Lesions in the oral cavity and esophagus caused by prescribed drugs: A review

Snezana Tesic-Rajkovic[a,b], Biljana Radovanovic-Dinic[a,b]

Almost all drugs, including some plant-based compounds, can have adverse effects, about 10% of which are expressed at the level of the digestive tract and in some cases resemble gastrointestinal diseases. Most commonly manifest as difficult and/or painful swallowing, nausea, vomiting, diarrhea and constipation. In rare cases, lesions caused by medications may be complicated by bleeding, strictures and perforations and can manifest in all segments of the gastrointestinal tract (GIT). The diagnosis is made from a detailed medical history and clinical examination *inter alia*. and best confirmed by proximal or distal endoscopy.

Key words: esophagus, drugs, oral cavity, side-effects

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[a]Faculty of Medicine, University of Nis, Serbia
[b]Clinic for Gastroenterology and Hepatology, University Clinical Center, Nis, Serbia
Corresponding author: Snezana Tesic-Rajkovic, e-mail: snezanatesic@yahoo.com

INTRODUCTION

Adverse effects of drugs may occur after a single drug dose or after continued, long-term taking of a drug, both topically or systemically. Almost every drug, including even some of the plant-based drugs, can have adverse effects. About 10% of adverse effects are expressed at the level of the digestive tract and in some cases these adverse effects may resemble particular gastrointestinal diseases[1]. Adverse effects of drugs on the digestive tract most commonly manifest with difficult and/or painful swallowing, nausea, vomiting, diarrhea and constipation. In rare cases, lesions caused by medicaments may get complicated by bleeding, strictures and perforations. These complications may manifest in all segments of the gastrointestinal tract (GIT) (ref.[2]).

The type and severity of an adverse effect of the drug depend both on the drug structure and composition, and duration and mode of administration, as well as on the sensitivity of the GIT to the applied drug. The use of some drugs may exacerbate an already present GIT disease. The diagnosis is made based on a detailed medical history and clinical examination, and it is necessary to obtain detailed information about the type and mode of administration, as well as about the time of onset of complaints. GIT changes occurring as the consequence of administration of certain drugs are best confirmed by proximal or distal endoscopy[1-3].

The therapy involves withdrawal or dose reduction of the drug that has caused GIT injury and prescription of a gastrointestinal therapy in accordance with the localization and nature of the injury.

Administration of any drug should involve careful consideration of the possible adverse effects, and in order to prevent them one should always be aware of the mode of administration of a drug, and substitute such a drug with another, without these or similar adverse effects.

A thorough insight into the clinical and pathophysiological characteristics of adverse effects of drugs on the oral cavity and esophagus should make possible their timely prevention, diagnosis and treatment.

ADVERSE EFFECTS OF DRUGS ON THE ORAL CAVITY

Taste disorders

Taste disorders can be the consequence of direct adverse drug effects (ADE) on the oral cavity or of preexisting oral cavity diseases that are also the consequence of ADE (candidiasis, xerostomia). The following drugs produce direct ADEs on the oral cavity: oral hypoglycemics (metformin), antibiotics (metronidazole, clarithromycin), amiodarone, corticosteroids and gold salts[4]. Taste disorders most commonly occur after the first oral dose of a drug, and persist for several weeks after the withdrawal of drugs. Metronidazole, the second most commonly prescribed drug in dentistry practice, usually produces metallic taste in the mouth.

Xerostomia

Xerostomia, or the sensation of oral dryness, occurs as the consequence of inadequate secretion of saliva, which often results in taste and/or swallowing disorders. Reduced salivary secretion caused by drugs occurs as the consequence of their antimuscarinic, anticholinergic effect on the parasympathetic nervous system. Xerostomia usually occurs after the use of anticholinergics (dicycloverine, hyoscine butylbromide, oxybutynin); tricyclic antidepressants (e.g., amitriptyline); and antipsychotic agents (e.g., chlorpromazine) (ref.[4,5]). Oral changes in individuals with reduced salivary secretion depend on the severity and duration of oligosialia. A short-term reduction of salivary secretion, usually emotional in nature, does

not have consequences. If longer, it can cause atrophy of the oral epithelium; the mucosa is dry and glossy (as if polished); oral candidiasis frequently occurs, as well as angular cheilitis and fissured tongue (lingua plicata).

Oral cavity ulcerations

One of the etiological factors that may lead to oral cavity ulcerations are ADEs. The drugs that most commonly cause these lesions are tacrolimus, hydroxyurea, nicorandil and alendronate[6]. The mechanism of occurrence of these ulcerations has not been sufficiently elucidated. An ulcer represents a mucosal defect involving, in addition to epithelium, also the dermis and submucosa. The changes are painful and with time become filled with granulation tissue, so that smaller ulcers heal without scarring while larger ones heal with scarring.

The patients are advised to stop with the medication which caused ulceration, to boost their oral hygiene and apply a topical anesthetic cellulose gel.

Erythema multiforme

Erythema multiforme (EM) can be localized in the oral cavity and on the lips, skin, eyes and genitals. Numerous etiological factors can lead to the onset of EM. In adults, in 10-50% of the cases, EM is associated with the use of drugs, especially NSAIDs, antibiotics, antimycotics and antiviral agents. The lesions of erythema multiforme exudativum (EME) can involve the lips, oral mucosa and conjunctiva. Oral manifestations of erythema involve bullae and erosions[7,8]. The disease may involve other mucosal membranes as well.

Oral lichen planus

Oral lichen planus (OLP) manifests in the form of papullar, ulcerative, atrophic or white lace-like lesions (Wickham striae). One of the reasons for the occurrence of oral lichen is the reaction to oral lichenoid drugs (NSAIDs, suplhonylurea agents, antiretroviral drugs, talidomide, methyldopa, angiotensin-converting enzyme inhibitors, carbamazepine, TNF-alpha inhibitors), when the changes in the oral cavity and on the lips have the form of single-sided erosions. These changes may occur weeks or even months after the initiation of therapy, and may persist for several months after the withdrawal of therapy, which complicates their diagnosis and treatment. The changes in the oral epithelium are most frequently localized in the buccal mucosa (the occlusal line and retromolar region), on the edges and dorsal surface of the tongue, as well as on the floor of the oral cavity. Characteristic lichen papulas occur, polygonal in shape and the size of the pinhead, which can be situated on the enanthematous and erosive mucosa. The papules are seen in the form of whitish lines or streaks, or in a lace-like pattern, and are known as the Wickham striae. There is a difference between oral lichen planus and lichenoid reaction. In oral lichen planus the lesions are symmetrical, whereas in lichenoid reaction they are asymmetric.

Topical corticosteroids constitute the first line of therapy for most of the symptomatic cases. Other alternative approaches include topical retinoids, topical calcineurin inhibitors and low level laser therapy. Long term follow-up of oral lichen planus is essential because of the controversial association with possible malignant transformation, estimated to occur in 1-3% of cases[9-11].

Hyperplastic gingivitis

Hyperplastic gingivitis can be the consequence of ADE (phenytoin, cyclosporine and calcium channel antagonists). Gingival changes are the consequence of exudative inflammation, vascular reactions and gingival hyperplasia. The changes are most conspicuous in the labial gingiva of the anterior upper teeth. It is an exudative, productive inflammation of the gingiva usually in the region of anterior teeth in the form of swelling and redness of the gingiva (especially interdental papillas). This gingival enlargement is not uniform or symmetrical[12]. The therapy involves discontinuation of the drug in question, application of antiseptic agents, sympatholytic drugs and, if necessary, physical therapy (high frequency currents) and gingivoplasty.

Teeth discoloration

Tetracyclines are broad-spectrum antibiotics that induce enamel hypoplasia and permanent teeth staining (gray-brownish). Tetracycline becomes irreversibly bound to the calcified dental structure when administered during the calcification phase of teeth development. The use of tetracycline is contraindicated during pregnancy and in children below 8 years of age. Minocycline, a semisynthetic tetracycline, can also cause the change of teeth color and similar events. It has also been associated with teeth discoloration of completely developed teeth. The proposed mechanisms of action involve systemic absorption via pulp vessels into the dentine, or entry by way of crevicular fluid through enamel defects[13].

Oropharyngeal candidiasis

Oropharyngeal candidiasis represents a fungal infection of the oral cavity, tongue and pharynx, most commonly caused by Candida albicans. It is one of the most common ADEs (immunosuppresants, inhaled corticosteroids, antibiotics). It manifests clinically as acute (pseudomembranous and atrophic forms) and chronic (atrophic, nodular and mucocutaneous forms) candidiasis. Oropharyngeal candidiasis manifests in the form of whitish lesions on the affected surfaces. It can spread to all parts of the gastrointestinal tract. The symptoms depend on the disease localization.

After a clinical examination and laboratory identification of Candida, appropriate antifungal agents are administered topically (Nystatin solution, Dactanol gel) or systemically (Fluconazole, Ketoconazole, Itraconazole, Amphotericin B, etc.), as well as regular oral hygiene and dental treatment. In some of the high risk groups the prophylaxis with antifungal preparations is used in order to reduce the incidence and severity of the disease. In most of the affected, the prognosis is good[14].

DRUG INDUCED ESOPHAGEAL INJURY

Many of the commonly prescribed drugs may produce adverse effects that affect the esophagus. Various drug ingredients are potentially aggresive to the esophagus, either by their direct toxic action on the mucosa or by the production of caustic acidic or alcaline solutions which may damage the mucosa or affect the esophageal muscles[4].

The factors that increase the risk of adverse drug effects on the esophagus are advanced age, obesity, taking drugs reclining in bed (especially before sleep), taking drugs with small amounts of liquid, large tablets (especially capsules), polypharmacy, external esophageal compression and pre-existing esophageal conditions[3,4]. A wide spectrum of drugs, most commonly antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs) and bisphosphonates, (Table 1) may have various adverse effects on the esophagus through various mechanisms[2,15]. However, Dömötör et al., in their most recent meta-analysis of 39,047 patients on bisphosphonate therapy, have reported that bisphosphonates do not produce significant adverse effects on the esophagus and other parts of the GIT (ref.[16]).

Most common esophageal lesions are erosions and ulcerations, that may be complicated with hemorrhage, fibrosis, stenosis and esophageal perforation[17]. These lesions are usually situated in the middle third of the esophagus, particularly when this portion of esophagus is compressed by the aortic arch or enlarged left atrium of the heart.

MECHANISMS OF OCCURRENCE OF DRUG-INDUCED ESOPHAGEAL INJURY

Damage to the esophagus caused by adverse drug effects occurs by direct topical injury to the organ induced by caustic drugs or by acid reflux induction (e.g. by calcium channel antagonists). The drugs that may directly damage the mucosa do that through: 1. toxic action on the mucosa; 2. create a hyperosmolar solution in contact with the esophageal mucosa (e.g., potassium chloride); 3. production of a caustic alkaline solution (e.g., alendronate); 4. production of a caustic acidic solution (e.g., ascorbic acid and iron sulphate). Drug composition also affects esophageal injury (e.g., tablets made of cellulose fibers and guar gum may swell up in the esophagus due to water absorption ability), leading to its complete obstruction[4,18,19].

The factors predisposing to esophagitis caused by direct, topical drug effects are anatomical disorders (esophageal compression by the enlarged heart, achalasia, esophageal cancer, postoperative anastomotic stenosis and hiatal hernia), esophageal motility disorders, or improper drug administration (e.g., when lying down or with small amounts of water). The duration of contact of the drug with esophageal mucosa is also an important factor[20-23]. In each of these cases, esophageal mucosa is exposed to the drug for longer than necessary periods of time.

It is believed that obesity induces slower esophageal clearance due to increased abdominal pressure or abnormal esophageal peristalsis[24]. Daigneault et al. have reported that 51% of patients with a mean BMI of 46 have

Table 1. Adverse drug effects on the esophagus.

Type of esophageal injury	Mechanism of injury	Drugs
Tablet/pill-induced esophageal injury	Pills stuck in the esophagus	Antibiotics (tetracyclin, doxicyclins, clindamycin, penicillin, rifampin)
	Caustic injury by topical medication	Bisphosphonates Potassium chlorid NSAIDs Iron formulations
Gastroesophageal reflux	Reduced pressure in the lower esophageal sphincter	Nitrates Calcium channel antagonists Dopamin/dopaminergic agents Anticholinergic drugs Progesteron Methylxanthines
Dysmotility	Inhibition of skeletal muscle function	Antipsychotics (dopamin antagonists)
	Inhibition of smooth muscle function	Anticholinergic drugs Calcium channel blockers Teophylline
	Xerostomia	Anticholinergics Opiates Antipsychotic drugs Antihistamines Clonidine

esophageal dysmotility regardless of their gastrointestinal symptoms[25].

In an esophagus with normal position and peristalsis local adverse drug effects are most common in the areas with normal hypomotility or when there is external compression, for instance in the lowest esophageal zone or at the level of the aortic or left bronchial impression on the esophagus[4].

Improper intake of drugs predisposing to esophageal injury includes drug intake without enough water and/or while lying down, or sleeping immediately after taking the medication. Taking the drug while lying down, especially before sleep, eliminates the assistance of gravity in esophageal transit and reduces saliva production and frequent swallowing, which normally occurs when we are awake. Radiographic studies have indicated a prolonged stay of capsules in the esophagus in individuals with normal esophageal function even when taken with water and in upright position[4,26].

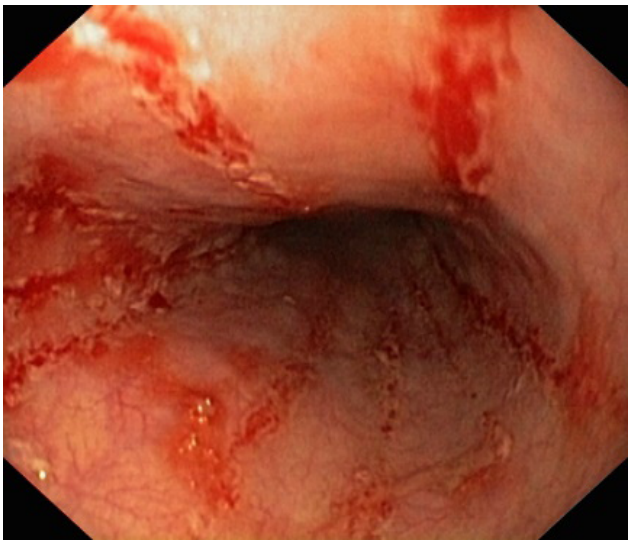

Fig. 1. Pill-induced esophagitis.

TYPES OF ESOPHAGEAL INJURY INDUCED BY ADVERSE DRUG EFFECTS

Pill-induced esophagitis ("pill esophagitis")

Pill-induced esophagitis was for the first time observed in 1970 by Pemberton in the form of retrosternal pain and a sensation that something "got stuck" in the thoracic portion of the esophagus after taking a potassium chloride tablet. Proximal endoscopy then established the presence of ulceration in the middle portion of the esophagus[27].

Pill-induced esophagitis is a relatively rare esophageal condition. Based on the results of a four-year Swedish study with 700,000 patients[26], the incidence of this pathological condition is 3.9 per 100,000. Over 100 drugs of different types, most frequently antibiotics, can cause this type of esophageal injury[4,28]. The most common reason for the condition to appear is inadequate drug intake or a pre-existing esophageal condition. A higher risk for the condition is present in older patients, since in them reduced salivary secretion is already present, as well as reduced esophageal motility or anatomical esophageal abnormalities (strictures due to chronic reflux, achalasia, compression by the enlarged heart) (ref.[15,29]). Drug-induced esophagitis is more common in women, and can as well occur in children[30].The condition is more common with the administration of capsules[31].

Pill-induced esophagitis clinically manifests with sudden-onset dysphagia, odynophagia or retrosternal pain regardless of swallowing, while in rare cases bleeding from the esophageal lesion may occur[26]. The complaints usually occur within 3 days of drug intake[4,15], and may also develop in a matter of hours or up to 10 days after taking the drug[32]. Concomitant gastroesophageal reflux disease may exacerbate pill-induced esophagitis[33].

The diagnosis of pill-induced esophagitis is made based on medical history information about drug intake, using proximal endoscopy and, if required, after histopathology analysis of the biopsy specimen of a confirmed lesion. Proximal endoscopy can confirm mucosal hyperemia, erosions and ulcerations (solitary or multiple). The presence of "kissing" ulcer disease is more common with this form of esophagitis compared to other etiologies of the disease[34]. The lesions occurring with this disease are usually identified in the distal and middle portion of the esophagus (Fig. 1). Higuchi et al. have reported that in their study 80% of ulcerations occurring as the consequence of drug intake have been identified in the middle portion of the esophagus[35].

Histopathology of pill-induced esophagitis reveals a non-specific ulcer or intraepithelial eosinophilic infiltration[26,27]. Some recent reports have suggested that intraepithelial eosinophilic infiltration in the esophagus is induced through a number of signaling pathways, including extracellular signal-regulated kinase (ERK), leptin and proteins associated with leptin signaling, such as signal transducer and activator of transcription 3 (STAT3) and mechanistic (mammalian) target of rapamycin (mTOR) (ref.[35]).

Regarding differential diagnosis, one should take into consideration reflux and eosinophilic esophagitis[26,35-37]. Proper differentiation between these two entities requires appropriate clinical and histopathological criteria[38]. Pill-induced esophagitis is more common in the elderly with a history of oral drug intake while lying down or immediately before sleep, with insufficient amounts of water, and that their symptoms have appeared within two weeks of taking their drugs[39,40].

One of the forms of pill-induced esophagitis is exfoliative esophagitis. It is a rare adverse effect of dabigatran (oral direct inhibitor of thrombin). The incidence of the condition is 0.03%. Exfoliative esophagitis can be induced by an immune disease, food, drugs, or it is idiopathic in origin. This type of esophagitis manifests endoscopically with whitish exfoliations in the form of membranes at the points of contact of the drug with the mucosa[22,23]. Histopathologically, the membranes consist of superficial layers of squamous epithelium with a missing basal cellular layer (Fig. 2).

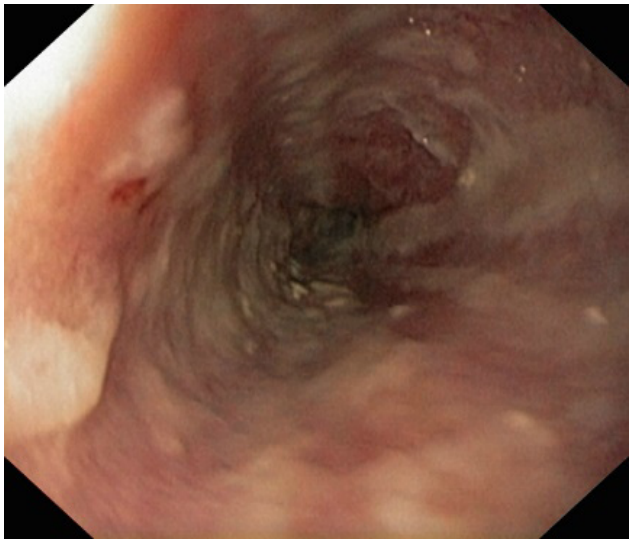

Fig. 2. Exfoliative esophagitis.

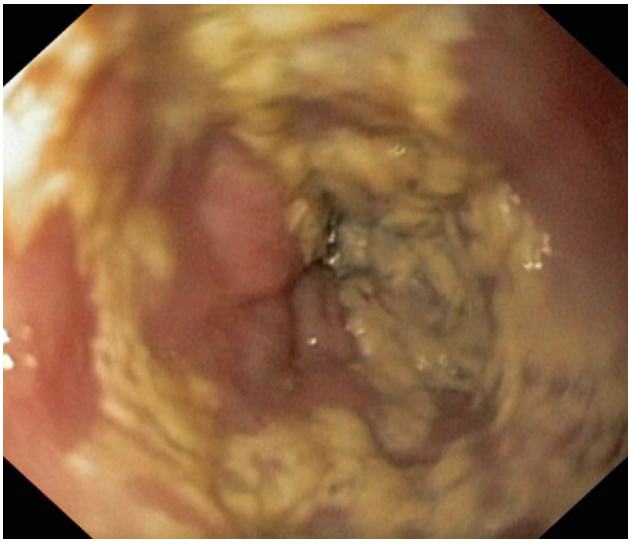

Fig. 3. Esophageal candidiasis.

Gastroesophageal reflux disease (GERB)

As the consequence of ADEs, GERB can occur due to their effect on the relaxation of lower esophageal sphincter (LES) and resultant reflux. The drugs that may potentiate or precipitate GERB are theophylline, calcium channel blockers, diazepine, tricyclic antidepressants, anticholinergic agents, beta-agonists, that are massively used by the asthmatics[4]. Elderly patients often use several of these medications. Studies have shown that the most common GIT reaction in individuals using low-dose aspirin has been gastroesophageal reflux, presenting clinically as regurgitation of acidic contents[40,41]. GERB manifests clinically with heartburn and regurgitation of stomach contents into the esophagus and oral cavity.

The therapy consists of dose reduction or discontinuation of the drug that has caused GERB, hygienic-dietetic regimen and standard therapy for GERB, where the drug of choice is a proton pump inhibitor.

Esophageal dysmotility

Esophageal dysmotility with consequential dysphagia can be one of the adverse effects of some drugs on the esophagus. Smooth muscle relaxants, such as calcium channel antagonists used in the treatment of ischemic heart disease, hypertension and esophageal spasms, can cause or aggravate the symptoms of reflux disease[4,26]. Some drugs may cause dysfunction of all esophageal muscles, or affected is only the lower esophageal sphincter (LES). The patients may remain asymptomatic or they have reflux symptoms, presenting in the form of regurgitation and/or pyrosis. With time, esophageal mucosa becomes damaged, which results in esophagitis, possibly complicated by fibrosis and stricture. Dysphagia can also develop or is exacerbated by the absent or reduced secretion of saliva (xerostomia) that have a lubricant effect in the esophagus[1,4,41].

Esophageal candidiasis

Widespread use of broad-spectrum antibiotics and immunosuppressants such as corticosteroids (especially for inhalation) can bring about opportunistic colonization of the esophagus with fungi, especially of the Candida species. The presence of Candida in the esophagus (Fig. 3) manifests with whitish changes[4]. The use of probiotics is usually advised for the prevention of candidiasis.

PREVENTION AND THERAPY OF ESOPHAGEAL INJURY BY ADVERSE DRUG EFFECTS

For the prevention of esophageal injury caused by drugs the following is usually recommended: drug intake with at least 200 mL of liquid; drug intake in upright position, which should be maintained for at least 30 min after drug intake; in patients with potentially increased basic risk for esophageal injury induced by drugs (e.g. inability to follow the previous recommendations, poor esophageal motility, anatomically reduced esophageal lumen), alternative safer drugs should be introduced or the risks and benefits of the drug to be used should be carefully weighted[31].

In the case of esophageal injury by the action of a drug, the drug should be discontinued, although it is not always a simple matter, especially if it is a drug that cannot be adequately substituted. The therapy of esophageal injury should focus on the control of symptoms and prevention of complications. Symptom control can be accomplished locally by topical anesthetics, such as the viscous lidocain solution. The treatment of superimposed reflux is best accomplished using proton pump inhibitors twice a day, although there is no data that would suggest that the prevention of acid reflux accelerates symptom improvement or histological healing of pill-induced esophageal injury. The patients with serious odynophagia, which would abolish adequate oral intake, require parenteral nutrition

and hydration until the disappearance of complaints and reinstitution of oral intake[4,15,26].

There is not any information concerning the question whether a repeated use of the drug that once induced esophagitis represents a higher risk if taken this time with proper caution.

CONCLUSION

Adverse effects of certain drugs on the oral cavity and esophagus can induce injury that may significantly impact further treatment and quality of life. If these adverse effects are not timely recognized complications are possible, resulting in unnecessary diagnostic procedures and inadequate treatment attempts. Moreover, the necessary discontinuation of the drugs in question in chronic patients may complicate the original disease.

In order to prevent any of the complications that may arise, the patients should be well informed about adverse effects of the drugs they use and the ways they should be taken. In the situations when patients report that they have experienced adverse effects of a drug, that drug should be substituted with another, alternative drug, or the minimal doses should be prescribed with all the available prevention measures undertaken.

Search strategy and selection criteria

We examined articles and studies from various resources (e.g. PubMed, MEDLINE).The search terms used included esophagus, drugs, oral cavity. Citation from journals of recent date and with high impact factors were used.

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