

## ADVERSE DRUG REACTIONS IN THE ORAL CAVITY

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**SUMMARY** – Every medication may lead to adverse effects, even when used in standard doses and mode of application. In the oral cavity, adverse effects may affect every part of oral mucosa and are the result of medications taken either locally or systemically. Oral adverse reactions to drugs are not typical and therefore sometimes not easy to recognize. On diagnosing adverse side effects in the oral cavity, experienced clinician will usually diagnose the condition on the basis of detailed medical history and clinical finding. However, the only objective evidence for the offending drug is ‘re-challenge’, i.e. exposure to the drug after its discontinuation. It carries a huge risk of anaphylactic reaction; therefore it has to be performed in a controlled hospital setting. Therapy is based on immediate exclusion of the offending drug and, if lesions are present in the oral cavity, topical or systemic corticosteroid therapy is prescribed. This article gives a review of patients with oral adverse drug reactions referred to the Department of Oral Medicine in Zagreb.

**Key words:** *Pharmaceutical preparations – adverse effects; Oral manifestations – diagnosis; Oral manifestations – therapy*

### Introduction

Every medication may lead to adverse effects, even when used in standard doses and mode of application. Adverse effects may develop on every organ. In the oral cavity, adverse effects may affect every part of the oral mucosa and are the result of medications taken either locally or systemically. Adverse drug reaction may develop after the medication has been used once or after few years of continuous medication use. Oral adverse reactions to drugs are not typical and therefore sometimes not easy to recognize.

Adverse effects of systemic medications may be numerous, but some that are more frequent are hypos-

alivation, burning mouth symptoms, oral ulcerations, erythema multiforme, gingival hyperplasia, lichenoid reaction and angioedema<sup>1</sup>.

Fifteen years ago, we retrospectively retrieved oral adverse effects of the drugs that patients used and were referred to our Department. Most frequently, sulfonamides such as sulfamethoxazole and trimethoprim (Sinersul®), antibiotics, nonsteroidal anti-inflammatory analgesics (NSAID) and propolis were the medications that induced oral adverse effects<sup>2</sup>. At the time, the same findings (except for propolis) were reported elsewhere throughout the world.

However, it is interesting to note that this trend is ever changing as new drugs are marketed and others are withdrawn. On diagnosing adverse side effects in the oral cavity, experienced clinician will usually diagnose the condition on the basis of detailed medical history and clinical finding. However, the only objective evidence for the offending drug is ‘re-challenge’,

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i.e. exposure to the drug after its discontinuation. It carries a huge risk of anaphylactic reaction; therefore it has to be performed in a controlled hospital setting. And the last but not the least, it is also considered unethical if the offending drug can be replaced by some other<sup>3,4</sup>. In the past, radioallergosorbent test, basophil degranulation test, as well as blastic transformation tests were performed; however, due to the huge number of false-positive and false-negative results, they are not considered accurate<sup>3</sup>. In certain cases when patients are taking lots of medications, detection of the offending drug is not straightforward and it seems prudent that a drug being already known to cause adverse effects is more likely to be the offending one. Therapy is based on immediate exclusion of the offending drug and, if lesions are present in the oral cavity, topical or systemic corticosteroid therapy is prescribed<sup>3</sup>.

Generally, there are no clinical and histopathologic presentations alone to relate oral adverse reactions to any specific medication. Many oral adverse reactions mimic oral lesions that are also seen in the absence of medication use<sup>5</sup>.

It is noteworthy that certain herbal infusions (such as *Calendula officinalis*), herbal products (*Tinctura adstringens*), as well as some antiseptic solutions may lead to oral mucosal damage<sup>6</sup>. In Croatia, the use of propolis is quite popular. However, quite frequently the use of propolis leads to adverse effects in the oral cavity<sup>5,6</sup>. Another frequent 'home medicine' for oral

use in Croatia is schnapps. From time to time, we encounter chemical burn/sloughing of the oral mucosa due to this phenomenon. A patient was referred to our Department due to oral lesions that were provoked by use of *Calendula officinalis*, colloid silver and schnapps (Fig. 1).

### Hyposalivation

It is known that more than 500 drugs may lead to hyposalivation. The medications which most frequently cause hyposalivation are the ones most commonly used, such as antihypertensives and psychotropic drugs. It is known that these groups of drugs cause dry mouth: antihypertensives, anticholinergics, antihistamines, benzodiazepines, cytostatics, diuretics, proton pump inhibitors and H<sub>2</sub> antagonists, antipsychotics, antidepressants, hypnotics, opioids, muscarinic antagonists and alpha receptor agonists, appetite suppressors, bronchodilators, drugs for HIV treatment, retinoids, medications for migraine treatment, decongestants, and skeletal muscle relaxants<sup>7</sup>. Drugs can cause parasympatholytic activity in several ways, including competitive inhibition of acetylcholine at the parasympathetic ganglia and at the effector junction. Drugs may also influence parasympathetic response indirectly *via* interactions with the sympathetic and central nervous systems<sup>8</sup>. A patient referred to our Department with severe hyposalivation due to drug use is illustrated in Figure 2.



Fig. 1. Oral burn after rinsing with *Calendula officinalis*, colloid silver and schnapps (source: archives of the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia).



Fig. 2. Severe hyposalivation due to drug use (source: archives of the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia).

Table 1. Drug-related oral ulceration

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– Antihypertensives (nicorandil, captopril, losartan)
– Antibiotics (penicillamine, vancomycin)
– Anticonvulsants (carbamazepine, phenytoin)
– Analgesics (diclofenac, indomethacin)
– Alendronate
– Allopurinol
– Dideoxycytidine
– Interferons
– Pancreatin
– Psychotropics (sertraline, olanzapine)

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### Burning Mouth Symptoms

Burning mouth symptoms are most frequently located on the tongue and are usually a consequence of using angiotensin converting inhibitors (ACE) such as lisinopril, captopril, enalapril, etc.<sup>9</sup>. Burning symptoms may develop few days after the medication use has been initiated, but also they can appear after years of the drug use. When the offending drug is replaced, sooner or later burning symptoms will resolve. The mechanism by which ACE inhibitors can lead to the burning mouth symptoms remains unknown.

### Oral Ulcerations

It is known that NSAIDs and beta blockers may lead to the development of oral ulceration<sup>9,10</sup>. Furthermore, sodium lauryl sulfate, which is found in most toothpastes, in some people can cause lesions that look



Fig. 3. Ulceration due to the use of methotrexate (source: archives of the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia).

Table 2. Drug-related angioedema

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– ACE inhibitors (captopril, enalapril)
– Analgesics (aspirin, ibuprofen, indomethacin, naproxen)
– Antibiotics (penicillamine, penicillin derivatives, clindamycin, cephalosporins, streptomycin) and cotrimoxazole, sulfonamides

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like ulcers. Mouth ulcers can occur as side effects of immunosuppressive therapy. Namely, immunosuppressants may lead to the activation of herpes virus or other viruses such as cytomegalovirus, which can be manifested as oral ulceration. Some drugs, such as phenylbutazone, can cause agranulocytosis, which may manifest with oral ulcerations<sup>11</sup>. NSAIDs may cause mucosal ulceration due to local vasoconstriction<sup>12</sup>. Nicorandil induced oral ulcerations are probably due to its metabolites as the onset of oral ulcerations may occur weeks to months after initiation of nicorandil therapy. There is large individual variation in the levels of activity of the enzyme nicotinamide N-methyltransferase that catalyzes methyl conjugation of nicotinamide, an intermediate formed by denitration of nicorandil<sup>13</sup>. A few years ago, for the first time probably, we described a side effect of taking Spiriva (tiotropium bromide) for the treatment of chronic obstructive pulmonary disease that occurred in a patient each time when he inhaled the drug<sup>14</sup>. The antimetabolite drug methotrexate may also cause oral ulcerations (Fig. 3). Table 1 summarizes drugs most frequently involved in the development of oral ulcerations.

### Angioedema

Angioedema may develop after taking many drugs listed in Table 2. Drug-induced angioedema can be differentiated into three main categories. Firstly, immediate hypersensitivity reactions to betalactam antibiotics constitute the most frequent allergic reactions, which are IgE-mediated<sup>15</sup>. Secondly, adverse reactions to NSAID and aspirin are generally non-allergic, in which inhibition of cyclooxygenase results in major alterations in arachidonic acid metabolism such as cysteinyl leukotriene overproduction<sup>15</sup>. ACE inhibitors do not mediate angioedema through an allergic or idiosyncratic reaction; they seem to facilitate an-

gioedema in predisposed individuals. The mechanism of angioedema with regard to ACE inhibitor therapy is believed to be related to the kallikrein-kinin plasma effector system. One hypothesis is that bradykinin, which is normally degraded by kininase II/ACE, accumulates in tissues<sup>15</sup>.

### Gingival Hyperplasia

A well known side effect of antihypertensive drugs, anticonvulsants and cyclosporine is gingival hyperplasia, which usually occurs several months after therapy with the drug has started. Hyperplasia worsens with a lack of oral hygiene, so frequent dental check-ups are recommended. Calcium channel blocker amlodipine, a medication used to lower blood pressure, can cause gingival hyperplasia (Fig. 4). Other drugs<sup>16-18</sup> can lead to gingival hyperplasia less frequently and some are listed in Table 3. Phenytoin has been shown to induce gingival overgrowth by its interaction with a subpopulation of sensitive fibroblasts<sup>19</sup>. Cyclosporine has been suggested to affect the metabolic function of fibroblast (e.g., collagen synthesis, breakdown), whereas nifedipine, which potentiates the effect of cyclosporine, reduces protein synthesis of fibroblasts<sup>20</sup>.

### Erythema Multiforme

Erythema multiforme (EM) lesions can appear on the lips, oral mucosa and conjunctiva. Oral manifestations of EM include bullae and erosions (Fig. 5). The condition can also affect other mucous membranes.



Fig. 4. Amlodipine induced gingival enlargement (source: archives of the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia).

Table 3. Drug-related gingival swelling

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- Antihypertensives (amlodipine, diltiazem, felodipine, lacidipin, nifedipine, verapamil)
  - Antimicrobials (erythromycin) and co-trimoxazole
  - Immunosuppressants (cyclosporin, interferon-alpha)
  - Psychotropics (lithium, sertraline)
  - Oral contraceptives
  - Anticonvulsants (lamotrigine, phenobarbitone, phenytoin valproate, vigabatrin)
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Many drugs<sup>21</sup> can lead to the development of EM and the most common ones are listed in Table 4. The etiopathogenesis of EM is not completely understood, but it seems to involve a hypersensitivity reaction to microbial and chemical agents. It seems that oral mucosa changes correspond to the ones seen in the skin of people affected with EM. In the beginning, epidermis becomes infiltrated with CD8 T-lymphocytes and macrophages, whereas the dermis shows slight

Table 4. Drug-related erythema multiforme

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- Analgesics (acetylsalicylic acid, codeine, diclofenac, phenylbutazone, piroxicam, tenoxicam)
  - Anticonvulsants (carbamazepine, hydantoin, phenytoin)
  - Antifungals (griseofulvin, fluconazole)
  - Antihypertensives (amlodipine, digitalis, diltiazem, nifedipine, verapamil)
  - Antimicrobials (clindamycin, chloramphenicol, ethambutol, penicillin derivatives, rifampicin, streptomycin, tetracyclines, vancomycin), co-trimoxazole
  - Diuretics (furosemide, hydrochlorothiazide, indapamide)
  - Hormones (minoxidil, mesterolone, progesterone)
  - Measles/mumps/rubella vaccines
  - Atropine
  - Allopurinol, busulfan, fluorouracil
  - Omeprazole
  - Retinol
  - Theophylline
  - Zidovudine
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Fig. 5. Erythema multiforme after taking Sinersul (sulfamethoxazole and trimethoprim) (source: archives of the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia).

influx of CD4 lymphocytes. These immunologically active cells are not present in sufficient numbers to be directly responsible for epithelial cell death. Instead, they release cytokines, which mediate the inflammatory reaction and lead to death of epithelial cells<sup>22</sup>.

Table 5. Drug-related lichenoid reactions

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- Analgesics (phenylbutazone, piroxicam)
  - Antidiabetics (chlorpropamide, metformin, tolbutamide)
  - Anticonvulsants (carbamazepine, phenytoin)
  - Antihypertensives (captopril, flunarizine, labetalol, methyldopa, oxprenolol, prazosin, procainamide, propranolol)
  - Antifungals (griseofulvin, ketoconazole)
  - Antimalarials (chloroquine, colchicine, dapsone, hydroxychloroquine, quinine)
  - Antimicrobials (levamisole, lincomycin, metronidazole, niridazole, penicillamine, penicillins, prothionamide, rifampicin, streptomycin, sulfonamides, tetracycline)
  - Drugs that act upon the central nervous system (amiphenazole, barbiturates, chloral hydrate, cinnarizine, lorazepam, lithium, phenothiazines)
  - Antiplatelet activity (dipyridamole, phenindione)
  - Oral contraceptives
  - Protease inhibitors
  - BCG, cholera, hepatitis B vaccines
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## Lichenoid Reaction

The emergence of oral lichenoid reactions to the medication has variable latency period that can last from several weeks to several years from the moment when the patient started taking the offending drug. Probably the formation of lichenoid reactions depends on many factors such as the type, dosage, previous exposure to the drug, etc.<sup>23</sup>. Today, it is considered that NSAIDs and ACE inhibitors often lead to lichenoid reactions in the oral cavity<sup>24,25</sup>. It is also known that other drugs may induce oral lichenoid reactions (Table 5). The most reliable evidence is disappearance of lichenoid reaction after drug discontinuation and recurrence of lesions after re-taking the drug, which is often difficult because of the risk of anaphylactic reaction<sup>1</sup>. Several years ago, a patient was referred to our Department and had lichenoid reaction to alendronate (Fosamax) (Fig. 6). The pathogenetic mechanism of lichenoid drug reaction is incompletely understood. T cells, keratinocytes, dendritic cells and endothelial cells, which express activation markers and adhesion molecules, are thought to be involved in the inflammatory reaction that ultimately leads to apoptosis of basal keratinocytes<sup>26</sup>.



Fig. 6. Lichenoid reaction to alendronate (Fosamax) (source: archives of the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia).

Table 6. Drug-related oral mucosal pigmentation

– Analgesics (aminophenazone)
– Antihypertensives (methyldopa, propranolol, quinidine)
– Antimicrobials (clofazimine, doxorubicin, doxycycline, ketoconazole, minocycline)
– Antimalarials (chloroquine, hydroxychloroquine)
– Antiretrovirals (zidovudine)
– Chemotherapeutic agents (busulfan, cyclophosphamide, fluorouracil)
– Hormone-replacement therapy, contraceptives, diethylstilbestrol
– Psychotropic drugs (fluoxetine)

### Oral Mucosal Pigmentations

Drugs can induce oral mucosal pigmentation. Most common drugs that induce oral mucosal pigmentations are listed in Table 6. Discoloration of oral mucosa also occurs with intoxication with bismuth (blue, brown and black), copper (green), bromine, gold, iron, manganese, lead and silver (gray and blue)<sup>1</sup>. The pathogenesis of drug-induced pigmentation depends on the causative drug. It can result from accumulation of melanin, deposits of the drug or one of its metabolites. Furthermore, some drugs may induce synthesis of pigments or iron can be deposited after damage to the blood vessels<sup>27</sup>.



Fig. 7. Oral mucositis due to 5-fluorouracil (source: archives of the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia).

### Mucositis

Chemotherapeutic agents such as 5-fluorouracil (Fig. 7), methotrexate, bleomycin, doxorubicin, melphalan and mercaptopurine may lead to the development of mucositis<sup>28</sup>. Mucositis occurs when chemotherapy induces breakdown of the rapidly dividing epithelial cells lining the gastrointestinal tract, leaving the mucosal tissue open to ulceration and infection. During the initiation phase, chemotherapeutic agents lead to the generation of free radicals and DNA damage<sup>29</sup>.

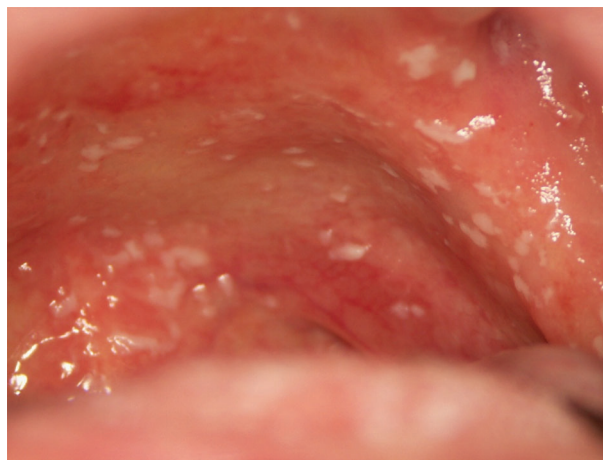


Fig. 8a and b. Atrophic and pseudomembranous candidiasis as a result of medication use (antibiotics and bronchodilators) (source: archives of the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia).

## Candidal Infection

The administration of broad-spectrum antibiotics, corticosteroids, cytotoxic medications and other immunosuppressants may predispose patients to candidal infection due to alterations in commensal oral microflora<sup>30</sup>. It is known that oral microflora controls *Candida* levels through competition for epithelial cell adhesion and dietary substrates<sup>31</sup>. A large number of drugs that induce xerostomia may also influence development of candidal infection either in atrophic or pseudomembranous forms. Reduction in the amount of saliva as well as its antimicrobial salivary constituents (immunoglobulins, lactoferrin, histatins, lysozyme) may lead to increasing commensal candidal levels in these patients<sup>1</sup> (Fig. 8a and b).

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#### Sažetak

### NUSPOJAVE UZIMANJA LIJEKOVA NA SLUZNICI USNE ŠUPLJINE

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Svaki lijek može imati neželjene nuspojave, čak i kada se koristi u terapijskim dozama i prema propisanom režimu. Neželjene nuspojave u usnoj šupljini mogu se pojaviti na bilo kojem dijelu oralne sluznice i mogu biti posljedica primjene lijeka lokalnim ili sustavnim putem. Nuspojave lijekova u usnoj šupljini nisu specifične i ponekad ih je teško prepoznati. Prilikom dijagnosticiranja nuspojava lijekova u usnoj šupljini iskusni liječnik obično će dijagnosticirati stanje na temelju detaljne povijesti bolesti i kliničkog nalaza. Međutim, jedini objektivni dokaz koji bi upućivao na uzročni lijek je tzv. *re-challenge*, odnosno ponovna izloženost lijeku nakon prestanka njegove primjene. S obzirom na to da takav način testiranja nosi veliku opasnost od razvoja anafilaktične reakcije treba ga provesti u kontroliranim bolničkim uvjetima. Liječenje se temelji na trenutnom prekidu uzimanja uzročnog lijeka, a ako su prisutne lezije u usnoj šupljini ordinira se lokalna i/ili sustavna terapija kortikosteroidima. Ovaj pregledni članak je nastao na temelju prikaza bolesnika koji su upućeni na Zavod za oralnu medicinu u Zagrebu.

*Ključne riječi: Farmaceutski pripravci – nuspojave; Oralne manifestacije – dijagnostika; Oralne manifestacije – terapija*