



Review

Side effects of drugs on the oral cavity[☆]

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ABSTRACT

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, pigmentations, halitosis, osteonecrosis, opportunistic infections and bleeding diathesis.

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Reacciones adversas a medicamentos en la cavidad oral

RESUMEN

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 polimedificados, 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 diátesis hemorrágicas.

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Palabras clave:

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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 patient².

The most frequent adverse events that occur in the oral cavity can be classified as follows^{3,4}:

1. Salivary gland alterations: xerostomia, ptyalism, swelling and pain.
2. Taste alterations.
3. Mucosal alterations: oral ulcerations or chemical burns, chemotherapy-induced mucositis, lichenoid reactions, erythema multiforme, pemphigus.
4. Pigmentations: dental staining, oral mucosal pigmentations, hairy tongue.
5. Gingival enlargements.
6. Halitosis.

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7. Osteonecrosis.
8. Necrotising sialometaplasia.
9. Opportunistic infections.
10. Haemorrhagic diathesis.

Salivary gland alterations

Xerostomia is defined as the subjective sensation of dry mouth. *Hyposialia* is defined as the decrease in salivary flow under conditions of rest. In order to be considered salivary hyposalivation, 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 mouth³ (table 1).

Medications cause xerostomia through a range of mechanisms. One of the most important of these is sympathomimetic or anticholinergic action; the M3 muscarinic receptor mediates cholinergic-parasympathomimetic neurotransmission to the salivary glands, although this would not be the only receptor involved⁵.

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

Drug-induced *polysialia* or *ptyalism* 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 acetylcholinesterase⁶. Catecholamines and other sympathomimetic drugs may cause ptyalism through the stimulation of α and β receptors⁴.

Other drugs that may cause polysialia 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 saliva³.

Other drugs can cause *inflammation* and *pain* in the salivary gland. In some cases, they are associated with hypersensitivity, 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, iodides and antipsychotics⁷.

Taste alterations

Drugs can cause loss of taste acuity (gustatory hypesthesia), 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 receptors⁸.

The drugs most commonly associated with this problem include: angiotensin-converting enzyme (ACE) inhibitors, β -

Table 1

Groups of medications that can cause xerostomia.

Antidepressants	Amphetamines	Anticholinergics
Antihistamines	Antihypertensives	Anti-migraine agents
Antipsychotics	Appetite suppressants	Anxiolytics
Drugs of abuse	Hypnotics	Diuretics
Muscle relaxants	Anti-HIV medications	Opiates

HIV: Human immunodeficiency virus.

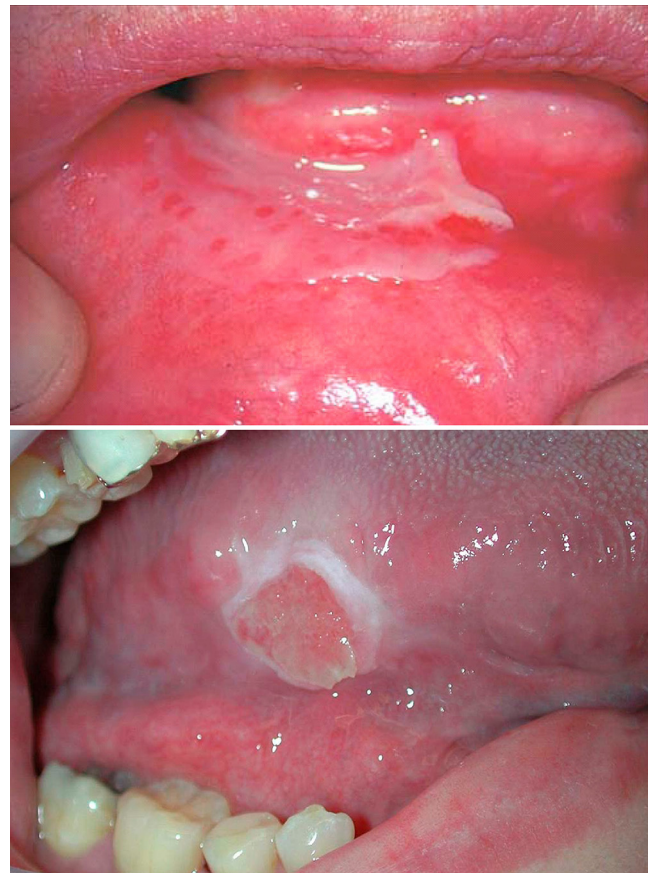


Figure 1. Ulcers induced by the local application of drugs.

lactam antibiotics, biguanides, chlorhexidine, antithyroid drugs and opiates. Typically, captopril causes a salty taste and for enalapril, a sweet metallic taste⁹.

These effects are reversible, although recovery takes several months after withdrawal of the drug⁴.

Oral mucosal alterations

Oral mucosal *ulcerations* 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 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, isoproterenol and potassium chloride, as well as some antineoplastics (methotrexate, 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 medication¹⁴. Cur-

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