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Case Report

Drug-Induced Esophagitis in Pediatrics: Case Series of 5 Patients

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Received: September 19, 2019; **Published:** October 29, 2019

Abstract

Drug induced esophagitis is an inflammation of the esophagus caused mainly by pill ingestion. There is an under-diagnose of this disease due to lack of awareness in pediatric patients. We retrospectively reviewed the files of 1049 upper gastrointestinal endoscopies performed between January 2015 to February 2019 in Hospital Metropolitano de Quito and recruited 5 pediatric patients that presented drug-induced esophagitis diagnosed clinically and by upper endoscopy, the treatment was also evaluated. Afterwards we established the frequencies, means and standard deviation. From the patients included 3 were males and 2 females with a mean age of 14.6 ± 1.9 years. The main symptom was retrosternal pain as it was present in 80% of the patients (n = 4). The most common causative agent was L-Arginine (n = 3), in 1 patient calcium, and in 1 patient doxycycline. The main endoscopic findings were; esophageal ulcers; number, size, and depth were variable. An adequate diagnosis of this clinical entity could avoid unnecessary investigations, clear indications by the pediatrician about the adequate intake of medications could avoid this pathology. Further studies are necessary in order to evaluate the treatment of drug induced esophagitis in pediatric patients.

Keywords: *Drug-Induced Esophagitis; Pediatrics*

Introduction

Drug-induced esophagitis is a clinical problem secondary to esophageal injury after the ingestion of drugs, and more specifically pills [1,2]. The prevalence of this disease in children is unknown, in the general population the incidence described is 4-7:100000 cases, but it has been considered that it might be higher due to the rise in drug prescriptions and because it is frequently subdiagnosed.

It should also be noted that pill esophagitis can affect healthy subjects at any age, but it is less frequent in pediatric age [3,4]. The lack of awareness of drug induced esophagitis might lead to unnecessary investigation. The symptoms are variable, but the main complaint is retroesternal pain, dysphagia, and odynophagia [1,5,7].

Patients and Methods

We retrospectively reviewed the files of 1049 upper gastrointestinal endoscopies performed between January 2015 to February 2019 in Hospital Metropolitano de Quito.

Inclusion criteria were: Pediatric patients between 12 and 17 years with clinical manifestations of esophagitis. Patients that consumed drugs that potentially caused drug-induced esophagitis. Patients that underwent an upper endoscopy from January 2015 to February

Category	Examples
Antibiotics	Doxycycline, tetracyclines, clindamycin, amoxicillin, ampicillin, erythromycin, rifampin, minocycline, penicillins, tinidazole.
NSAID	Naproxen, aspirin, ibuprofen, indomethacin, diclofenac, piroxicam
Other	Potassium Chloride, alendronate, ferrous sulfate, qunidine, mycophenolate, warfarin, ascorbic acid, nifedipine

Table 1: *Common drugs associated with esophagitis.*

Decreased saliva production
Polypharmacy
Preexistent esophageal disorders (achalasia, strictures, ineffective esophageal motility)
Duration of contact with the mucosa
Insufficient fluid intake with medication
Pharmacological factors: size of the capsule or tablet, chemical, pH of the chemical, slow release of the formulation, presentation (capsule or tablet).
Fasting
Prone or supine position after medication intake
Altered local anatomy (aortic aneurysm, enlarged left atrium, tumors or adenopathies)
Medication that affects the tone of the lower esophageal sphincter

Table 2: *Risk factors for drug induced esophagitis.*

2019 in Hospital Metropolitano de Quito. Exclusion criteria were patients with other causes of esophagitis (for example; reflux, infectious, and corrosive). Patients that did not have a subsequent consultation in the outpatient clinic of Pediatric Gastroenterology of Hospital Metropolitano de Quito.

We recruited 5 pediatric patients that presented drug-induced esophagitis diagnosed clinically and by upper endoscopy, the treatment was also evaluated. Afterwards we established the frequencies, means and standard deviation.

Case Report

The mean age of the patients was 14.6 ±1,9 years, 3 were male and 2 female. The main symptom was retrosternal pain, and it was present in 80% of the patients (n = 4). Other clinical manifestations were; dysphagia (n = 2), epigastric pain (n = 2) and foreign body sensation (n = 1). The mean between initial symptoms and upper endoscopy was 7.2 ±4.2 days.

Causative agent in 3 patients was L-Arginine, in 1 patient calcium, and in 1 patient doxycycline capsule. The patients that ingested L-Arginine were high-performance athletes. All of them referred that the medicine was ingested with a small quantity of water.

The main endoscopic findings were; esophageal ulcers; number, size, and depth were variable. In 4 patients ulcers were located in the mid-third of the esophagus and in 1 patient in the lower third. A histologic study was performed in 2 patients. The endoscopic and histologic findings are resumed in table 3.

	Ingested drug	Endoscopic and histologic findings	Histologic findings
1	L-Arginine	Esophagus: In the middle third there were several ulcers, some in a mirror pattern, covered with fibrin, with well-defined edges (6 - 10 mm)	Compatible with eosinophilic ulcerative esophagitis. Ulceration with abundant granulation tissue, numerous eosinophils and intraepithelial exocytosis of eosinophils.
2	L- Arginine	Esophagus: In the middle third there are four mirror ulcers, covered with fibrin (6 - 10 mm). In the lower third there is a friable ulcer with irregular borders, covered with fibrin, contact bleeding (2 cm)	Not performed
3	L- Arginine	Esophagus: In the lower third there were 5 fibrin-covered ulcers (5 - 10 mm)	Not performed
4	Calcium	Esophagus: In the mid-third there are three ulcers (5 - 10 mm), with high edges, central fibrin Erosive gastropathy in the body	Esophageal ulcer with extensive granulation tissue covered by fibrinohematic material that includes frequent groups of eosinophils.
5	Doxycycline	Esophagus: In the mid-third there are two mirror ulcers, covered with fibrin (10 - 15 mm). In the lower third there is a pearly white mucosa. Erythematous gastropathy of the fundus, erosive gastropathy of the body and petechial gastropathy of the antrum.	Not performed

Table 3: *Endoscopic and histologic findings in 5 patients.*

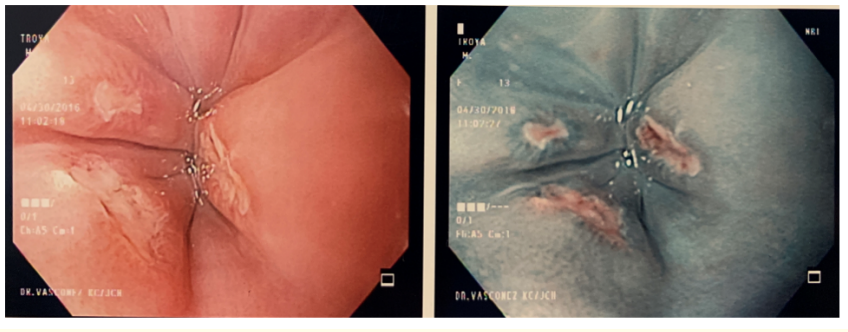

Figure 1: *Patient with L- Arginine consumption, ulcers in the lower third of the esophagus.*

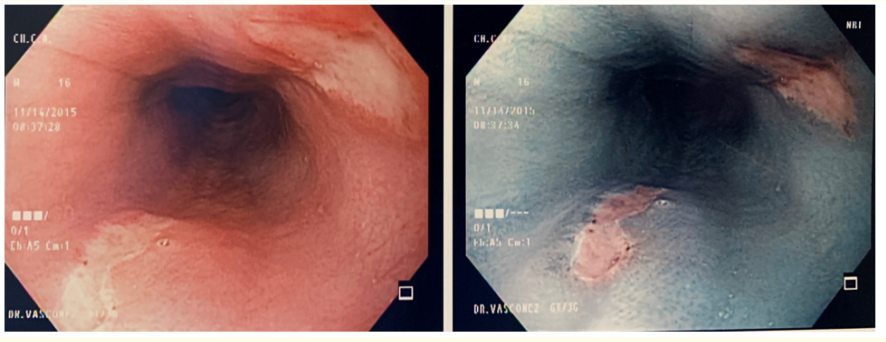

Figure 2: *Patient that consumed Doxycycline, ulcers in the mid-third of the esophagus, in a mirror pattern.*

Subjects were treated with sucralfate and proton pump inhibitors and the drug that induced the esophagitis was suspended. All patients had clinical remission after a week and a control upper endoscopy was performed 4 weeks after the diagnosis to evaluate treatment efficiency. In the follow-up endoscopy the ulcers in the esophagus were cured.

Discussion

The mechanisms of esophageal mucosal lesion may vary depending on the causative agents, however some risk factors are related to an increased probability of presenting pill-induced esophagitis (see table) [1], [2]. Among the risk factors we saw in our patients, medication intake with an insufficient amount of water was present in all subjects. Also, in patients taking L-arginine, these were large tablets as mentioned earlier, patients taking this substance were high-performance athletes and therefore their goal was to gain muscle mass by increasing growth hormone; in this case the indication is to take the tablet before sleeping and on an empty stomach [3,4], therefore ulcers in this case could be related to the size of the tablet, the decubitus position and the condition of fasting, which increased the contact time of the drug with the esophageal mucosa. During the lying position and sleep, saliva production is diminished and the esophageal transit is longer [2,5].

Regarding the patient taking doxycycline, the factor we could identify was the presentation of the medication, which in this case was a capsule. Some studies have shown that capsules become more adherent when taken with an insufficient amount of liquid. In addition, a study by Carlborg and Densert showed that doxycycline capsules remain 3 times longer in the esophagus than doxycycline tablets, as a result the contact time with the esophageal mucosa is increased [12]. Another factor that is related to doxycycline is the pH of this substance; drugs such as doxycycline, tetracyclines, ascorbic acid, ferrous sulfate produce a pH less than 3.0 when dissolved in 10 ml of water or saliva. In addition, these drugs accumulate in the cells and cause an inhibition of protein synthesis which causes the lesion [6,7].

As for the patient taking calcium, the tablet was large. Only one case of esophagitis caused by calcium has been described in the literature and it is an adult patient who develops esophagus stricture after taking a calcium tablet [8].

The diagnosis of this pathology is based on the clinical history that includes a history of consumption of tablets or capsules and an acute development of esophageal symptoms plus endoscopic findings. In regards to the clinical manifestations, our patients presented retrosternal pain, dysphagia, epigastric pain and foreign body sensation, which is consistent with reports from other studies [2,9-11]. Among the endoscopic findings in this pathology we can find; ulcers located in the middle or lower third of the esophagus with normal adjacent mucosa, erosions, bleeding ulcers, fragments of impacted tablets and ulcers in kisses or mirrors [9,12,13]. Extensive ulcers in large portions of the esophagus have been reported in adult patients, but are rare in pediatric patients with pill-induced esophagitis [10]. In our study the most frequent endoscopic finding were mirror ulcers. In most of our patients we found that esophageal lesions were located in the middle third, which is consistent with data from other studies [10,14]. This is because in the middle third of the esophagus we find a physiological narrowing due to external compression of the aortic arch and a physiological reduction of the amplitude of the peristaltic wave at this level [10,11]. In general, a biopsy is not required for diagnosis since the changes that can be found in the histopathological study are not specific, acute inflammatory changes, necrosis, inflammatory exudate with a predominance of lymphocytes and eosinophils can be evidenced. Biopsy is useful to rule out malignancy, viral infections and other causes of esophagitis [7,10,13,14].

Usually the course of this pathology is benign and complications in children are rare. It is usually self-limited and symptoms subside within the first 7 days of treatment and the mucosa recovers in approximately 2 to 5 weeks [10,14]. It has been seen that most patients improve by removing the causative agent along with treatment with sucralfate and proton pump inhibitors [9]. Currently 3 PPIs are approved by the FDA for the treatment of erosive esophagitis in children: Esomeprazole (1 - 17 years), Omeprazole (2 - 16 years) and Lansoprazole (1 - 17 years) [10]. In other cases, oral injections of epinephrine have been used in patients with bleeding ulcers [12]. In our patients, only the use of sucralfate and proton pump inhibitors was required and the causative agent was discontinued, after which a control endoscopy was performed in 4 weeks where healing was evident in all patients.

Conclusion

An adequate diagnosis of this clinical entity could avoid unnecessary investigations, clear indications by the pediatrician about the adequate intake of medications could avoid this pathology. The prevention of drug-induced esophagitis is based on the proper intake of the medication, medication must be taken in a sitting or standing position, with a sufficient amount of liquid, at least 100ml, the patient should not lie down after the administration of the drug for at least 30 minutes, all these simple indications could decrease the presentation of this entity since any drug, even those that are apparently safe, can potentially cause esophagitis if they are not taken properly. This is why clear information should be given to patients on how to take the drug [5,13]. In addition, in pediatric patients, suspension presentations should be preferred or if the drug is larger than 2 cm, it should be checked whether it can be crushed or emptied of its contents [1].

Endoscopy is the method of choice for diagnosis, kiss ulcers in the middle third of the esophagus is a frequently observed finding. Histopathology is not necessary for diagnosis, because inflammatory findings are nonspecific [9,12]. Sucralfate, PPI and discontinuation of the medication causing esophagitis is usually the treatment of choice. Further studies are needed in order to assess treatment in drug induced esophagitis in patients.

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Volume 8 Issue 11 November 2019