

Clinical and endoscopic features of pill-induced esophagitis

Dhruv Kumar M. Patel¹, Yash N. Panchal^{2*}, Maitri M. Patel³, Sanjay L. Rajput⁴,
Mukundkumar V. Patel⁵, Mayank J. Patel⁶

¹Department of Internal Medicine, Louisiana State University, Shreveport, LA, USA

²Department of Pharmacology, ⁶Department of Community Medicine, AMC MET Medical College, Maninagar, Ahmedabad, Gujarat, India

³MBBS Student, GCS Medical College, Hospital and Research Centre, Asarwa, Ahmedabad, Gujarat, India

⁴Ansh Clinic, Maninagar, Ahmedabad, Gujarat, India

⁵Department of Internal Medicine, Dr. Kiran C. Patel Medical College and Research Institute, Bharuch, Gujarat, India

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***Correspondence:**

Dr. Yash N. Panchal,

E-mail: dryashpanchal95@gmail.com

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ABSTRACT

Background: Medication can cause an injury in the esophagus by local and systemic effect, leading to esophagitis. Many such medications have been identified as a cause of pill-induced esophagitis. This study was performed to evaluate the clinical and endoscopic findings of pill-induced esophagitis.

Methods: This was retrospective observational study, conducted among patients diagnosed endoscopically with pill-induced esophagitis at Ansh gastroenterology clinic, Ahmedabad, India, from April 2017 to March 2021. The data of these patients were recorded in pre-designed case record form by evaluating their past medical records.

Results: Total 90 patients were diagnosed with pill-induced esophagitis. Retrosternal chest pain (68.9%), odynophagia (41.1%), dysphagia (25.6%), and epigastric pain (14.4%) were common clinical findings. The major culprit medications were antibiotics, and NSAIDs (non-steroidal anti-inflammatory drugs). Common esophageal endoscopic findings were ulcer (84.4%), erosion (17.8%), and active ulcer bleeding (12.2%). Kissing ulcers were observed in the majority (46.7%) of cases. The majority of ulcer and erosion were located in middle third of the esophagus. All the patients were recovered within 6 to 10 days after treatment with PPIs (proton pump inhibitors) and/or antacids, and withdrawal of the causative medication.

Conclusions: Pill-induced esophagitis commonly manifests as retrosternal chest pain, odynophagia and dysphagia, and endoscopy reveals kissing ulcer and erosion in the majority of cases. The condition can be treated with PPIs and/or antacids, and withdrawal of the offending medication.

Keywords: Pill, Esophagitis, Endoscopy, Kissing ulcer

INTRODUCTION

Pill-induced esophagitis refers to offending medication induced injury to the esophageal mucosa.¹ The first known case of pill-induced esophageal injury was reported by Pemberton et al. where culprit medication was potassium chloride tablets.² Since then, more than 650 such a case of esophageal injury has been reported,

caused by various medications.³ To date, many drugs such as antibiotics like doxycycline and tetracycline, non-steroidal anti-inflammatory drugs like ibuprofen, aspirin and naproxen, oral bisphosphonates like alendronate, and drugs like ascorbic acid, phenytoin, quinidine, rifampin, warfarin, and many more have been identified as a cause of PIE (Pill-induced esophagitis).³⁻⁶ Elderly individuals are more prone to develop pill-induced esophagitis due to

higher prevalence of esophageal motility disorders, reduction in salivation, and frequent use of high-risk drugs. According to previous reports, women are more likely than men to develop pill-induced esophagitis.

Retro-sternal chest pain, dysphagia, localized odynophagia, and epigastric pain are frequent clinical manifestations of pill-induced esophageal injury, while hematemesis is infrequent. Many clinicians, on the other hand, do not recognize this condition as a cause of chest pain or odynophagia, because in most patients, condition is self-limited, and patient recover completely, and thus this diagnosis is frequently overlooked.⁷ Although, this condition can be self-limited, but continued exposure to the causative medication might lead to serious complications such as severe ulceration, strictures, and in rare cases, perforation of the esophagus.⁸ Patients who are not diagnosed with pill-induced esophagitis early and correctly, may undergo unneeded work-up or diagnostic examination for the chest problems. To avoid such unfavorable situations, awareness of this disease must be raised. Limited understanding of this disease is available as many studies on pill-induced esophagitis are case reports, so we conducted this study. The objective of this study was to evaluate the clinical and endoscopic features of pill-induced esophagitis.

METHODS

This was retrospective observational study, conducted after the approval of study protocol by Institutional Ethics Committee (Sangini Hospital Ethics Committee, Ahmedabad). The patients presenting with the history of intake of medication and acute esophageal manifestations like retrosternal chest pain, odynophagia, dysphagia, and epigastric pain, and diagnosed endoscopically with pill-induced esophagitis at Ansh gastroenterology clinic, Ahmedabad, India from April 2017 to March 2021 were the study population.

The past medical records of such 90 patients were reviewed and evaluated. The patients of esophageal malignancy, infectious esophagitis (viral or fungal), esophageal varix, cases of esophageal injury other than esophagitis, and cases of reflux esophageal symptoms for more than two weeks were excluded. The information related to demographic details of these patients, clinical symptoms, esophageal endoscopic findings, culprit medication, formulation of medication, and treatment given were recorded in pre-designed case record form. Confidentiality of collected data was also maintained.

Data was compiled into the Microsoft Excel sheet. We used Statistical Package for the Social Sciences (SPSS) software, version 20.0 to carry out statistical analysis. Categorical data was presented as numbers and percentage, while quantitative data was presented as mean±SD. Categorical variables between two groups were analyzed using χ^2 test.

RESULTS

Among 90 patients, 37.8% (n=34) were males and 62.2% (n=56) were females. Their mean age was 48.6±16.6 years. Age and gender wise distribution of patients diagnosed with pill-induced esophagitis is given in the Figure 1.

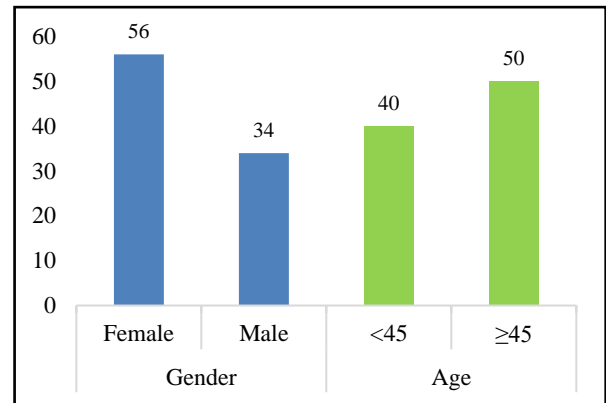


Figure 1: Age and gender wise distribution of patients diagnosed with pill-induced esophagitis (n=90).

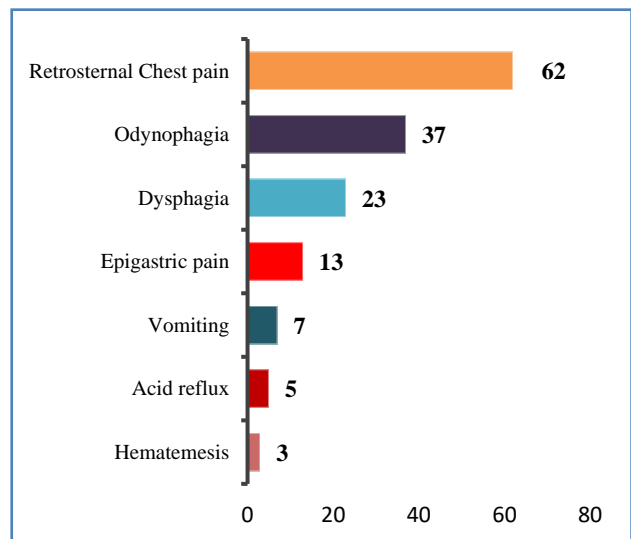


Figure 2: Clinical manifestations of patients diagnosed with Pill-induced esophagitis (n=90).

Multiple clinical manifestations were observed in our study, which appeared between 4 to 12 hours after the ingestion of drug. Common symptoms were retrosternal chest pain (n=62, 68.9%), localized odynophagia (n=37, 41.1%), dysphagia (n=23, 25.6%), and epigastric pain (n=13, 14.4%). While, vomiting (n=7, 7.8%), acid reflux (n=5, 5.6%), and hematemesis (n=3, 3.3%) were uncommon. The clinical manifestations of patients diagnosed with pill-induced esophagitis are given in the Figure 2.

In our study, ulcer and erosion of the esophagus were two common findings observed during esophageal endoscopy,

which were observed in 76 (84.4%) and 16 (17.8%) patients respectively, where 70 patients had ulcer, 10 had erosion, and 6 had both erosion and ulcer. The majority of ulcers (n=42, 46.7%) were kissing ulcers (pair of ulcers on opposite side of esophagus). The ulcers ranged in size from 5 mm to 16 mm. The ulcers were single or multiple. The majority of ulcers were found at the middle third of esophagus (76.3%), while proximal and distal esophagus was involved in the 5.3% and 18.4% cases of ulcers, respectively. Erosions were found mainly in the middle and distal third of the esophagus with a rate of 62.5%, and 31.2%, respectively. Other endoscopic findings were drug material coating (n=4, 4.4%), impacted pill fragments within ulcer (n=5, 5.6%), and active ulcer bleeding (n=11, 14.5%). Esophageal fistula,

stenosis or perforation was not observed in any patient. The esophageal endoscopic findings of these patients are given in the Table 1. Description of esophageal ulcers and erosions are given in the Table 2.

Table 1: Endoscopic findings of patients diagnosed with pill-induced esophagitis (n=90).

Endoscopic findings	Number of patients (%)
Ulcer	76 (84.4)
Erosion	16 (17.8)
Active ulcer bleeding	11 (14.5)
Impacted pill fragment	5 (5.6)
Drug material coating	4 (4.4)

Table 2: Description of esophageal ulcers and erosions.

Features	Location	Number	Appearance	Size
Ulcer (n=76)	Proximal third=4	Single=24 Multiple=52	Kissing=42	5-16 mm
	Middle third=58		Geographical=25	
	Distal third=14		Oval=5 Circular=4	
Erosion (n=16)	Proximal third=1	Single=2 Multiple=14		
	Middle third=10			
	Distal third=5			

Table 3: Offending medications for pill-induced esophagitis (n=90).

Drug	Number of patients (%)
Doxycycline	22 (24.4)
Tetracycline	11 (12.2)
Ibuprofen	11 (12.2)
Naproxen	9 (10)
Clindamycin	8 (8.9)
Aspirin	7 (7.8)
Alendronate sodium	5 (5.6)
Ascorbic acid	4 (4.4)
Ferrous sulfate	3 (3.3)
Warfarin	2 (2.2)
OCP	2 (2.2)
Metronidazole	2 (2.2)
Ciprofloxacin	2 (2.2)
Amoxicillin	2 (2.2)

We discovered 7 different classes of the drugs as a cause of esophageal injury. The major culprit drugs were antibiotics, mainly doxycycline, tetracycline, clindamycin, metronidazole, ciprofloxacin, and amoxicillin in 47 (52.2%) patients. NSAIDs (non-steroidal anti-inflammatory drugs) mainly aspirin, ibuprofen, and naproxen, which was responsible for 27 (30%) cases, were the second common drug class. While other culprit drugs were alendronate in 5 (5.6%) patients,

ascorbic acid in 4 (4.4%) patients, ferrous sulfate in 3 (3.3%) patients, warfarin in 2 (2.2%) patients, and oral contraceptive pill in 2 (2.2%) cases. Capsule form of the drug was responsible for 55 (61.1%) cases, while tablet form accounted for 35 (38.9%) cases. Antibiotics were shown to be a more common cause of pill-induced esophagitis in younger patients (<45 years) than in elderly patients (≥45 years) (67.5% versus 40%, p=0.017, significant at p<0.05, χ^2 test), while no such significant difference was observed between the two age groups with NSAIDs as an offending medication (32.5% versus 28%, p=0.81, not significant at p<0.05, χ^2 test).

Among the 90 cases, 38 (42.2%) patients had a history of drug intake with insufficient amount of the water, 14 (15.6%) patients had history of medication intake in recumbent position, and 4 (4.4%) patients reported intake of medication just before going to the bed. While history of both; medication intake with insufficient water and in recumbent position was found in 21 (23.3%) patients, and none of these factors were observed in 13 (14.4%) patients. Offending medications for pill-induced esophagitis are given in the Table 3.

All the patients were recovered within 6 to 10 days after withdrawing the causative drug and treatment with proton pump inhibitors and/or antacids. Fifteen patients (16.7%) underwent for follow-up endoscopy and revealed healed ulcers or normal esophagus mucosa. The remaining 75 (83.3%) patients were non-symptomatic and didn't

undergo for follow-up endoscopy or refuse for the endoscopy.

DISCUSSION

According to the literature, pill-induced esophagitis is more frequently observed in the females than in males, this might be attributable to the fact that women consume more culprit medications than men.⁹ Female gender dominance was also observed in our study, where 56 (62.2%) patients were females. Pill, patient, and esophageal motility disorders related factors are responsible in the development of pill-induced esophagitis. The chemical structure and pharmaceutical form of the pill are the most important pill-related factors because the capsule form might adhere to the esophagus and pose a greater risk than the tablet dosage form.¹⁰ Capsule forms of doxycycline, tetracycline, clindamycin, ferrous sulfate, and ibuprofen accounted for 61.1 % cases in our study. Intake of medication with insufficient amount of water and/or intake in recumbent position or maintaining recumbent position after intake are major patient related predisposing risk factor for pill-induced esophagitis, these risk factors were observed in 77 (85.6%) cases in our study.¹¹ The esophageal factors are related with esophageal disorders of motility or structural anomalies such as esophageal varix.¹² We did not perform esophageal motility studies in any patient, however no esophageal dysmotility or structural anomalies were discovered during endoscopy. According to reports, elderly individuals are more likely to suffer from pill-induced esophageal damage than younger ones, as they consume more medications including NSAIDs or bisphosphonates due to multiple co-morbidities, have more disorders of esophageal motility or compression of middle esophagus due to cardiac enlargement, and are less aware about the instructions of medication use.¹³ The esophageal transit time was shown to be significantly longer in elderly individuals than in younger subjects in a study.¹⁴ But pill-induced esophageal injury can be seen in different age groups with different medications. In our study, the proportion of elderly patients (≥ 45 years) with pill-induced esophagitis was higher than younger patients (55.6% versus 44.4%). But, in younger patients, antibiotics were found to be more common cause of pill-induced esophagitis than in elderly patients (67.5% versus 40%).

Symptoms of pill-induced esophagitis may appear from hours to ten days after taking the medication, according to Boyce.¹⁵ Commonly reported clinical manifestations are retrosternal chest pain, localized odynophagia, dysphagia, and epigastric pain.^{16,17} In our study, the majority of patients experienced multiple clinical symptoms, which appeared between 4 to 12 hours after medication intake, where the most frequent clinical finding was retrosternal chest pain (68.9%), followed by odynophagia (41.1%) and dysphagia (25.6%), while hematemesis was an infrequent finding (3.3%).

In case of pill-induced esophageal injury, commonly observed endoscopic findings are esophageal ulcer, and erosion, while active ulcer bleeding, impacted pill fragment, and drug material coating has also been observed.¹⁸ Esophageal ulcer and erosion were two common endoscopic findings observed in our study. The shape of the esophageal ulcers was oval, kissing, geographical, and circular shaped, where kissing ulcers were evident in the majority (46.7%) of cases, which is consistent with previous study.⁷ But as kissing ulcers are also found in esophageal injury other than pill-induced esophagitis, they are not pathognomonic.¹⁹ Higuchi et al. in his study discovered the etiologies of esophageal ulcers as RE (Reflux esophagitis) in 65.9% cases, pill-induced esophagitis in 22.7% cases, and infectious (viral/fungal esophagitis) in 11.4% cases.²⁰ If esophageal ulcers are discovered during endoscopy, reflux esophagitis or pill-induced esophagitis should be considered initially if no other disorders (example- viral/fungal esophagitis, Crohn's disease, or Levin tube injury) are suspected. Higuchi et al also discovered that the majority (91.4%) of ulcers in case of RE were located in the lower esophagus, while 80% of ulcers were located in the middle esophagus in case of pill-induced esophagitis.²⁰ Other studies also discovered that middle third of the esophagus is common site of lesions in case of pill-induced esophagitis, which was also seen in our study, where 76.3% of esophageal ulcer, and 62.5% of esophageal erosion were found in the middle third of the esophagus.^{21,22} Because the aortic arch or enlarged left atrium compress the middle third of the esophagus, which makes the passage of pill difficult, pill-induced esophagitis is common there.¹⁰ Thus, RE can be differentiated from pill-induced esophagitis based on the location of the esophageal ulcers, and individual with typical reflux esophagitis have persistent reflux symptoms, while patient with pill-induced esophagitis presents with sudden onset chest symptoms. Active ulcer bleeding was evident in 45% of pill-induced esophageal ulcers in study by Higuchi et al., compared to 14.5% in ours.²⁰ This difference is attributed to difference in the proportion of patients taking NSAIDs (65% versus 30%). Based on these findings, when NSAIDs are culprit medications, pill-induced esophagitis should also be considered as a cause of upper gastrointestinal bleeding.

Prolonged exposure to the offending medication can lead to serious complications such as severe ulceration, stricture and, in rare cases, perforation of the esophagus. Up to one-third of patients may develop a stricture, and life-threatening hemorrhage and perforation of the esophagus.²³ Broncho-esophageal fistula has also been documented.²³ None of such complications were found in our study.

Seven different drug classes were identified as a cause of pill-induced esophagitis, in our study. Antibiotics (Tetracycline, doxycycline, and their derivatives) are the most frequent or second most common cause of pill-induced esophagitis, according to the literature.^{2,24}

Antibiotics were the commonest (52.2% cases) offending medications in our study, followed by NSAIDs in 30% cases. Our study found that offending medications were different between different age groups, where a proportion of antibiotics as an offending medication was significantly higher among the younger patients, but proportion of NSAIDs as a cause of pill-induced esophagitis did not show any significant difference between two age groups. Medication may cause esophageal mucosal damage in various ways. The suspected mechanism in case of tetracycline is thought to be corrosive damage by solution (formed when tetracycline dissolved in water) with very low pH.²³

The gold standard for diagnosing pill-induced esophagitis is upper gastrointestinal endoscopy, which enables for the identification of mucosal changes, taking biopsy sample in suspected case of malignancy, and intervention in esophageal bleeding.¹⁶ Histopathological investigation should only be performed to rule out malignancy and infectious diseases, especially when malignancy or infectious pathologies are suspected. In our study, patient presenting with history of intake of suspected medication, and typical clinical manifestations were subjected for esophageal endoscopy, and endoscopic findings were sufficient to establish the diagnosis. As no malignancy or infectious pathologies were observed during endoscopy, we did not take biopsy in any patient for histopathological examination. To treat pill-induced esophagitis, first the culprit medication is discontinued, followed by the supportive therapy with PPI and/or antacids. With their acid-inhibiting properties, PPIs are found to be effective, whereas antacids have acid neutralizing property. The majority of mucosal lesions heal within few days to weeks after discontinuation of culprit medication.²⁵ We also treated all the patients with PPIs and/or antacids in different dose and duration, after discontinuing offending medication, and quick clinical recovery (within 6-10 days) was observed in all the patients. We performed follow-up endoscopy in fifteen patients to look for mucosal healing, which revealed normal esophageal mucosa or healed ulcers. With appropriate patient education, pill-induced esophagitis can be prevented to a considerable extent. Patients should be educated to take medications with sufficient amount of water (at least 100 ml) and in upright position, and to remain upright for some time after medication intake.

CONCLUSION

Many drugs, particularly antibiotics like doxycycline, tetracycline, and clindamycin, and NSAIDs can cause esophageal injury. Pill-induced esophagitis should be suspected in the patient presenting with the history of intake of suspected medication and typical clinical manifestations such as retrosternal chest pain, localized odynophagia, dysphagia, epigastric pain, and vomiting. Diagnosis is confirmed by upper GI endoscopy. Endoscopic findings reveal kissing ulcer and erosion in the majority of cases. Histopathological examination is

usually not required unless there is strong suspicion of malignancy. Pill-induced esophagitis can be prevented to a considerable extent by educating the patients about taking medications with sufficient amount of the water and in sitting up position, both of which are major predisposing risk factors.

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