

The Diagnostic and Management of Drug Induced Esophagitis

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ABSTRACT

There are several factors that involve in drug induced esophagitis such as: drugs, esophagus, patients. The drug can cause direct effect to the esophageal mucosa. The drugs that often cause esophagitis: alendronate, tetracycline and its derivatives and anti retroviral agents. Most of these drugs can cause esophageal damage due to corrosive nature of the drug.

Esophageal factor that can cause the drug induced esophagitis: rheumatic heart disease, enlargement of the left atrium mass and aortal aneurysma. These conditions will disturb drug passage and prolongs drug contact with esophageal mucosa. The patients factor that influences this problem is the patients position when taking the drug, the patients age, the amount of water taken along with the drug, the time when drug was taken, and the amount of saliva.

Endoscopy is a good procedure to evaluate the esophageal mucosa and establishing differential diagnosis through direct inspection, biopsy.

In the management of esophagitis, PPIs are currently the most effectiveness agents available for treating esophagitis. Esomeprazole, an optical isomer of omeprazole is the first PPI to show greater efficacy than other PPI is in esophagitis healing.

Key Words: *Esophagitis, drug induced, proton pump inhibitor.*

INTRODUCTION

One of the main functions of the esophagus is to transport food bolus from the mouth to the stomach. During this process, the esophagus is exposed to various toxic substances, including drugs, which could damage the esophageal squamous epithel.¹

Drug-induced esophagitis or esophageal damage due to drugs was first reported by Pemberton in the year 1970.²⁻⁴ Esophageal damage was caused by the use of oral potassium chloride.

Drug-induced esophagitis is damage of the esophageal mucosa due to local effects of drugs.³

There are over 70 kinds of drugs that could induce damage of the esophagus.^{1,3} Several drugs related to drug-induced esophagitis are as follows:^{1,3,5}

Table 1. Drugs That Cause Drug-Induced Esophagitis

Antibiotics
Doxycycline
Tetracycline
Clyndamycin
Erythromycin
Penicillin
Non-Steroidal Anti Inflammation
Potassium Chloride
Ascorbic Acid
Sulphasferrosus
Quinidine
Anti-retroviral agents
Zalcitabine
Zidovudine
Alendronate (Fosanax)

The extent of damage varies from mild, asymptomatic inflammatory changes that can only be discovered by means of endoscopy or absence of histological changes, to severe damage accompanied by ulcer and stricture. Damage is often acute, and self heals without any sequel. Symptoms subside 10 days following termination of treatment.⁴

Collin et al reported 41 cases of drug-induced esophagitis caused by eight different kinds of drugs, nine of which resulted in death.⁴ Setijoso et al reported four cases out of 12 patients with non-cardiac acute chest pain undergoing endoscopy.⁷

Luigi Bonavina, in a retrospective study of patients with esophageal stricture, found 20% out of 55 to be drug-induced.⁸

Drug-induced esophagitis is often found in old age and women.^{3,4}

This paper discusses the pathogenesis, diagnosis, treatment, and several drugs that cause drug-induced esophagitis.

PHYSIOLOGY OF ESOPHAGEAL MUCOSAL INTEGRITY

The physiology of esophageal integrity is determined by 2 factors as follows:

- mucosal offensive factors
- mucosal defense factors

Offensive mucosal factors are those that destroy the mucosa. They include gastric secretion, pyloric competence, drugs and acidic or alkaline substances.

Defense mucosal factors comprise of anti-reflux barrier, lumen clearance, and tissue resistance.^{8,9}

ANTI-REFLUX BARRIER

Anti-reflux barrier is an esophageal defense factor in maintaining the mucosa. The anti-reflux barrier limits the frequency and volume of the reflux from the gaster to the esophagus. The anti-reflux barrier comprises of the lower esophageal sphincter, the intra-abdominal esophageal segment and the diaphragmatic crura.

ESOPHAGEAL LUMEN CLEARANCE

The esophageal lumen clearance includes gravity, peristalsis, and acid clearance, particularly with bicarbonate secretion from the saliva and esophageal glands. Gravity increases bolus clearance from the esophagus to the gaster when standing. During sleep, peristalsis and bicarbonate secretion play a more important role in the esophageal lumen clearance process.

TISSUE RESISTANCE

Tissue resistance is not a single factor, but a unity of the intrinsic structure of the mucosa and esophageal function that interacts dynamically to minimize mucosal damage during contact with hazardous substances. Tissue resistance consists of pre-epithelial, epithelial, and post-epithelial defense mechanisms.^{8,9}

PRE-EPITHELIAL DEFENSE MECHANISM

The most important pre-epithelial defense mechanism is the mucous layer, the unstirred water layer, and the bicarbonate complex. The mucous layer resembles a gel that prohibits bacterial adherence to the epithel, and epithelial exposure to hazardous substances. Bicarbonate secretion by the cell surface into the unstirred layer protects cell damage due to lumen acidity by creating an alkaline condition from H⁺ ion re-diffusion.^{8,9}

EPITHELIAL DEFENSE MECHANISM

Epithelial defense mechanism comprise of structural and functional cell components. Structural cell components consists of the cell membrane and intercellular junctional complex that protect damage from acids by inhibiting H⁺ ion re-diffusion into the cell and intercellular spaces between the epithel.^{8,9}

POST-EPITHELIAL DEFENSE MECHANISMS

Post-epithelial defense mechanism is regulated by blood flow. Blood flow transports oxygen, nutrients, and bicarbonate, as well as releases H⁺ ions and CO₂.^{8,9}

PATHOGENESIS

Drug-induced esophagitis involve several factors, as follows:⁴

- drugs
- esophagus
- patient

DRUG FACTORS

Esophageal damage occurs due to direct effect of the drug to the esophageal mucosa and caustic effect as well as the pH of the drug, which will change the barrier of the esophageal mucosa, thus prolonging drug contact with the esophageal mucosa and will damage the esophageal wall, causing esophagitis.^{4,7,8,11}

The effect of the damage that occurs varies, since it is influenced by various factors such as the chemical nature, the concentration of chemical substances, drug

formulation, such as tablet, capsule, liquid, as well as combination with other substances.⁴

A near acidic pH of the drug, such as iron sulphate, doxy and tetracycline, and vitamin C will create severe damage of the esophagus.⁴

An in vitro study on drug pH changes prior and following dilution with 10 ml of saliva demonstrate near acid pH changes for tetracycline, salicil acid, and vitamin C,^{4,7} while the potassium chloride and quinidine do not cause pH changes. Thus, it is suspected that the level of local drug is the factor causing damage of the esophageal mucosa.⁷

Table 2. pH Changes Prior to Drug pH Diluted with 10 ml Saliva

Drug	Saliva pH	Time for dilution	pH following dilution
KCl (slow release)	6.3	>72 degrees Celsius	6.5
KCl elixir	6.4		
Doxycycline	6.1	37	3.2
Aspirin	6.3	5	3.4
Ascorbic acid	6.2	58	2.8
Tetracycline	6.2	42	1.6
Sodium phenitoin	6.2	15	10.4
Gluconic quinidine	6.4	>72 degrees Celsius	6.9

Large tablets such as gluconic quinidine with a 12 cm diameter of ½ from the normal esophageal lumen causes esophageal damage.⁴

Gelatin capsules will become sticky during the dilution process if not taken with adequate amounts of water or going through a long transit time.⁴ The capsule will get stuck in the esophagus and cause esophageal damage.⁴ A study on esophageal transit on 18 volunteers with a gelatin capsule taken with 15 ml of water demonstrated that in 11 out of 18 volunteers, the capsule would get stuck in the esophagus, while the gelatin capsule only got stuck in 3 out of 18 volunteers when taken with 120 ml of water.⁷

Aspirin and other non-steroidal anti-inflammatory agents cause direct caustic effect and a pH that changes the esophageal mucosal barrier in the process of cyto-protection.

ESOPHAGEAL FACTOR

In a great number of patients with drug-induced esophagitis, no esophageal disorder, neuro-motor abnormality, or obstruction is found. Thus, the main cause of esophageal damage is the chemical nature of the drug, drug formulation, and the patient's position when ingesting the drug.⁴

Rheumatic heart disease, enlargement of the left atrium, following surgery for mediastinal abnormality, mass, and aortal aneurysm, disturb drug passage and prolongs contact with the esophageal mucosa.⁴

Narrowing of the esophageal lumen of the aortal arc

and distal esophagus delays drug passage. In normal subjects, the aortal arc is the most common location of esophageal damage.

PATIENT FACTORS

The patient factor that influences drug-induced esophagitis is the patient's position when taking the drug, the patient's age, the amount of water taken along with the drug, the time when the drug was taken, and the amount of saliva.⁴ In several studies, drug-induced esophagitis was often found in patients taking drugs in a sleeping position. Elderly patients have a reduced production of saliva, and reduced esophageal motility, thus facilitating drug-induced esophagitis.

ESTABLISHING DRUG-INDUCED ESOPHAGITIS

The diagnosis of drug-induced esophagitis is established based on history, esophagography evaluation, and endoscopy.

HISTORY

Retrosternal pain is the most frequent complaint (61-72%) occurring after drug intake.^{1,4,5,10,11} Odinophagy, or pain when ingesting, is found in 20-40% of patients. It is caused by stimulation of pain receptors on the esophageal mucosa. Odinophagy is often caused by antibiotics, non-steroidal inflammatory agents, and alendronate. Administration of antibiotics such as doxycycline, after dilution with saliva, there is a change of pH towards acid. Such pH changes would stimulate chemical receptors on the esophageal mucosa, thus inducing pain.^{1,4,5,10,12} Disphagia found in 20-40% of patients due to esophageal stricture or stenosis is often found in patients receiving potassium chloride, quinidine, and alendronate.^{1,4,5,7}

Quinidine can cause severe esophageal damage with stricture without causing any pain.⁴

ESOPHAGOGRAPHY

Most patients with drug-induced esophagitis without complications undergo esophagogram examination using normal contrast.⁴ In the year 1983, Kikendal, et al, found 8 cases out of 143 with discrete ulcer during esophagogram. While Sakai et al found ulcer in 4 out of 6 cases using the double contrast technique.

Esophagography with contrast also assists the evaluation of external esophageal pressure, which plays a role in the pathogenesis of drug-induced esophagitis.⁴

ENDOSCOPY

Endoscopy is a good technique for determining damage of the esophageal mucosa and establishing differential diagnosis through direct inspection, biopsy, and cytological examination, as well as microbiological, when indicated. Abnormal endoscopy is found in 99% of all patients with drug-induced esophagitis. When indicated, examination is performed immediately after the onset of complaints.

During endoscopic examination, discrete erosions or ulcerations are found from pin-point to circumferential sizes over 6 cm in diameter. Focal ulceration or erosion with the absence of stenosis is found after administration of antibiotics, non-steroidal anti-inflammatory agents, and emepromium bromide.¹⁶

Drug-induced esophagitis due to quinidine, potassium chloride, and alendronate demonstrated mucosal erosion or ulceration and bleeding during endoscopic evaluation.⁴⁻⁶ Endoscopic evaluation is not an indication for patients with a history and chronology of acute retrosternal pain and drug-associated odinophagy.

VARIOUS DRUGS THAT OFTEN CAUSE ESOPHAGITIS

1. Alendronate

Sodium alendronate is an osteoclast-selective inhibitor that prevents bone resorption. Alendronate is used for treatment of post-menopause osteoporosis. The drug increases bone mass, reduces the incidence of vertebral fracture, and deformity.

The use of 40 mg of alendronate daily increases the incidence of upper gastrointestinal tract disturbance, including esophagitis and gastritis.

The pathophysiology of esophageal damage due to alendronate is caused by direct irritation of the esophageal mucosa and gastric acid reflux containing drug substances. Disturbed passage of alendronate tablet prolongs the contact between the drug and the esophageal mucosa.

After-sales studies on esophageal damage due to use of alendronate demonstrate 199 out of 1213 patients with damage of the esophageal mucosa.^{14,15} Damage of the esophageal mucosa varies, as can be found in the following table.

According to endoscopic diagnosis, damage due to alendronate may inflict all of the middle and distal esophagus.

The onset of the incidence of symptoms in this study is one week, one month, and two months after administration of alendronate. Several factors that

Table 3. Esophageal Damage in Patients Receiving Alendronate Treatment

Esophageal damage	Number of patients
Serious or severe	51
Esophageal ulcer	22
Esophagitis	21
Odinophagia	12
Dysphagia	11
Regurgitation or dyspepsia	5
Reflux esophagitis	4
Hematemesis or bleeding	2
Stricture	2

Quoted from ^{14,15}

influence esophageal damage in this study are as follows: the amount of water taken during drug ingestion, body position, and the time of drug intake.^{14,15} Esophageal damage is found in patients taking less than 180 ml of water. Patients taking the drug while not standing for approximately 30 minutes had a higher chance of esophageal damage. The same was true for those taking the drug before bed. These factors prolong contact/irritation of the esophageal mucosa by the drug, thus causing esophageal damage.

2. Tetracycline and its derivatives

Tetracycline and its derivatives are drugs that commonly cause esophagitis. Esophageal damage is caused by the corrosive nature of the drug. The pH of the drug changes to acidic after dissolving in saliva.^{4,7,16}

There are several reports of tetracycline-related esophagitis, where severe esophagitis occurring after ingestion of tetracycline with inadequate intake of water right before bed.¹⁶

Esophagitis has been reported in malaria patients treated with quinine and doxycycline. Patients complained of hiccups, and endoscopic evaluation found erosion and esophageal ulcer.^{17,18}

3. Anti-retroviral agents

Zidovudine is an anti-retroviral agent that inhibits in vitro replication of the HIV. Zidovudine is used for the treatment of AIDS and AIDS-related complex.

In drug-induced esophagitis due to zidovudine, abnormality in the form of ulcer is found in the esophagus, particularly multi-circumferential ulcer and large, single ulcers. In the patient, there was history of drug intake without water, in a sleeping position.¹⁹

TREATMENT

Drug-induced esophagitis caused by various drugs, all causing focal esophagitis, rarely with complications. The best treatment is termination of the drug in addition to supportive treatment.¹

Termination of the drug alleviates complaints and causes spontaneous healing. Analgetics are administered to eliminate the pain. H₂ receptor antagonists are administered to reduce esophageal damage due to acid. PPI such as omeprazole, rabeprazole, and lansoprazole can be used to reduce pH of gastric juice. In a majority of patients, once daily PPI therapy in the morning gives prompt relief of heartburn and heals esophagitis, within eight weeks. PPI should be given twice daily to patients who have responded poorly to a standard once daily dose.²⁰ Esomeprazole, an optical isomer of omeprazole is the first PPI to show greater efficacy than omeprazole in esophagitis erosive healing. The study from Castell et al., showed Esomeprazole (40 mg) demonstrated significantly higher healing rates than lansoprazole at week 8.²¹

Patients with odynophagia with lack of oral intake may be given intravenous fluids.^{1,4,6}

If esophageal stricture develops due to quinidine, potassium chloride and alendronate, perform dilatation and gauging.

CONCLUSION

1. Drug-induced esophagitis refers to damage of the esophageal mucosa due to local drug effects.
2. The pathogenesis of drug-induced esophagitis is by direct effect of the drug on the esophageal mucosa and caustic effect as well as drug pH, causing changes of the esophageal mucosal barrier.
3. Risk factors for drug-induced esophagitis are as follows:
 - Drug formulation, tablet size
 - Patient's age
 - History of chest surgery
 - Enlarged left atrium
 - The time, position, and amount of fluid intake during drug ingestion

SUGGESTION

Patients with high risk, particularly those receiving drugs that can potentially cause drug-induced esophagitis, should receive adequate education.

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