# Drug-induced acute esophageal lesions and use of ciprofloxacin

## *Lesiones esofágicas agudas inducidas por drogas y uso de ciprofloxacino*

**V.M. Santos[1,2], M.V. Carneiro[3], L.R. Cruz[2], G.T.G. Paixão[2]**


## RESUMEN

Presentamos el caso de una mujer de 95 años con lesiones agudas del esófago que tomaba ciprofloxacino por cistitis aguda. La paciente refería dolor y sensación de cuerpo estraño retroesternal asociados con hematemesis y melena, después del segundo día de tratamiento. No había antecedentes personales de trastornos gástricos o esofágicos. La endoscopia digestiva objetivó lesiones sangrantes en el tercio medio del esófago. El uso de ciprofloxacino fue suspendido y se utilizó un inhibidor de la bomba de protones. Una semana más tarde, el aspecto endoscópico del esófago fue considerado normal. Dos únicos casos de lesiones esofágicas inducidas por ciprofloxacino han sido previamente publicados. Se presenta una revisión breve acerca de este tipo de lesiones del esófago, con énfasis a los principales factores de riesgo y medidas de prevención.


**Palabras clave**. Anciano. Ciprofloxacino. Esofagitis inducida por drogas. Endoscopia.


## ABSTRACT

We report the case of a 95-year-old woman who had acute esophageal lesions while being treated with oral ciprofloxacin for an acute cystitis. On day 2 of treatment, she reported retroesternal pain with a globus sensation, and presented hematemesis and melena. There was no history of gastric or esophageal disturbances. An upper digestive endoscopy showed bleeding lesions on the middle third of the esophagus. Ciprofloxacin was discontinued and a proton pump inhibitor was administered. One week later, the endoscopic aspect of the esophagus was normal. Only two cases of ciprofloxacin-induced esophageal lesions have been reported previously. A short review of this kind of esophageal injuries is presented, focusing on the main risk factors and preventive measures.


**Key words.** Aged. Ciprofloxacin. Drug-induced esophagitis. Endoscopy.

*An. Sist. Sanit. Navar. 2012; 35 (1): 127-131*

1. Catholic University and Medicine Department from Armend Forces Hospital. Brasilia – DF Brazil
2. Medicine Departement from Armed Forces Hospital. Brasilia – DF Brazil
3. Gastroenterology Division from Armed Forces Hospital. Brasilia – DF Brazil

**Correspondencia:**
Vitorino Modesto dos Santos
Armed Forces Hospital.
Estrada do Contorno do Bosque s/n
Cruzeiro Novo
70658-900 Brasilia DF Brazil
E-mail: vitorinomodestos@gmail.com

Recepción: 4 de octubre de 2011
Aceptación provisional: 25 de octubre de 2011
Aceptación definitiva: 25 de octubre de 2011

## INTRODUCTION

Case reports of pill-induced esophageal lesions have increased in the last years, but this entity has been probably underdiagnosed and underreported[1-4]. Abid et al reviewed records of 92 patients with this condition, and the main etiologies were non-steroidal anti-inflammatory drugs, tetracyclines, potassium chloride and alendronate[1]. Predisposing factors include female sex, advanced age, anatomical and functional changes of the esophagus, and the body position at the time of the medicine ingestion[1,5]. The use of ciprofloxacin is very rarely described as a causal factor of these injuries[4,5]. Although the exact mechanism by which ciprofloxacin may cause esophageal injury is unknown, some molecular component as carboxylic acid may have a harmful effect[6]. Data of single case studies can contribute to support the hypothesis that film-coated tablets of ciprofloxacin might be included among the causal agents of these injuries. New or rare adverse effects of drugs usually considered safe should merit register and due attention, because they can become relevant to the general daily clinical practice. The objective of this study was to increase the general physician awareness about the possible role of oral ciprofloxacin as an inducer of underestimated esophageal lesions.

## CASE REPORT

A 95-year-old woman, with mild Alzheimer's disease, presented with urinary infection associated with intense apathy. Due to socio-economic factors, she had stopped taking galantamine hydrobromide about six months prior to this hospitalization. She did not have a history of esophageal or gastric disorders and was not receiving medicines, except for the recent use of fluoroquinolone to treat an acute cystitis. Four days before admission to our hospital, the patient started using ciprofloxacin (500 mg, twice a day) and was taking the oval pills with a half glass of milk. Because of her fragile condition and limited mobility the drug was ingested in the lying down position. The patient complained of retrosternal pain with a globus sensation since the day 2 of antibiotic use, and there was an episode of severe hematemesis and melena on the day 4. On admission, her BMI was 23 kg/m$^2$ and she was conscious, pale and restricted to bed. She received emergency care in our hospital and her hemodynamic management consisted of bood transfusion and intravenous hydration. Furthermore, an upper digestive endoscopy evidenced acute erosions with bleeding in the distal third of the esophagus (Fig. 1A). Histopathologic data of samples from esophagus and stomach were unremarkable, and the rapid urease test for *Helicobacter pylori* was negative. Ciprofloxacin was discontinued, and a proton pump inhibitor was utilized. The endoscopic evaluation of control done one week later showed total healing of the esophageal lesions (Fig. 1B). Comparative laboratory data are showed in table 1.

The patient was asymptomatic on the occasion of discharge, and her relatives received full information about the diagnosis and correct management for long-term home care.

**Table 1.** Comparative data of a 95-year-old female with upper gastrointestinal bleeding due to acute esophageal lesions associated with the ingestion of ciprofloxacin tablets

| Date (2010) | #Jan/29 | Feb/1 | *Feb/2 | Feb/5 | Feb/7 | Feb/10 |
|---|---|---|---|---|---|---|
| Hemoglobin (g/dl) | 13.0 | 10.3 | 9.1 | 9.3 | 8.5 | 8.9 |
| Hematocrite (%) | 37.0 | 31.9 | 28.2 | 28.7 | 25.8 | 27.3 |
| Leukocytes ($10^3$/mm$^3$) | 23.7 | 19.1 | 14.5 | 23.8 | 18.8 | 21.0 |
| Bands/ segmented (%) | 3/ 74 | 7/ 78 | 10/ 61 | 8/ 70 | 0/ 83 | 5/ 75 |
| Platelets ($10^3$/mm$^3$) | Nd | 174 | 189 | 322 | 349 | 385 |
| Urea (mg/dl) | 44.0 | 97.3 | 86.6 | 30.7 | Nd | 36.7 |
| Creatinine (mg/dl) | 0.9 | 2.1 | 1.9 | 1.2 | Nd | 0.9 |
| Prothrombin activity (%) | Nd | 54 | 58 | 52 | Nd | 55 |
| INR | Nd | 1.54 | 1.47 | 1.59 | Nd | 1.52 |
| TTPA | Nd | 1.01 | 1.09 | 1.15 | Nd | 1.30 |

#Pre-admission/ pre-ciprofloxacin. *Admission/ day 5 post-ciprofloxacin. Nd: not done.

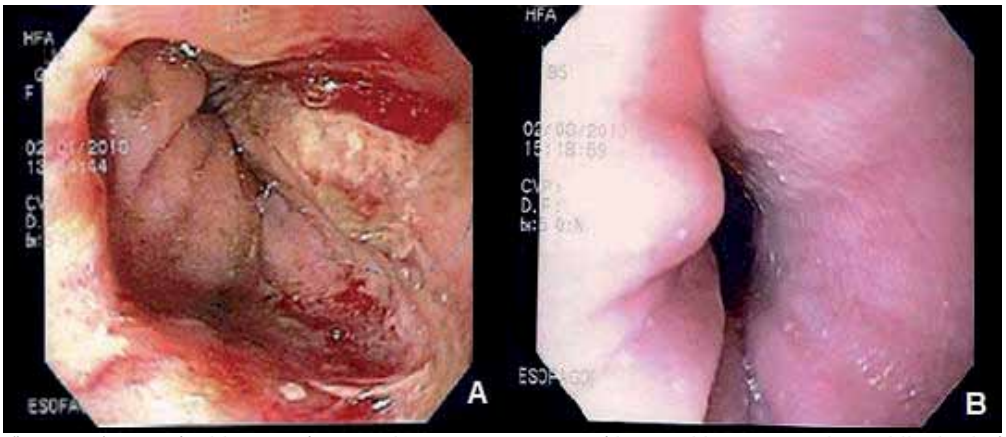


**Figure 1**. A Large friable area of mucosal erosions containing fibrin and hematin on the middle third of the esophagus, with extension to the esophagogastric transition. B Normal aspect of the esophageal mucosa one week after discontinuation of ciprofloxacin, and use of a proton pump inhibitor

## DISCUSSION

The first case of esophageal lesions and stasis by intense spasm related with medication was described by Pemberton in 1970[7]. The 44-year-old woman had heart failure and was using extended-release tablets of potassium chloride, which caused ulcerations on the posterior wall of the esophagus at the level of the left atrium[7].

Since 1970, the therapeutic arsenal diversification and the increment of diagnostic methods, mainly the upper digestive endoscopy, have contributed to the increasing number of reports about drug-induced esophageal lesions[8-10]. In 2009, Zografos et al reviewed about 650 cases of drug-induced esophageal injuries described in the whole world, and more than 30 medications were causal factors. Induced injuries were located in the middle third of the esophagus and behind the left atrium in 75.6% of the cases[10]. Although in the majority of cases the affected patients are asymptomatic, the usual manifestations are odynophagia of sudden beginning (differing from gastro esophageal reflux disorder, and other esophagites), and dysphagia[2,5]. Severe complications include stenosis, perforation, mediastinitis and death[2,5,8-11].

Diagnosis suspicion is based on the clinical data, and is confirmed by upper gastrointestinal endoscopy[12]. Endoscopic findings include: erythema (83%), erosions (58%), ulcers (26%), bleeding lesions (18%), and stenosis (8%)[1]. The esophageal sites more commonly affected correspond to the anatomical areas of narrowing, like at the level of the aortic arch, left main bronchus, and cardia, in addition to the area of esophageal compression by an increased left atrium[7,10,13].

Predisposing factors include advanced age, female sex, dismotility, use of capsules that increase adherence (gelatinous and with cellulose film), pills of great size, incorrect time to take the pills, insufficient amount of fluids for ingestion, supine position and restriction to bed[5,8,13].

Preventive measures should be based on the ingestion of drugs with about 100ml of water and in ortostatic position; ingestion of the pills or capsules at least 30 minutes before going to bed, and the use of proton pomp inhibitors if necessary[5,8,9,11].

Main differential diagnoses include infectious esophagitis, gastroesophageal reflux disorder, and acute necrotizing esophagitis (black esophagus) in erderly adults[5,14]. Both drug-induced esophageal lesions and black esophagus have been scarcely reported, and may be underestimated. Although clinical data and compli-

cations may be similar, the typical lesions of black esophagus occur in the distal third of the organ[14], which is not the prevalent site of drug-induced esophageal injuries. In this patient, the lack of characteristic endoscopic features of black esophagus ruled out this hypothesis[14].

Ciprofloxacin is a fluoroquinolone widely utilized to treat diverse bacterial infections, which is usually well tolerated even by individuals of the elderly group[15]; however, some of the untoward events related to this drug might be underestimated. Adverse effects include anxiety, arrhythmias, arthralgias, tendinitis, blurred vision, confusion, convulsion, dark urine, depression, diarrhea, dizziness, drowsiness, fainting, fever, hallucinations, headache, myalgias, nausea, paresthesias, pharmacodermia, photosensibility, sleep disturbances, vomiting, weakness, and pale or yellowish skin[15].

This is the third case report about ciprofloxacin-induced esophageal lesions[4,5]. Naranjo's algorithm was utilized to evaluate the association between the ingestion of ciprofloxacin and the concurrent development of acute esophageal lesions. The final score was 7 (with answers **yes** for questions 1, 2, 3 and 10, and **no** for question 5), a which is highly indicative of a probable causal relationship[6].

The first description was published in 1990[4]; Emami et al. reported the second case study of this condition and emphasized its rarity, fourteen years later[5]. The 46-year-old male patient was taking round tablets of ciprofloxacin (500mg twice daily) for chronic prostatitis and presented with odynophagia, dysphagia, and retroesternal pain two weeks before the diagnosis was established by endoscopic examination. Acute kissing ulcers were found on the upper third of the esophagus with indicative features of a chemical injury, in absence of local signs of recent bleeding or narrowed lumen. The patient was taken the pills of ciprofloxacin for a week with a glass of water and in upright position, and the symptoms persisted three months after the drug discontinuation[5].

The empirical formula of ciprofloxacin is $C_{17}H_{18}FN_3O_3$ [1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid]. The $pK_a1$ and $pK_a2$ values are respectively 6.20 ± 0.10 and 8.59 ± 0.10, by the solubility method at 37° C[16]. Ciprofloxacin hydrochloride is the monohydrochloride monohydrate salt of the film-coated tablets, that contain inactive igredients like cornstarch, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide. Worth of note, ciprofloxacin comes from nalidixic acid ($pK_a1$ = 6.10 at 25° C) and this fact can be associated with some chemical injury. This elderly patient was taken large tablets with insufficient fluid, and almost in a horizontal position, factors that cause delayed passage through the esophagus[8,13]. Moreover, the concomitant ingestion of milk may have reduced the absorption of ciprofloxacin and can have played a role in the origin of the acute esophageal lesions. Another concern is about possible effect of some caustic coating component of the tablet, which could cause local injuries by long contact with the esophageal mucosa[8,10,12]. The purpose of this report is to enhance the suspicion index of general physicians about underestimated esophageal drug-induced injuries, especially those associated with ciprofloxacin. In addition, we aim to emphasize the role of preventive measures, which include clear instructions to patients, family members, and caregivers.

## REFERENCES


1. 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: 740-744.
2. Akhtar Aj. Oral medication-induced esophageal injury in elderly patients. Am J Med Sci 2003; 326: 133-135.
3. Arora As, Murray Ja. Iatrogenic esophagitis. Curr Gastroenterol Rep 2000; 2: 224-229.
4. No authors listed. [Drug-induced esophageal injuries–an overview. Adverse effects of felodipine and ciprofloxacin observed during 2 years]. Lakartidningen 1990; 87: 2368-2369.
5. Emami Mh, Haghighi M, Esmaeili A. Esophagitis caused by ciprofloxacin: a case report and review of the literature. Govaresh 2004; 9: 272-276.

6. Naranjo Ca, Busto U, Sellers Em, Sandor P, Ruiz I, Roberts Ea et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.
7. Pemberton j. Oesophageal obstruction and ulceration caused by oral potassium therapy. Br Heart J 1970; 32: 267-268.
8. Kikendall Jw. Pill esophagitis. J Clin Gastroenterol 1999; 28: 298-305.
9. Leong Rw, Chan Fk. Drug-induced side effects affecting the gastrointestinal tract. Expert Opin Drug Saf 2006; 5: 585-592.
10. Zografos Gn, Georgiadou D, Thomas D, Kaltsas G, Digalakis M. Drug-induced esophagitis. Dis Esophagus 2009; 22: 633-637.
11. O'Neill Jl, Remington Tl. Drug-induced esophageal injuries and dysphagia. Ann Pharmacother 2003; 37: 1675-1684.
12. Jaspersen D. Drug-induced oesophageal disorders: pathogenesis, incidence, prevention and management. Drug Saf 2000; 22: 237-249.
13. Kikendall Jw. Pill-induced esophageal injury. Gastroenterol Clin North Am 1991; 20: 835-846.
14. Santos Vm, Villaça Rb, Gouvêa Lp, Sá Dar. Comment on the clinical note: Acute necrotizing esophagitis in an unstable patient. An Sist Sanit Navar 2009; 32: 439-442.
15. Stahlmann R, Lode H. Safety considerations of fluoroquinolones in the elderly: an update. Drugs Aging 2010; 27: 193-209.
16. Escribano E, Calpena AC, Garrigues TM, Freixas J, Domenech J, Moreno J. Structure–absorption relationships of a series of 6-fluoroquinolones. Antimicrob Agents Chemother 1997; 41: 1 996-2000. Erratum in: Antimicrob Agents Chemother 1997; 41: 2595.