

## Original Article

# Clinical and Endoscopic Characteristics of Medication Induced Esophageal Injury

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### Abstract:

Medications can cause several complications in the esophagus and lead to medication-induced esophageal injury. This study was carried out among patients diagnosed as medication-induced esophageal injury from June 2015 to October, 2018 in the Department of Gastroenterology, Enam Medical College and Hospital, Savar, Dhaka to investigate clinical and endoscopic characteristics of medication-induced esophageal injury as well as outcome of these patients with treatment. Patients diagnosed as malignancy, viral or fungal esophagitis, esophageal varix, corrosive and sclerotherapy induced ulcer and GERD were excluded. Clinical and endoscopic characteristics of patients diagnosed as medication-induced injury were analyzed. After given treatment, clinical improvements as well as mucosal healing of oesophageal injury were noted. Thirty seven patients were diagnosed as medication-induced esophageal injury. Their median age was 40; 17 were males and 20 were females. Common symptoms were chest pain (94.6 %), odynophagia (78.4 %) and dysphagia (62.2 %). Symptoms appeared between 3 hours to 15 hours after ingestion of medication. Predisposing factors for 75.67% of the patients were related to taking the medicine with insufficient water or in recumbent position, or both. The main causative agents were antibiotics, Non-steroidal anti-inflammatory drugs (NSAIDs) and Alendronate sodium. Common diseases that required treatment with these drugs were various urinary system diseases, osteoporosis and migraine. During endoscopy, 25 had only ulcer, 7 had only erosion and 5 had both ulcer and erosion. Most of the ulcers and erosions were located at the middle third of the oesophagus with a rate of 70%, and 58.3% respectively. Appearance of the ulcer was oval, circular, kissing and geographical shaped and their sizes vary between 6 mm to 18 mm and single or multiple in numbers. All the patients were treated with proton pump inhibitors (PPIs) or sucralfate, and the causative drugs were discontinued. Symptoms resolution occurred within 5 to 12 days after treatment and mucosal healing were detected in all patients after 4 weeks who were performed endoscopy. Almost every kind of medication, particularly doxycycline, NSAIDs can cause oesophageal ulcer and erosion. It can be successfully treated with PPIs and discontinuation of the causative medication and prevented by warning patients about drinking water sufficiently and sitting up while taking the pill.

**Key words:** Oesophageal Injury, Doxycycline, Capsule, Female gender, Endoscopy.

### Introduction:

Medication-induced esophageal injury may occur at any age and with a variety of commonly used medications<sup>1</sup>. They presented in different spectrums of

injury such as mucosal erosion, ulceration, bleeding, penetration, stricture and perforation on the esophagus<sup>2</sup>.

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Almost 100 different substances have been implicated. The majority of cases are caused by tetracycline, doxycycline, potassium chloride, non steroidal anti inflammatory drugs (NSAIDs), and alendronate sodium<sup>3-5</sup>. The overall incidence of medication induced oesophageal injury has been estimated at 0.004% per year in United States of America, but ranges from 0.04% for alendronate sodium to as high as 20% for NSAIDs. Because of the frequent use of high-risk medications, decreased salivation, and a higher prevalence of esophageal dysmotility, elderly patients are at increased risk for medication induced esophageal injury. Similarly, women are more likely to be treated with high-risk medications and are twice as likely as men to have medication induced esophageal injury<sup>5, 6</sup>.

Many clinicians do not recognize the medication induced injury as a cause of chest pain or odynophagia.

The majority of the patients usually report self-limited symptoms, so the diagnosis is often underestimated<sup>7</sup>. However, lack of awareness of medication-induced injury can lead to persistent exposure to causative medicines, resulting in severe complications<sup>8,9</sup>. Patients who are not initially accurately diagnosed as medication induced injury may suffer from unnecessary work-up or extensive diagnostic evaluation for chest symptoms. To avoid these undesirable situations, awareness of this disease must be improved. Nonetheless, most of the studies on medication induced esophageal injury are case reports or reviews of case reports, which provide limited understanding of this disease. Aim of this study was to investigate the clinical and endoscopic characteristics of medication induced esophageal injury and outcome of these patients with treatment.

### Materials and Methods:

This prospective observational study was performed in the Department of Gastroenterology Enam Medical College and Hospital, Savar, Dhaka, over a period from June 2015 to October, 2018. Thirty seven patients, aged 15-70 years were diagnosed having medication induced esophageal injury on endoscopy. These patients with a definite history of taking medicines and having temporal relationship between medication intake & acute esophageal symptoms (chest pain, odynophagia and dysphagia) occurred in less than two weeks time were considered having medication induced esophageal injury.

Patients' demographic features, clinical history, medications intake history, primary indication of medication intake, medication formulation and other oesophageal comorbidities were recorded. Informed written consent was taken for every patient during endoscopy. All endoscopic procedures were carried out using a PENTAX® Video endoscope (PENTAX Corporation, Japan). Endoscopic features such as the location, size and number of ulcers on the esophagus were recorded and described. The number and location of the erosions on the oesophagus were also described.

*Esophageal ulcer* was defined as a discrete break in the esophageal mucosa with a clearly identifiable margin. The term *oesophageal* erosion refers to a superficial lesion that remains confined to the lamina propria and muscularis mucosa. Endoscopic characteristics of ulcer were larger size usually more than a few millimeters (5 mm or more), excavated with distinct border, usually single. Endoscopic characteristics of erosion were small, a few millimeters, flat, often indistinct border, usually multiple. Erosions or ulcers may appear isolated or confluent and they commonly coexist with one another.

Patients with malignancy, viral or fungal esophagitis, esophageal varix and esophageal ulcers after sclerotherapy, corrosive injury and connective tissue disorders manifested on esophagus were excluded. Patients with esophageal reflux symptoms that were persistent for greater than two weeks were also excluded.

Treatment was given with proton pump inhibitors and sucralfate. Seven days after treatment follow up was done to see the clinical improvement. Four weeks after completion of treatment, patients who agreed, had undergone upper gastrointestinal endoscopy to see the mucosal healing of oesophageal injury. Statistical Package for Social Sciences (SPSS) for Windows 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data were entered into a database and were verified by a second independent person. Data are presented as mean  $\pm$  SD numerical/quantitative data and as percentage and numbers for categorical data.

### Results:

#### *Demographic profile:*

Among the patients diagnosed as medication-induced esophageal injury; 17 were males and 20 were females. Their age range was from 15 to 70 with a median of 40; 30 (81%) were married, 5 (13.5%) were unmarried and 2 (5.4%) were divorced. Regarding occupation, 12 (32.4%) were house-wives, 11 (29.7%) were businessmen, 9 (24.3%) were service holder, 4 (10.8%) were farmers and 1 (2.7%) was student. According to educational qualification, 5 (13.5%) were Illiterate, 4 (10.8%) studied up to Class X, 5 (13.5%) passed SSC, 9 (24.3%) passed HSC, 13 (35.1%) were Graduate and 1 (2.7%) was postgraduate.

Their average monthly income also varied, 8 (21.6 %) had < 5000 taka/month, 15 (40.5%) had 5000 to 20,000 taka/month and 14 (37.8 %) had > 20,000 taka/month.

#### *Clinical presentations:*

Majority of the patients had multiple clinical presentations; symptoms appeared between 3 to 15 hours after ingestion of medication. Clinical presentations of patient diagnosed as medication-induced esophageal injury are given in the Table I.

**Table I:** Distribution of patients according to Clinical presentations (n=37).

Clinical Presentations	Number of Patients (%)
Chest pain	35 (94.6)
Painful swallowing	29 (78.4)
Dysphagia	23 (62.2)
Epigastric pain	8 (21.6)
Acid reflux	3 (8.1)
Haematemesis	2 (5.4)

**Medication type, Consumption history and Formulation:**

Among the patients; 15 (40.54%) had a history of medication intake with insufficient water, 5 (13.51%) described ingestion of medication in recumbent position, 2 (5.4%) patients described medication intake just shortly before going to bed, 8 (21.6%) had a history of drinking insufficient water and in recumbent position, and neither of these factors were found in 7 (18.9%) patients.

For 37 cases, we found a total of 7 different classes of medications that caused esophageal injury. The most common medication is Doxycycline and Tetracycline and they are 11 (29.7%) and 5 (13.5%) respectively. The second common cause was non-steroidal anti-inflammatory drugs (NSAIDs), and then Clindamycin and Alendronate Sodium. Capsule formulations were found in 25 (67.56%) and tablet formulations were found a in 12 (32.43%). Capsule was the frequent formulation for the medications found. (Table II)

**Table II:** Distribution of patients according to medications responsible for oesophageal injury (n=37)

Drug	Frequency (%)
Doxycycline	11 (29.7)
Tetracycline	5 (13.5)
Ibuprofen	3 (8.1)
Naproxen	3 (8.1)
Alendronate Sodium	4 (10.8)
Ferrous sulfate	3 (8.1)
Clindamycin	6 (16.2)
Ciprofloxacin	1 (2.7)
Oral Contraceptive pill	1 (2.7)
Total	37 (100)

The most frequent primary diseases that required treatment were various urinary system diseases (USDs), osteoporosis and migraine. The primary diseases for which patients took medications are given in Table III.

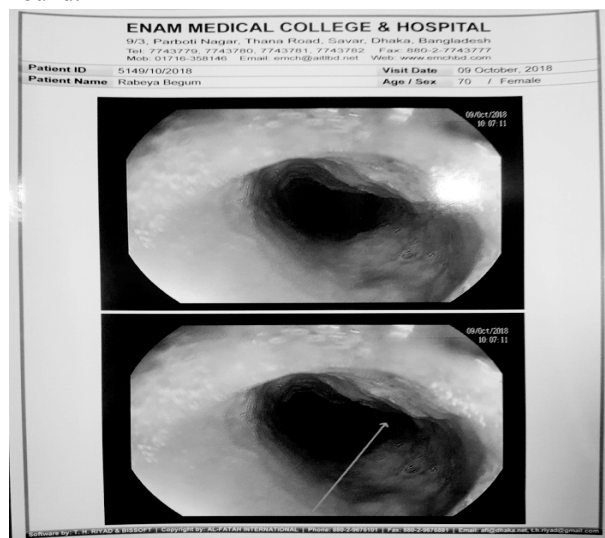
**Table III:** Distribution of patients according to primary diseases for which medications were taken (n=37).

Primary Disease	Frequency (%)
Urinary system disease	12 (32.4)
Acne vulgaris	2 (5.4)
Menstrual disorder	1 (2.7)
Contraception	1 (2.7)
Depressive disorder	1 (2.7)
Anxiety	1 (2.7)
Migraine	5 (2.7)
Sinusitis	1 (2.7)
Osteoporosis	5 (13.5)
Seborrheic dermatitis	1 (2.7)
Anemia	2 (5.4)
Epilepsy	1 (2.7)
Gingivitis	1 (2.7)
Ulcer	3 (8.1)
Total	37 (100)

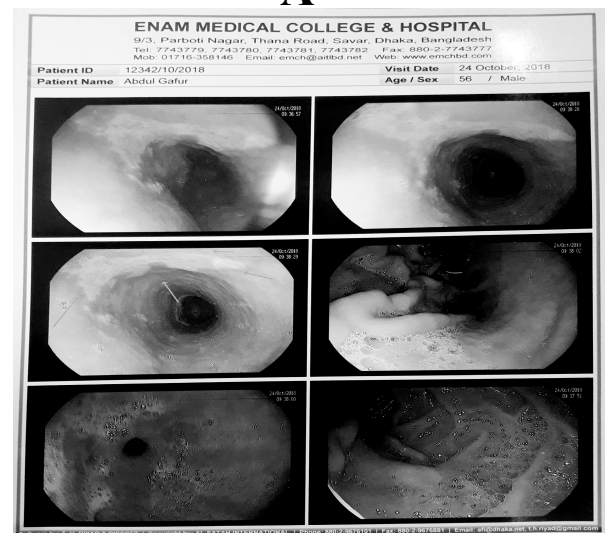
**Endoscopic feature:**

During endoscopy, ulcer and erosion were detected in 30 (81%) and 12 (32%) patients respectively. Among them 25 had only ulcer, 7 had only erosion and 5 had both ulcer and erosion. Ulcers were located at the proximal, middle and distal third of the oesophagus with a rate of 6.66%, 70%, and 23.3%, respectively. Erosions were located at middle and distal third of the oesophagus with a rate of 58.3% and 41.66% respectively.

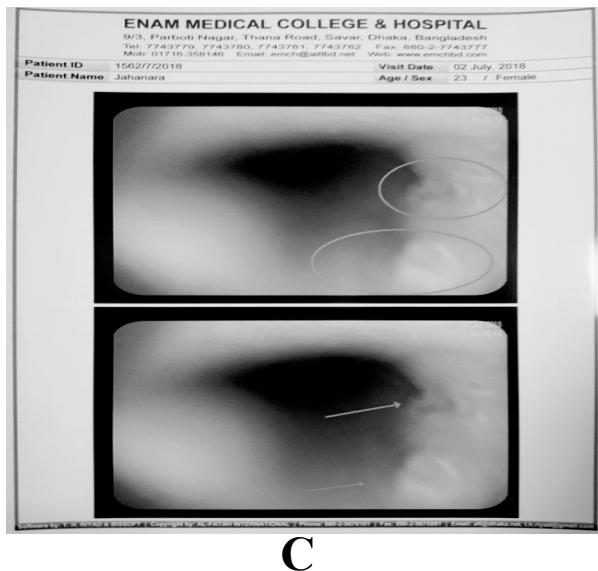
Endoscopic appearance of the ulcer was oval, circular, kissing and geographical shaped. The sizes of the ulcers varied between 6 mm to 18 mm and these were single or multiple in number (Table IV). During endoscopy only 3 patients had evidence of haemorrhage. No oesophageal stenosis, fistula and perforation were found.



**A**



**B**



**Figure I:** Endoscopic finding of medication-induced oesophageal injury. A & B: Ulcers in the middle third of esophagus; B: Typical kissing ulcer in the middle third of esophagus.

**Table IV: Endoscopic features of medication-induced esophageal injury.**

Features	Location	Number	Appearance	Size
Ulcer (n-30)	Proximal third=2	Single=10	Oval=4	6-18 mm
	Middle third=21	Multiple=20	Circular=5	
	Distal third=7		Geographical=11 Kissing=10	
Erosion (n-12)	Proximal third=0	Single=0		
	Middle third=7	Multiple=12		
	Distal third=5			

Out of 37 patients, 30 patients had ulcer and 12 patients had erosion (25 had only ulcer, 7 had only erosion and 5 had both ulcer and erosion).

During treatment different Proton Pump Inhibitors (PPIs) and Sucralfate were used in different periods and doses. Symptoms resolution occurred within 5 to 12 days after treatment. Due to refusal of the patients, endoscopy could only be performed in 11 patients to see the mucosal healing. Full mucosal recoveries were detected after 4 weeks in the patients those were performed endoscopy. No oesophageal penetration, perforation, and stricture were seen in follow up endoscopy.

## Discussion:

In our study, we found that the most common offender medications for oesophageal injury is doxycycline (and tetracycline), next is non steroidal anti-inflammatory drugs (NSAIDs) and clindamycin is the third common. Oesophageal injury was seen more often in the female gender who used the capsule form of the medicine. Medication induced oesophageal injury is seen more frequently in female gender in case series of the literature<sup>10-12</sup>. In our study, female gender dominance is seen. In the literature, most of the cases ranged between ages 20 to 40 years, while medication induced oesophageal injury can be seen in different ages with different medications<sup>13,14</sup>. Most of our patients were young individuals less than 40 years and in their reproductive age and they used doxycycline for indications, such as USD and acne vulgaris. Tetracycline, doxycycline, and their derivatives are by far the most common causes of medication-induced oesophageal injury, as many cases reported<sup>17</sup>, in our study we also found the same.

In addition, we also found that predisposing factors of medication-induced oesophageal injury is almost always associated with a history of taking medications with insufficient water and/or taking medications in recumbent position or maintaining recumbent position after ingestion of the medications (75.67%); these two are preventable predisposing factors.

Common clinical presentations are chest pain, painful swallowing and dysphagia reported with varying frequencies in the literatures<sup>10,12,14</sup>. In this study, the most frequent clinical presentation was chest pain 94.6% (35), next common was painful swallowing 78.4% (29), while hematemesis was an uncommon clinical presentation. Majority of the patients had multiple clinical presentations.

Various factors relating to the medication, patient, and esophagus play a role in developing medication induced oesophageal injury. The most important medication related factors are the chemical structure and pharmaceutical form of the medication, because the capsule form can adhere to the esophagus and pose a higher risk than the tablet form<sup>15,16</sup>. Capsule forms of medication, such as doxycycline, tetracycline, clindamycin, ferrous sulfate, account for 67.5 % of injuries in our cases. The most important patient-related factors are insufficient water consumption and taking drugs in recumbent position. These two factors together or separately played role in 75.67% in our patients. The factors related to the esophagus are mostly associated with motility disorders or structural abnormalities such as luminal narrowing and varix<sup>15</sup>. We did not do motility studies but during endoscopy no esophageal dysmotility or structural lesions were found.

In this study, 7 different classes of medicines led to medication induced oesophageal injury were identified. Medication can lead to mucosal damage of the esophagus in different ways. The mechanism of injury is felt to be corrosive damage because tetracycline dissolved in water produces a solution with a very low pH<sup>18</sup>. In this study, doxycycline and tetracycline were the most frequent offending drugs (43.2%). NSAIDs are another common cause of medication-induced esophageal injury. Aspirin, naproxen, indomethacin and ibuprofen account for the majority of cases<sup>17</sup>. Not surprisingly, hemorrhage, which may be severe<sup>19</sup>, is a common complication of these esophageal ulcers, especially when compared with other medication related esophagitis. Broncho-esophageal fistula has also been reported<sup>20</sup>. Notably, it is over-the-counter use of NSAIDs that is most commonly associated with injury<sup>21</sup>, in keeping with their more commonly used venue. We found 6 NSAIDs including naproxen and ibuprofen as the offending medications. Bisphosphonates, used to treat osteoporosis, has in fact become the most prevalent cause of medication-induced esophagitis; to date, injury has been reported mostly with alendronate<sup>22, 23</sup>. Reflux-type symptoms are common and can be difficult to distinguish from medication-induced mucosal injury. Diagnosis is best made endoscopically, with marked exudates and inflammation. Stricture formation occurs in up to one third of patients<sup>17</sup>, and life-threatening hemorrhage<sup>24</sup> and esophageal perforation<sup>25</sup> have been reported. In our study, bisphosphonates were responsible for oesophageal injury in 4 cases.

Upper gastrointestinal endoscopy is the gold standard for diagnosis of medication-induced oesophageal injury. It allows the detection of the mucosal changes, taking biopsy sampling, and intervening in bleeding and other complications of the esophagus<sup>10,12,16,26</sup>. In the upper GI endoscopy, we found that most of the ulcers were located in the middle third of the esophagus (n-21), which is compatible with the literature<sup>10,14</sup>. Although the histopathological examination is rarely pathognomonic, it is generally non specific and includes mostly benign ulcer and acute inflammatory changes<sup>13</sup>. However; histological evaluation should only be performed for differential diagnosis, especially in cases where malignancy and infectious pathologies are suspected. In this study, patient presented with typical clinical feature and history of medication usage. So, endoscopic appearances were sufficient to establish the diagnosis. While no infectious or malignant changes were suspected during endoscopy we could not take biopsy for histopathological examination.

Medication induced oesophageal injury can largely be prevented with appropriate patient education. Patients should be instructed to ingest medications in an upright

position with at least 100 ml of fluid, and to remain upright for 30 min after ingestion. If possible, patients with known esophageal compression, stricture, or dysmotility, and those patients confined to a bed, should avoid medications most frequently associated with esophageal injury<sup>5</sup>. In most cases, drugs are discontinued first, and supportive treatments, such as PPI, sucralfate are introduced. PPIs are found to be very effective with their acid-inhibiting properties, while sucralfate has local protective barrier and cytoprotective effects. Most mucosal lesions heal within days to weeks of withdrawal of the offending agent<sup>4-6,13,27</sup>. In our cases, the offender drug was immediately stopped, and supportive treatment was started, along with PPIs and/or sucralfate in different doses and periods. Thus, rapid clinical (within 5-12 days) recovery was achieved for all patients. Due to refusal of the patients, follow up endoscopy could only be performed in 11 patients to see the mucosal healing. Full mucosal recoveries were detected after 4 weeks. No oesophageal penetration, perforation, and stricture were seen.

#### **Limitation of the study:**

This study was an observational study and lacks a control group. Therefore, it is difficult to measure the significance of the descriptive results. However, from the results of our study on 37 subjects, the clinical characteristics, common endoscopic findings and main causative medications could be identified. Motility study was not done to detect oesophageal dysmotility. Biopsy and histopathology was not done to exclude malignancy or infectious etiology.

#### **Conclusion:**

Almost every kind of medications, especially the doxycycline and tetracycline, can cause ulcer in the esophagus. Diagnosis of medication induced oesophageal injury can be performed easily with a history of intake offending medication, clinical presentation, and upper GI endoscopy. Histopathological evaluation is generally unnecessary, unless high suspicion of malignancy or infectious etiology exists. Medication induced oesophageal injury can be prevented to a large extent by warning the patients about sufficient intake of drinking water and sitting up position while taking the medication, which are the major predisposing factors.

**References :**

1. Katzka DA. Esophageal Disorders Caused by Medications, Trauma, and Infection. In: Feldman M, Friedman LS, Brandt LS (editors). Sleisenger Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. 9<sup>th</sup> ed. Saunders; 2010.p.735-37.
2. Dag MS, Ozturk ZA, Akin I, Tutar E, Cikman O, Gulsen MT. Drug-induced esophageal ulcers: Case series and the review of the literature. Turk J Gastroenterol. 2014;25:180-4.
3. Dellon ES, Shaheen NJ. Miscellaneous diseases of the esophagus: Foreign bodies, physical injury, and systemic and dermatological diseases. In: Tadataka Yamada (editor). Textbook of Gastroenterology.5th ed. Blackwell Publishing; 2009.p.877.
4. Jaspersen D. Drug-induced oesophageal disorders: pathogenesis, incidence, prevention and management. Drug Saf. 2000;22(3):237-49.
5. Kikendall JW. Pill esophagitis. J Clin Gastroenterol. 1999;28(4):298-305.
6. Winstead NS, Bulat R. Pill Esophagitis. Curr Treat Options Gastroenterol. 2004;7(1):71-76.
7. Zografos GN, Georgiadou D, Thomas D, Kaltsas G, Digalakis M. Drug-induced esophagitis. Dis Esophagus. 2009;22(8):633-37.
8. Cummin AR, Hangartner JR. Oesophago-atrial fistula: a side effect of tetracycline? J R Soc Med. 1990;83:745-46.
9. Henry JG, Shinner JJ, Martino JH, Cimino LE. Fatal esophageal and bronchial artery ulceration caused by solid potassium chloride. Pediatr Cardiol. 1983;4(3):251-52.
10. Abid S, Mumtaz K, Jafri W, Hamid S, Abbas Z, Shah HA et al. Pill-induced esophageal injury: endoscopic features and clinical outcomes. Endoscopy 2005; 37:740-44.
11. Yap I, Guan R, Kang JY, Gwee KA, Tan CC. Pill induced oesophageal ulcer. Singapore Med J. 1993;34:257-58.
12. Kadayifci A, Gulsen MT, Koruk M, Savas MC. Doxycycline-induced pill esophagitis. Dis Esophagus. 2004;17(2):168-71.
13. Fernandes PA, Pires MS, Gouvea AP. Ulcerative esophagitis associated with the use of alendronate sodium: histopathological and endoscopic features. Arq Gastroenterol. 2002;39(3):173-76.
14. Fernandopulle AN, Navarathne NM. Oesophageal injury suspected to be due to doxycycline ingestion. Ceylon Med J. 2011;56(4):162-63.
15. Valean S, Petrescu M, Catinean A, Chira R, Mircea PA. Pill esophagitis. Rom J Gastroenterol. 2005; 14(2):159-63.
16. Champel V, Jonville-Bera AP, Bera F, Autret E. Esophageal involvement after tetracycline ingestion. Therapie. 1997;52(6):587-89.
17. Kikendall JW. Pill-induced esophageal injury. In: Castell DO, Richter JE (editors). The esophagus, 4<sup>th</sup> ed. Philadelphia: Lippincott Williams & Wilkins;2004:572.
18. Bonavina L, DeMeester TR, McChesney L, Schwizer W, Albertucci M, Bailey RT. Drug-induced esophageal strictures. Ann Surg. 1987;206(2):173-83.
19. Schreiber JB, Covington JA. Aspirin-induced oesophageal haemorrhage. JAMA. 1988;259:1647-48.
20. McAndrew NA, Greenway MW. Medication-induced esophageal injury leading to broncho-esophageal fistula. Postgrad Med J. 1999;75:379-81.
21. Kahn LH, Chen M, Eaton R. Over-the-counter naproxen sodium and esophageal injury. Ann Intern Med. 1997;126(12):1006.
22. Ribeiro A, DeVault KR, Wolfe JT, Stark ME. Alendronate-associated esophagitis: Endoscopic and pathologic features. Gastrointest Endosc. 1998;47(6):525-28.
23. Abdelmalek MF, Douglas DD. Alendronate-induced ulcerative esophagitis. Am J Gastroenterol. 1996;91:1282.
24. DeGroen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, Freedholm D. Esophagitis associated with the use of alendronate. N Engl J Med. 1996;335:1016-21.
25. Famularo G, De Simone C. Fatal esophageal perforation with alendronate. Am J Gastroenterol. 2001;96:3212-13.
26. Pace F, Antinori S, Repici A. What is new in esophageal injury (infection, drug-induced, caustic, stricture, perforation)? Curr Opin Gastroenterol. 2009; 25(4): 372-79.
27. Candelli M, Carloni E, Armuzzi A , Cammarota G, Ojetti V, Pignataro G, et al. Role of sucralfate in gastrointestinal diseases. Panminerva Med 2000;42(1):55-59.