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REVIEW ARTICLE

Drug-induced esophagitis and helpful management for healthcare providers

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ABSTRACT

In recent decades, the number of cases developing drug-induced esophagitis (DIE) has reportedly been growing, which indicates the significance of detecting medicines capable of causing this adverse reaction. This study aims to provide an updated review on recent case reports of DIE, to evaluate the possible mechanism of this side effect, and to provide helpful management. Data was gathered through searches of three databases, namely PubMed, Medline, and Cochrane. Seven drug categories were evaluated: antibiotics, bisphosphonates, cardiovascular medicines, chemotherapeutic agents, non-steroidal anti-inflammatory drugs (NSAIDs), other medications, and supplements. According to the findings, retrosternal pain, heartburn, odynophagia, and dysphagia are typical symptoms of DIE, and in most cases, DIE is a self-limiting side effect which can be resolved by removing the causative agent and providing supportive therapy.

Keywords: Adverse drug reaction, Esophagus, Esophagitis, Medication, Supplement.

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Introduction

According to the estimates, the incidence of drug-induced esophagitis (DIE) is around 3.9 per 100,000 population annually mainly in middle-aged women, as they consume more medications (1). Esophagitis is associated with the inflammation of esophageal mucosa. Several underlying factors are involved in the development of this condition, including ingestion of some medications, gastroesophageal reflux disease (GERD), radiation, and infections (2, 3). To date, many drugs have been reported to cause DIE as a common adverse effect, including antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, potassium chloride, ferrous sulfate, ascorbic acid, chemotherapeutic regimens, warfarin, anti-hypertensives, quinidine, phenytoin, rifampin, metronidazole, theophylline, mycophenolate mofetil, cyproterone acetate, and ethinylestradiol (4–8).

Retrosternal pain, heartburn, odynophagia, and dysphagia are clinical manifestations of DIE, which may start abruptly because of the released chemical content of the drug. Other less common symptoms are hematemesis and abdominal pain (4, 9). Typical findings in endoscopic pictures of about 50-60% of cases of esophagitis are erythema, erosions, ulcers, and esophageal strictures (10, 11).

Inadequate water consumption or taking pills while in an inappropriate position (e.g., supine) can increase the risk of developing DIE (12). Other risk factors for pill-induced esophagitis include old age, decreased salivary flow due to sicca syndrome or consumption of anticholinergic medications, and esophageal motility disorders such as achalasia and strictures (13). Medication-induced esophageal injury should be

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diagnosed based on the patient's clinical history and endoscopic findings. Intraepithelial eosinophilic infiltration is a typical characteristic of esophagus histological findings, though esophagitis due to GERD can imitate the same histological features (14). Thus, taking the patient's medical history regarding the use of predisposing medications could be helpful in the differential diagnosis. Furthermore, patients with DIE do not respond to anti-reflux regimens (15).

Medications contributing to DIE can affect the esophagus directly or indirectly. Studies have reported that cytotoxic agents and immunosuppressive drugs can predispose patients to esophagitis by precipitating herpetic and candida infections (16). Other medications also promote this situation by reducing the lower esophageal sphincter pressure (LESP) and reflux of gastric contents into the esophagus, subsequently leading to mucosal injury (17). In contrast, some irritant medicines can induce DIE directly due to their inherent physicochemical properties, such as low pKa (2).

In this review, we aimed to shed light on medications that can potentially predispose patients to esophagitis and to provide an overview on managing this condition.

Methods

A comprehensive literature search of PubMed, Medline, and Cochrane databases was performed. Data was collected by two pharmacists. The mesh terms used in this study were "esophagitis" AND "drug-Induced" OR "medication-Induced" OR "pill-Induced" OR "supplement." Only original articles and case reports written in English with a publication date of 1/1/1990 to 1/6/2021 were included in this study. Published studies with inadequate data and letters to the editors were excluded from the report.

Results and discussion

Antibiotics

Antibiotics are one of the critical causative agents for direct esophagitis, especially tetracycline, doxycycline, and clindamycin. As these agents provide an acidic solution in contact with water, they may cause localized distinct ulcers without forming stricture which would be cured after drug discontinuation (18).

A case-control study reported several cases of doxycycline-induced esophagitis. The main reported symptoms were sudden onset of odynophagia and retrosternal pain. All patients stated that they swallowed the medicine with a small amount of water and were in a resting position after use. The endoscopic reports revealed focal epithelial injury and discrete single or multiple ulcers in the proximal or mid-esophagus (19). Endoscopic characteristics of doxycycline-induced esophagitis generally include erythema, erosions (20), and vascular injury with prominent perivascular edema and endotheliitis (21). The involvement of the distal and middle parts of the esophagus is mainly reported in endoscopic findings of esophagitis caused by clindamycin (22, 23).

Another class of antibiotics associated with esophagitis are fluoroquinolones, especially ciprofloxacin (24). In some case reports, sudden chest pain was reported by patients diagnosed with urinary tract infection and prostatitis treated with ciprofloxacin 48 to 72 hours after starting the antibiotic. On esophagogastroduodenoscopy, ulcers in the middle and lower third of the esophagus with inflammatory margins were detected, which was compatible with chemical injury. Ciprofloxacin belongs to the fluoroquinolone category with pKa1 of 6.10 at 25 ℃, which can be an irritant when in contact with esophagus mucosa (25–27).

Kaewdech et al. reported the first case of amoxicillin-clavulanic acid-induced esophagitis in 2020. The endoscopy of this case demonstrated hallmark features of kissing ulcers at the mid-esophagus, and the biopsy showed inflamed granulation tissue, which was consistent with a typical medication-induced esophageal injury (28).

Bisphosphonates

With bisphosphonates used to prevent and treat osteoporosis, alendronate can irritate the upper GI mucosa and cause direct esophagitis. Endoscopic findings generally show erosion or ulcerations as well as exudative inflammation with thickening of the esophageal wall (29). The possible mechanism of esophageal damage caused by these drugs may be their amino side chain (30). According to a post-marketing surveillance study, esophageal complications occur during the first month of alendronate therapy in most patients, whereas patients with preexisting esophageal

disorders and acidic environment of GI (pH <3.5) were more susceptible to developing DIE (31). Ryan et al. reported acute esophagitis and severe esophagus stricture due to oral alendronate therapy in a 71-year-old woman (32).

Cardiovascular medicines

Among cardiovascular medicines, calcium channel blockers (CCBs), anti-coagulant agents, and nitrates are most commonly associated with esophagitis (33). Amlodipine is a CCB that can expose the esophagus to gastric content by reducing the LESP or lowering esophagogastric motility (34). Researchers observed esophagitis in nine patients taking amlodipine and ramipril (an angiotensin-converting enzyme (ACE) inhibitor) (35). Furthermore, a retrospective study on 371 patients treated with CCBs detected new reflux symptoms in 241 patients. Based on their analysis, the risk of developing reflux was 2.7 times higher in the dihydropyridine CCBs group than in the non-dihydropyridine group (36). Dabigatran is an oral anticoagulant agent in the form of a prodrug that can turn into an active form in the small intestine. Adverse GI effects of dabigatran, such as dyspepsia-like syndrome, are well recognized, and recent case studies have mentioned a higher risk of dabigatran-induced esophagitis (37–39). Although the exact pathophysiology of the lesion formation is not fully understood, it is proposed that direct contact of esophagus mucosa with the chemical content of the dabigatran coating, i.e. the tartaric acid core, is the cause of esophageal mucosa injuries (40). The risk factors for developing dabigatran-induced esophagitis include female gender, old age, nonwhite, and consumption of cyclooxygenase-2 inhibitors, proton pump inhibitors (PPIs), H2 blockers or NSAIDs (41). Nitrates can lead to DIE through a mechanism similar to CCBs (33). Additionally, Kono et al. reported a case of apixaban-induced esophagitis in a 60-year-old man complaining of epigastric pain (42).

Chemotherapeutic agents

Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor used to treat metastatic renal carcinoma and GI stromal tumors resistant to imatinib, which could act through targeting endothelial growth factor (VEGF). GI side effects of sunitinib, such as GERD, are often mild, though some studies have reported esophagitis as its adverse effect. The pathological mechanism is unknown; however, it has been proposed that this medicine interferes with the role of VEGF and mitogen-activated protein kinase in protecting the mucosal membrane from gastric acidity and hinders mucosal lesions repair. Two studies reported exfoliative esophagitis induced by this medicine (43, 44). Pegylated liposomal doxorubicin is a chemotherapeutic agent effective in many solid tumors. Although this medicine's adverse reactions and pharmacokinetic profile differ from those of doxorubicin, it may cause mucocutaneous reactions. One study reported DIE in a case of multiple myeloma on the third day of liposomal doxorubicin infusion as a rare adverse reaction. This patient developed severe stomatitis and esophagitis associated with minor palmar-plantar erythrodysesthesia (45). Methotrexate (MTX) is a dihydrofolate reductase inhibitor that interferes with thymidylate and purine production. Endoscopic findings of a 14-year-old girl with Crohn's disease revealed esophagitis and mild gastritis (46).

Nivolumab and ipilimumab are monoclonal antibodies approved for the treatment of several cancers which act by inhibiting immune checkpoints including programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) (47). Ulcerative esophagitis associated with combined nivolumab and ipilimumab therapy was reported in a patient diagnosed with melanoma (48).

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are the most commonly prescribed group of medications globally, and their gastrointestinal (GI) toxicities are well known. Several studies have indicated that NSAIDs are the leading cause of esophageal stricture and ulceration (49–51). In the majority of prospective studies on patients treated with this class of medicines for rheumatic diseases, the frequency of upper GI complications was higher than that of lower events, with esophagitis being the commonly reported side effect (52). The pathophysiology behind the effect of NSAIDs on ulcer formation could be their reducing of the protective effect of prostaglandins on gastric mucosa and direct cellular injury (35, 53). These drugs have acidic properties with pKa values within 4 to 5. In the setting of GERD, the pH of the distal esophagus would be lower than 4, which facilitates the entrance of these

drugs into mucosal cells. This situation would exacerbate esophagitis in patients with reflux and increase the risk of stricture formation (30).

Other medications

One case report revealed reflux esophagitis (grade 4) associated with a hiatal hernia in a 58-year-old chronic schizophrenic patient administered clozapine as an antipsychotic agent. These GI adverse effects, hypomotility, and changes in digestive secretion appeared in response to the anti-serotoninergic and anticholinergic properties of this medicine and were resolved by lowering the plasma level of clozapine (54). Moreover, zidovudine and zalcitabine are two anti-AIDS drugs associated with DIE as a rare adverse reaction (55, 56). It was reported that short intervals (every four hours) of taking zidovudine might be the reason behind this adverse reaction, as the patient may not drink a bolus fluid or lie down after consumption. This can lead to the sticking of a drug to the esophageal mucosa (55).

Supplements

The effects of potassium chloride on small intestinal damage and esophageal injury along with its pathological mechanism have been completely characterized and reported in several cases. Esophagitis caused by potassium chloride usually arises at the junction of the middle and distal third of the esophagus. This side effect can be diagnosed with spasm and edema, leading to esophageal stricture (30). Since this supplement can provide a neutral aqueous solution, the mucosal injury caused by potassium chloride could not be associated with low pH (4). In contrast, ferrous sulfate and ascorbic acid can induce localized injury by providing an acidic solution after dissolution without stricture formation. Another suggested mechanism regarding ferrous sulfate-induced esophagitis is the formation of reactive oxygen species due to ferrous and ferric ions oxidation, leading to mucosal injury. Endoscopic findings of a discrete ulcer due to ferrous sulfate consumption revealed brown-black crystals as a typical diagnostic feature (35). A case series study reported DIE in six adolescents administered L-arginine for short suture. Endoscopic findings showed ulcers in the mid-esophageal mucosa. The corrosive nature of this agent due to its acidic solution would explain this event (57).

Preventive approaches and managements

Many medicines have the potential to precipitate esophagitis, and this rate could increase through newly developed drugs that are intrinsically irritant or may cause this side effect through the mechanisms mentioned in previous sections. Thus, it is imperative to educate healthcare providers regarding drug categories with the risk of DIE and its management to increase patient's compliance with their treatment process. Here are some helpful hints to prevent or manage acute cases of DIE (1, 4, 30, 58, 59).

- Patients should be fully informed about the best posture to assume when taking medicine and drinking adequate liquid (180 mL) after swallowing a pill. For instance, alendronate should be taken with an empty stomach and a glass of water while in an upright position. The patient is not allowed to lie down for at least 30 minutes after taking this pill. It is reasonable to take alendronate in the middle of the day (60).
- For patients with pre-existing conditions such as esophageal motility disorders, using the liquid form or dispersing crushed medication in water could be advisable (61).
- High-risk patients (females, the elderly, patients with a history of GERD or other GI disorders) should be closely monitored.
- Among uncomplicated cases, DIE is a self-limited condition and resolves after discontinuation of the offending drug (62).
- To hinder esophageal injury, it is suggested to use alternative medicines with fewer side effects, if possible (30).
- Use of a liquid form instead of pill and using sugar- or film-coated tablets instead of gelatin capsules could be an option regarding DIE, as these drug formulations have a shorter esophageal transit time (63, 64).
- To treat DIE, various medications are prescribed to relieve the symptoms, including antacids, H2 receptor blockers, proton pump inhibitors, sucralfate, and even local anesthetic agents. Patients should avoid consuming irritating foods such as citrus fruits and alcohol in this condition (4).

- Surgery or esophageal dilatation is necessary for complicated patients with strictures and bleeding (65).

Conclusion

The current review focused on studies that reported medicines that induce DIE as a side effect and evaluated several drug categories, including antibiotics, bisphosphonates, cardiovascular medicines, chemotherapeutic agents, NSAIDs, other medications, and supplements. According to the findings, the number of cases with DIE has increased recently, mainly due to the irritating nature of some medicines to the esophageal mucosa. Developing modified formulations with fewer corrosive features could be a possible solution; nevertheless, the most crucial management is preventive care, including informing patients about the best way of taking pills and taking a medical history, which are among the primary responsibilities of healthcare providers.

Conflict of interests

All authors declare that they have no conflict of interest.

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