

Brief Original Article

Long-term gastrointestinal adverse effects of doxycycline

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Abstract

Introduction: Doxycycline is an antibiotic with known gastrointestinal (GI) adverse effects. Esophagitis is the most pronounced among these effects, and might be associated with a prolonged duration of therapy. The aim of this study is to evaluate the incidence of esophagitis and other GI side effects in adults who received doxycycline for at least a month.

Methodology: This retrospective descriptive study included adults who received oral doxycycline for at least one month between 2016 and 2018. The primary outcome was the frequency of esophagitis. The secondary outcomes were frequency of and discontinuation due to GI adverse effects.

Results: A total of 189 subjects were included with a median age of 32 years. The median duration of doxycycline use was 44 days (interquartile range 30-60). Twelve patients (6.3%) reported having GI adverse effects resulting in doxycycline discontinuation in five of them (2.6%), and three patients (1.6%) had esophagitis. The incidence of GI adverse effects was significantly higher in patients who were ≥ 50 years than < 50 years old (8/50 vs. 4/139; $p = 0.003$) and in those who received a daily dose of 200 mg than 100 mg (12/93 vs. 0/96; $p < 0.001$).

Conclusions: GI adverse events, including esophagitis, are not rare with long-term use of oral doxycycline, particularly in older age and a higher dose of 200 mg/day. Future large and randomized studies are needed to compare the efficacy and safety of different doxycycline doses.

Key words: doxycycline; tetracyclines; gastrointestinal; esophagitis; esophageal.

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Introduction

Antibiotics that belong to the tetracyclines group are primarily bacteriostatic and they exert their antibacterial effect by the inhibition of protein synthesis [1]. Doxycycline is an old tetracycline that was first approved by the US Food and Drug Administration in 1967. It is synthetically derived from oxytetracycline and is considered a second-generation tetracycline that has lesser toxicity than the first-generation tetracyclines [1,2]. It is active against a wide variety of bacteria including Gram-positive, Gram-negative, atypical, and some spirochetes, allowing its use in various microbial infections [3-5]. Doxycycline can be administered intravenously or orally [2].

In terms of drug safety, doxycycline is associated with several adverse effects and drug interactions. The most important drug interaction is caused by chelation with divalent and trivalent cations [1]. Few other antibiotics that have the same type of drug interaction include fluoroquinolones and cefdinir, where such interaction necessitates the separation of administration by a few hours [6,7]. One of the most common adverse effects associated with doxycycline use is its effects on

the gastrointestinal (GI) system, [8]. Esophagitis is a relatively rare GI adverse event, and it has been reported in patients receiving capsule and tablet forms of the drug [1,9]. Nonetheless, the risk of esophagitis usually increases when doxycycline is taken immediately before going to bed, without sufficient amount of water, and with a longer duration of therapy [1,10]. This study aimed to describe the incidence of esophagitis and other GI adverse effects of doxycycline in adults who received it for at least one month.

Methodology

Study design and patients

This was a retrospective descriptive study that took place at an academic tertiary care medical center in Jeddah, Saudi Arabia. The study protocol was approved by the unit of the biomedical ethics research committee. Patients aged 18 years or older who were treated with a regimen that included doxycycline of any dose for at least one month between January 2016 and December 2018 were included in the study. The source of data was the patients' electronic medical records. Data collected included age, gender, nationality, history of GI

disorders, doxycycline regimen (dose, frequency, duration), and concomitant use with acid-suppressing drugs.

Study outcomes and data analysis

The primary outcome was the frequency of esophagitis, confirmed by endoscopy. The secondary outcomes were the incidence of total GI adverse effects, specific GI adverse effects (abdominal pain, nausea, vomiting, diarrhea), and doxycycline discontinuation due to GI adverse effects. The data were summarized by descriptive statistics including median and interquartile range (IQR) for non-normally distributed continuous data, and frequency (percentage) for categorical data. The two-tailed Fisher's exact test was used for the comparison of proportions in the subgroup analyses based on age (≥ 50 vs. < 50 years) and doxycycline daily dose (200 mg/day vs. 100 mg/day). The data were analyzed using the SPSS software, version 24 (IBM, Chicago, IL, United States).

Results

Patient characteristics

A total of 829 subjects using doxycycline were screened. Out of them, 186 were included in the study, and the remaining were excluded due to receiving doxycycline for less than one month. All included patients received the doxycycline hyclate capsules. Baseline patient and medication characteristics are illustrated in Table 1. The majority of patients were Saudi (74.7%), half were male, and the median age was 32 years (IQR 25-51 years). Eight patients had upper GI disorders, whereas four had irritable bowel syndrome. Only 13 patients (7%) were on an acid-suppressing medication during doxycycline therapy and before experiencing GI adverse events. Maintenance daily

Table 1. Baseline patient and medication characteristics.

Variable	Number of Patients (N = 189)
Patients' demographics	
Age (years)	32 (25-51)
Male	88 (46.6)
Saudi nationality	142 (75.1)
History of gastrointestinal disorders ^a	12 (6.3)
Daily maintenance dose of doxycycline	
100 mg	96 (50.8)
200 mg	93 (49.2)
Duration of doxycycline (days)	44 (30-60)
Concomitant use with acid-suppressing drugs	13 (6.9)

Data are presented as median (interquartile range) or n (%); ^aGastrointestinal disorders were as follows: One gastric ulcer, two gastritis, two gastroenteritis, three gastroesophageal reflux disease, and four irritable bowel syndromes.

Table 2. Study outcomes.

Variable	Number of Patients (N = 189)
Esophagitis	3 (1.6)
Gastrointestinal adverse effects ^a	12 (6.3)
Abdominal pain	9 (4.8)
Nausea	5 (2.6)
Vomiting	4 (2.1)
Diarrhea	1 (0.5)
Discontinuation due to adverse effects	5 (2.6)

Data are presented as n (%). ^aAll gastrointestinal adverse effects were reported in patients who received the 200 mg daily dose ($p < 0.001$), and their incidence was significantly higher in patients who were ≥ 50 years than those who were aged < 50 years (8/50 vs. 4/139; $p = 0.003$).

doses of 100 and 200 mg were almost equally distributed in the patient cohort (50.8% vs. 49.2%, respectively). The median duration of doxycycline use was 44 days (IQR 30-60 days).

Study outcomes

The study outcomes are summarized in Table 2. Esophagitis was reported in only three patients (1.6%), two of whom did not have a history of GI disease, whereas the third had a history of gastroesophageal reflux disease. Other GI adverse effects were reported in 12 patients (6%). These adverse effects resulted in the discontinuation of doxycycline in only five patients (2.6%) of the total cohort (33.3% of all 15 patients with adverse effects). Notably, the incidence of GI adverse effects was significantly higher in patients who were aged ≥ 50 years than in those who were aged < 50 years (8/50 vs. 4/139; $p = 0.003$). All GI adverse effects were reported in the group that received the higher 200 mg daily dose (12/93 vs. 0/96; $p < 0.001$). The three patients who developed esophagitis stopped doxycycline and either continued or started proton pump inhibitors, and one was also started on nifedipine.

Discussion

This retrospective study found that doxycycline administration for at least a month was associated with esophagitis in 1.6%, total GI adverse effects in 6%, and discontinuation due to GI adverse effects in one-third of them. GI adverse effects occurred significantly more frequently in older patients and only in those who received the higher daily dose of doxycycline (200 mg/day). Elderly patients are usually more prone to drug-induced GI adverse effects and esophagitis due to polypharmacy, higher risk of esophageal obstructive lesions and motility disorders, having less saliva, staying longer period in the recumbent position, and being more likely to not remember administration

instructions [11]. Future studies, preferably randomized controlled trials, are needed to compare the safety as well as the efficacy of a doxycycline dose of 200 mg per day to 100 mg per day. If the 100 mg per day is as effective and safer, then it could become preferred over the 200 mg per day for some indications. Prescribers should probably attempt to not prescribe the 200 mg/day when 100 mg/day is an option. When the doxycycline dose of 200 mg/day is not tolerated, then the 100 mg/day should be considered.

Pill esophagitis is a term for a rare clinical diagnosis that is used in the literature to describe esophagitis resulting as an adverse effect of an orally administered drug, such as doxycycline [12-14]. Studies have shown that doxycycline may induce gastric mucosal injury, but the confirmation of this correlation requires a correct diagnosis by a physician and a pathologist [15,16,17]. There are multiple case reports of patients who developed pill esophagitis with doxycycline [8]. In one study that included 48 patients who had drug-induced esophagitis, doxycycline was responsible for 24 (52%) of them. The intervention included stopping the medications and starting proton-pump inhibitors, which is consistent with our study [18].

A randomized controlled trial compared doxycycline 40 mg/day to minocycline 100 mg/day continued for about 16 weeks for rosacea treatment [19]. While the sample size was small (40 vs. 40 patients), doxycycline was numerically associated with a higher frequency of stomachache (5 vs. 0 patients, respectively) and a lower frequency of nausea (1 vs. 7 patients, respectively) even though the doxycycline dose of 40 mg was lower than the standard doses of 100-200 mg. Shih *et al.* described 13 patients who developed GI adverse effects associated with doxycycline based on clinical and pathological diagnosis, of which eight (61.5%) had their symptoms resolved after discontinuation [15]. The common symptoms associated with the adverse effects of doxycycline in this study were epigastric abdominal pain, dysphagia, and odynophagia [15]. Similarly, Guo *et al.* described 12 patients who received doxycycline for acne vulgaris and developed endoscopically confirmed esophageal ulceration. After surveying the patients, it was found that eight of them ingested doxycycline with insufficient water, while the other four took the pills at bedtime [20]. A small case series of five patients with doxycycline-induced esophagitis found that insufficient water intake along with doxycycline administration or going recumbent shortly after was common [13].

As described in the previous reports, certain strategies can help prevent or mitigate the effect of

doxycycline on gastric mucosa. These include taking the pill with copious amounts of water (at least 100 mL), keeping sitting or standing upright after swallowing it, and timing it further from bedtime to avoid lying down for at least 30-60 minutes after dose administration [21-23]. One novel strategy that was developed by Huang *et al.* was the design of a new formulation for the delivery of doxycycline, where the drug is incorporated in modified-release pellets that skip the stomach and dissolve in the duodenum [24]. In this formulation, doxycycline is coated with a layer that dissolves at the duodenal pH of 5.5 (about 85%) rather than the gastric pH of 1.2. The results of the experiments were compatible with the U.S. Pharmacopeia for modified-release formulations indicating that this novel formulation can be a promising solution for pill esophagitis resulting from doxycycline oral administration.

In addition to tetracyclines, fluoroquinolones and macrolides are other classes of antibiotics with activity against atypical bacteria and are used frequently in bacterial respiratory infections similar to doxycycline [3]. Comparing GI adverse effects between tetracyclines, fluoroquinolones, and macrolides is difficult because individual agents might have different tolerability [25]. One retrospective study of patients with inflammatory acne who used antibiotics for several weeks (the average exceeded 8 weeks) observed GI adverse effects in 20% with doxycycline, 25% with minocycline, 25% with erythromycin, and 14% with azithromycin [26]. Another unique adverse effect that tetracyclines share with fluoroquinolones is photosensitivity [27]. Both tetracyclines and fluoroquinolones are also indicated in brucellosis, a condition that requires a prolonged duration of therapy of at least six weeks [28]. They also share the same drug interaction of potential chelation with divalent and trivalent cations contained in minerals and antacids; though, doxycycline is not significantly affected when co-administered with milk, unlike tetracycline [1]. Additionally, unlike fluoroquinolones and macrolides, doxycycline does not cause QTc prolongation and might be preferred when QTc-prolonging agents are concomitantly used [29]. This favored drug interaction profile of doxycycline makes it a good alternative to fluoroquinolones and macrolides for conditions where these agents are indicated but potential risk for drug interaction with the latter may arise. The gastrointestinal side effects are common with several tetracycline derivatives, including the more recent ones [30].

Our study has a few limitations that should be noted. First, it is a single-center retrospective study that included all patients without specifying a disease condition and the patients were not randomized. Moreover, as data were collected retrospectively from the patients' medical records, their healthcare providers may have overlooked these adverse effects or missed documenting them. This study did not include all patients who received doxycycline as most of them receive only a short course of therapy. It should be also noted that the GI adverse effects could have been caused by factors other than doxycycline. However, esophagitis is more unique to doxycycline, and we could not find other causative factors for esophagitis. Although it was interesting that all the GI adverse effects were reported with the higher 200 mg/day dose, large, randomized studies are needed to confirm this finding.

Conclusions

In conclusion, the GI adverse effects, including esophagitis, are not uncommon with long-term use of doxycycline; however, they can be of particular importance in older patients and when the higher dose of 200 mg/day is administered. Future large and prospective randomized studies should compare the efficacy and safety of different doxycycline doses.

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