and the oral cavity and its associated structures is just one example. The adverse events that appear in this area are heterogeneous because of the tissue where they appear and the clinical consequences they have for the patient⁵.

The most frequent adverse events that occur in the oral cavity can be classified as follows¹⁴:

2. Taste alterations.
3. Mucosal alterations: oral ulcerations or chemical burns, chemotherapy-induced mucositis, lichenoid reactions, erythema multiforme, pemphigus.
5. Gingival enlargements.
6. Halitosis.

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7. Osteonecrosis.
8. Necrotising sialometaplasia.

Salivary gland alterations

Xerostomia is defined as the subjective sensation of dry mouth. Hyposalivation is defined as the decrease in salivary flow under conditions of rest. In order to be considered salivary hypossecretion, figures below 0.1-0.2 ml/min at rest or below 0.5-0.7 ml/min under stimulation must be found. This condition is one of the most frequent adverse drug events that occur in the oral cavity, with medications being the main cause of dry mouth\(^7\) (table 1).

Medications cause xerostomia through a range of mechanisms. One of the most important of these is sympathomimetic or anticholinergic action; the M\(_3\) muscarinic receptor mediates cholinergic-parasympathomimetic neurotransmission to the salivary glands, although this would not be the only receptor involved\(^8\).

The groups of medications most commonly associated with xerostomia are antidepressants, antipsychotics, antihypertensives, antihistamines, antiarrhythmics and anticholinergics\(^4,5\).

Drug-induced polyxilia or ptysialis is an increase in the salivary secretion rate. It is infrequent but clinical cases have been reported in relation to certain drugs. Parasympathomimetic medications are those most frequently involved. They cause salivary hypersecretion, either by direct action on acetylcholine receptors or through the inhibition of acetylcholinesterase\(^6\). Catecholamines and other sympathomimetic drugs may cause ptysialis through the stimulation of \(\alpha\) and \(\beta\) receptors\(^9\).

Other drugs that may cause polyxilia by direct action on the central nervous system are cocaine, reserpine, clonazepam or ketamine and, indirectly, morphine and digitalis drugs. Mercury, bromide and iodised compounds may have an effect on the salivary gland that increases the production of saliva\(^3\).

Other drugs can cause inflammation and pain in the salivary gland. In some cases, they are associated with hypersensitivities, but in others, the pathogenesis is unclear, as it is related to the compound’s pharmacokinetics and pharmacodynamics. The drugs associated with this effect are those derived from pyrazolone, antihypertensives, anti-ulcer drugs, antibiotics, iodosides and antipsychotics\(^7\).

Taste alterations

Drugs can cause loss of taste acuity (gustatory hyposthesia), distortion in the perception of the correct taste of a substance (dysgeusia) or loss of taste (ageusia). These disorders can occur in 3 ways: 1) the excretion of the drug or its metabolites in saliva, which interferes with the chemical composition of the saliva; 2) by affecting the transduction signal, and 3) by directly damaging the taste ridges or taste receptors\(^8\).

The drugs most commonly associated with this problem include: angiotensin-converting enzyme (ACE) inhibitors, \(\beta\)-lactam antibiotics, biguanides, chlorhexidine, antithyroid drugs and opiates. Typically, captopril causes a salty taste and for enalapril, a sweet metallic taste\(^8\).

These effects are reversible, although recovery takes several months after withdrawal of the drug\(^6\).

Oral mucosal alterations

Oral mucosal ulcers and burns occur when the patient uses a drug topically when its use is not topical or when the patient takes it in the wrong way. One of the most frequent cases is the “acetylsalicylic acid burn.” The acid may soothe the dental pain when applied topically but it produces a superficial necrosis of the oral epithelium. Other medications that can cause ulcers are phenylbutazone, indomethacin, silver nitrate, hydrogen peroxide, isoprotrenol and potassium chloride, as well as some antineoplastics (metothrexate, 5-fluorouracil or doxorubicin)\(^10,11\) (fig. 1).

Chemotherapy-induced mucositis appears as an inflammation and ulceration of the oral mucosa with formation of pseudomembranes and is associated with chemotherapy treatment. It can present different levels of severity and this, and its frequency depend on the type and dose of chemotherapy medication used, the age of the patient, the patient’s haematological and nutritional status, and oral hygiene. It usually appears between the fourth and tenth day after initiating oncological treatment. On days 4-5, an erythema is observed and the patient does not tolerate spicy foods. On days 7-10, ulcerations appear that affect the patient’s intake pattern\(^12,13\).

Lichenoid reactions refer to the appearance of lesions in the oral mucosa, clinically and histologically similar to those of a lichen planus, but associated with the intake of a medication\(^14\). Cur-
Currently, the drugs most often involved in this type of reactions are the non-steroidal anti-inflammatory drugs and ACE inhibitors. Lichenoid reactions can also appear with the intake of anti-hypertensives, psychiatric drugs or oral hypoglycaemic drugs\(^5\) (fig. 2).

_Erythema multiforme_ is a self-limiting, polymorphic, acute, mucocutaneous inflammatory disease that can affect the skin, oral mucosa, several mucous membranes or skin and mucosa. Its aetiology is unclear and there are several possible causes, including drugs. When the oral mucosa is affected, it typically affects the lips with serohaematic crust formation. Diagnosis is based on its sudden appearance, its relation with the previous intake of a drug and the appearance of the crusts on the lips\(^6\) (fig. 3).

_Pemphigus_ is an autoimmune disorder that occurs with the formation of intraepithelial blisters on the skin and mucosa, caused by the production of antibodies against specific epithelial cell junction proteins. Some drugs induce antibody formation that results in acantholysis through a mechanism identical to that found in pemphigus vulgaris. The clinical characteristics of this drug-induced pemphigus are similar to those of pemphigus vulgaris.

Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine</td>
<td>Yellowish-greyish-brown</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>Grey-brown</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Green</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>Yellow or greyish-brown</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Yellow</td>
</tr>
<tr>
<td>Iron salts</td>
<td>Black</td>
</tr>
<tr>
<td>Fluoride</td>
<td>White-brown</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Chalk white</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Grey-black</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Yellowish-greyish-brown</td>
</tr>
<tr>
<td>Potassium permanganate</td>
<td>Purple-black</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>Grey</td>
</tr>
</tbody>
</table>

Depending on their chemical structure, these drugs can be divided into 2 groups:\(^7\):

- Medications that contain the sulfhydryl radical or thiol drugs. For example, penicillamine or ACE inhibitors (captopril or enalapril). The sulfhydryl groups are similar in structure to desmoglein-3, one of the antigens involved in pemphigus, and they trigger a cross immune response.
- Non-thiol drugs. These contain an active amino group in their molecules. They produce acantholysis via an autoimmune mechanism coinciding with that of pemphigus.

**Pigmentations**

Many drugs can cause _dental staining_ (table 2), both intrinsic and extrinsic. Extrinsic stains are located on the tooth surface and can be removed in different ways. One drug that can cause these stains is chlorhexidine, when used continuously\(^8\).

Intrinsic stains are located inside the dental structure. Some, but not all, intrinsic stains can only be treated by whitening. These stains are caused by the administration of drugs during the tooth calcification period. Some of the drugs involved are tetracyclines and fluourine. Tetracyclines have an affinity for calcium and behave as chelating agents, forming a calcium tetracycline-orthophosphate complex in the hydroxyapatite crystals that is incorporated into the tooth structure during the mineralisation periods in tooth development. The teeth affected present yellowish or greyish-brown bands. Fluorine interferes in the ameloblastic function, affecting the formation of the adamantine substance matrix and their calcification. Above all, it affects permanent dentition. Lesions are usually bilateral and symmetric, in the form of horizontal stripes\(^9,10\).

Drug-related _oral mucosal pigmentations_ are superficial and the mechanism that causes them is unknown. They normally disappear when the drug is withdrawn. Some of the medications that can cause them are antimalarial drugs, chlorpromazine, minocycline or cisplatin\(^11,12\).

_Hairy tongue_ is a benign disorder of the tongue that is characterised by the hypertrophy of the filiform ridges, resembling short hairs, and a colouring that goes from yellowish-white to black, depending on diet, oral hygiene, tobacco consumption and the presence of colonies of chromogenic bacteria. It is usually associated with the intake of antibiotics over long periods of time, is located at the back of the tongue, and may cause a burning sensation and halitosis\(^13\).

**Gingival enlargement**

This refers to an increase in the size of gingival tissues caused by an increase in extracellular matrix production, mainly collagen,
Halitosis

Halitosis is bad breath. It can be caused by different factors such as bad oral hygiene, oral and dental infections, the intake of certain foods, some systemic diseases, or as an adverse event after the intake of certain medications. Isosorbide dinitrate, dimethyl sulfide or disulfiram can cause halitosis directly or indirectly as they can cause xerostomia.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Table 3</th>
<th>Drugs</th>
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<tr>
<td>Amlodipine</td>
<td>Nifedipine</td>
<td>Cotrimazole</td>
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<td>Norvisterone</td>
<td>Erythromycin</td>
<td>Cyclosporine</td>
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<td>Diclofenac</td>
<td>Mestranol</td>
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<td>Etoposide</td>
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<td>Ketocanazole</td>
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<td>Lamotrigine</td>
<td>Topiramate</td>
<td>Contraceptives</td>
</tr>
<tr>
<td>Valproate</td>
<td>Phenytoin</td>
<td>Lithium</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Mephenytoin</td>
<td>Vigabatrin</td>
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</tbody>
</table>

Osteonecrosis

This is a rare clinical entity described as an adverse event of treatment with certain drugs, especially bisphosphonates and, particularly, following their intravenous administration. It is associated with a blood supply alteration or an inhibition of osteogenesis and an increase in the apoptosis of osteocytes. It can be defined as an “area of exposed bone that persists for more than 8 weeks in the absence of prior radiation and/or metastasis in the mandible.” In order to diagnose bisphosphonate-induced osteonecrosis, the clinical features should meet 3 requirements:

- Current or prior use of bisphosphonate.
- Presence of exposed or necrotic bone in the maxillofacial region that persists and does not heal in 8 weeks.
- Absence of radiotherapy in the maxillary bones.

The aetiopathogenesis is unknown, but some related factors have been described, such as alteration of immunity and repair mechanisms due to neoplasia, vascular compromise, low bone turnover rate, bisphosphonate bone toxicity and biophosphate toxicity of soft tissues.

There are 3 clinical stages of bisphosphonate-induced osteonecrosis:

- Stage I: presence of exposed or necrotic bone in asymptomatic patients without evidence of infection.
- Stage II: presence of exposed or necrotic bone in patients with pain and evident signs of infection.
- Stage III: presence of exposed or necrotic bone in patients with pain, infection and one or more of the following signs: pathological fracture, extraoral fistula or osteolysis extending to the lower edge.

Bisphosphonates reduce the bone turnover rate by inhibiting osteoclastic activity. Once deposited on the bone surface, bisphosphonates are internalised by osteoclasts, causing interruption of bone resorption. Moreover, they have antitumour and antiangiogenic effects. These drugs are used in the treatment of osteoporosis and other metabolic bone diseases. However, the greatest risk of osteonecrosis seems to appear in cancer patients. Tumours like multiple myeloma or breast carcinoma tend to involve the skeleton. Treatment with bisphosphonates significantly reduces the metastatic and local dissemination of these skeletal lesions, as well as the associated morbidity and mortality. More than 90% of the published cases of bisphosphonate-induced osteonecrosis occurred in the context of cancer treatment.

Necrotising sialometaplasia

Necrotising sialometaplasia is another drug-related adverse oral reaction that is caused by the injection of a vasoconstrictor (associated with local anaesthetics) in the palate (fig. 5). It is defined as a necrotising inflammatory reaction that affects minor salivary glands in the hard palate. It is a rare benign process that resolves spontaneously within 4-10 weeks after onset, without leaving functional or anatomic sequelae. It appears as a crater-shaped ulcer, with indurated and well-defined edges, generally unilateral, and it can be asymptomatic or painful. The subjacent bone is not usually affected. Its importance resides in its similarity.
to a malignant ulcer, so a biopsy needs to be performed to confirm diagnosis\(^{24}\).}

**Opportunistic infections**

Treatment with systemic drugs, such as glucocorticosteroids, broad-spectrum antibiotics, immunosuppressants and antineoplastics, may alter the oral flora, giving rise to a predisposition to the appearance of oral fungal or bacterial infections. One of the most frequent opportunistic infections is that caused by *Candida albicans*. It can appear in different forms: acute atrophic, chronic atrophic or acute pseudomembranous (muguet). The latter is characterised by the presence of whitish plaques that can be detached by scraping, leaving a painful, red, ulcerated, surface\(^{13}\).

The drugs that produce xerostomia favour the appearance of oral infections, such as candidiasis or suppurative parotitis. Furthermore, the prolonged use of broad-spectrum antibiotics may cause the appearance of candidiasis. Another favourable mechanism for the appearance of opportunistic infections is the modification of the host defensive response. A clear example is neutropenia, caused by the depression of spinal function induced by the cytotoxic drugs used in cancer treatment. Another mechanism is the immune suppression that takes place in patients infected with human immunodeficiency virus or under chronic treatment with corticosteroids\(^{1,4}\)\(^{1,4}\).

**Haemorrhagic diathesis**

Possible intraoral haemorrhages constitute another disorder that can be induced by the intake of certain drugs (table 4). These haemorrhages are be associated with several factors, such as thrombocytopenia, defective vascular integrity or coagulation alterations\(^{1,5}\).8.

Drugs can cause thrombocytopenia, either by spinal toxicity (cytotoxic drugs or thiazide diuretics) or by peripheral platelet destruction via the immune mechanism (quinine, quindine or methylodopa). Clinically, this appears in the form of petechiae that appear following minimal trauma to the lateral edge of the tongue, lips, buccal mucosa and the junction of the hard palate and soft palate\(^{1}\).

Certain drugs can cause gingival haemorrhage directly or indirectly. The gum may bleed spontaneously after brushing or other activities such as mastication. This can occur in patients under treatment with anticoagulants like heparin, acenocoumarol or warfarin. Anticoagulant drugs that are Vitamin K antagonists interfere with the production of vitamin K-dependent coagulation factors (II, VII, IX and X)\(^{1}\).

**Conclusion**

As we have said, a wide number of drugs can cause several adverse events in the buccal cavity. The most frequent events are xerostomia, taste alterations, gingival enlargement and mucositis caused by oncological treatment.

It is important for the clinician to obtain a complete medical record of the medications the patient takes, including prescription drugs, over-the-counter drugs and dietary supplements. Thus, the clinician will be able to individually prevent, diagnose and treat adverse effects occurring in the oral cavity.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

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