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Original Research Article

Investigating the relationship between lactose intolerance and doxycycline-induced gastrointestinal disturbances

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ABSTRACT

Background: Doxycycline, a highly effective broad-spectrum antibiotic, is frequently prescribed for dermatological conditions due to its anti-inflammatory and anti-bacterial properties. The adverse effects (AE) doxycycline-induced gastrointestinal (GI) are well described in the literature and clinical practice. However, the use of lactose as an excipient in doxycycline formulations is not commonly known and may contribute to symptoms in patients with lactose intolerance.
Methods: We conducted a retrospective, phone-based survey of patients with documented doxycycline use. Participants reported lactose intolerance status and GI symptoms experienced during therapy. The association was assessed using odds ratios (OR) with 95% confidence intervals (CI) and statistical significance testing.
Results: Out of 98 participants, 46% experienced GI AE. We observed that individuals with lactose intolerance are 1.979 times more likely to experience any GI AE than those without (95% CI 0.598-6.547) with a p=0.257. With a threshold of $p<0.05$, we could not appreciate a statistically significant association between lactose intolerance and GI AE.
Conclusions: Although lactose intolerance was associated with increased odds of GI AE, the relationship was not statistically significant. However, findings noted in this study suggest a possible trend that warrants further investigation. Larger, prospective studies are needed to confirm our observation and clarify the clinical impact of lactose-containing doxycycline formulations.

Keywords: Doxycycline, Antibiotic, Drug side effects, Lactose intolerance

INTRODUCTION

Since its approval for clinical use by the FDA in 1954, tetracyclines have become one of the most widely used semisynthetic antibiotics.[1] Further structural modifications introduced a new generation of tetracyclines, including doxycycline, which received its own FDA clearance in 1967.[2] Doxycycline has been lauded for its biological activity against a broad spectrum of microbial pathogens and anti-inflammatory properties ever since.

Primarily a bacteriostatic agent, doxycycline inhibits the 30S ribosomal subunit of gram-positive and gram-negative bacteria.[3] However, doxycycline's therapeutic profile has dramatically expanded beyond its antibiotic properties. Tetracyclines can affect many cell processes, including inflammation, immune regulation, apoptosis, and angiogenesis.[4] Doxycycline is more lipophilic than its predecessor, allowing greater distribution to organs such as the skin. Importantly, studies have shown that doxycycline's anti-inflammatory effects result from suppressing the production of key inflammatory

mediators, including cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), as well as hydrolases like phospholipase A2.[5] Given these properties, doxycycline has become a staple medication in the dermatology field.[6] Part of the appeal of second-generation tetracyclines is their prolonged half-lives and increased absorption, offering the advantage of lower oral doses.[7]

Tetracyclines and their analogs are not without AE. Some of the side effects of doxycycline include photosensitivity and discoloration of developing teeth.[8] However, doxycycline's most common AE is GI distress. A systematic review of the frequency of adverse events in 24 clinical trials of doxycycline use between 1966 and 2003 reported rates of any GI event ranging from 0.54% to 51.7%.[9-11] Heartburn, nausea, vomiting, diarrhea, and gastritis are frequently reported. Of note, pill esophagitis, which is a relatively rare GI AE, has also been associated with doxycycline.[12–15]

Doxycycline is prepared as capsules or tablets. In the pharmaceutical industry, lactose is a key inactive ingredient used in the capsule and tableting processes, providing weight or volume and enhancing the flowability of the formulation.[16,17] Although a safe and natural excipient, lactose may lead to GI upset in lactose-intolerant individuals.[18] Lactose intolerance occurs due to the reduction or loss of the activity of the intestinal enzyme lactase, which digests the sugar lactose found in dairy products. Symptoms of lactose intolerance include abdominal pain, diarrhea, and flatulence.[19]

Among medical specialties, dermatologists lead in prescribing oral antibiotic courses per clinician, often for durations lasting several months.[20] Antibiotics, particularly doxycycline, are prescribed for a variety of dermatological concerns, including acne, rosacea, and other inflammatory conditions.[6,21] There are growing concerns about the clinical consequences of antibiotic treatment, aside from developing antibiotic resistance. Tetracyclines may be associated with the development of inflammatory bowel disease, and chronic antibiotic use has been linked to an increased risk of colorectal cancer.[22-24] Given these concerns, it is important to elucidate other potential side effects and their underlying causes, such as the relationship between doxycycline-induced GI issues and lactose intolerance. We aimed to investigate whether symptoms of GI distress associated with doxycycline were more prevalent in patients with lactose sensitivity. Recognizing the role of lactose intolerance may improve management of doxycycline-associated GI AEs and enhance patients' quality of life.

METHODS

We conducted a cross-sectional phone survey between January 2024 to July 2024 among patients treated at Keck Medicine of USC in Los Angeles, California, USA who had been previously or were currently prescribed doxycycline. Patients prescribed doxycycline were identified using the Keck clinical data warehouse (TrinetX, LLC). The ICD-10 codes for acne, along with those of patients who had been prescribed doxycycline, were used to conduct the medical record search. Eligible patients were then called and invited to participate in the survey if they were 18 years or older and were being prescribed doxycycline for a dermatological condition. Patients younger than 18 years or those prescribed doxycycline for a non-dermatologic indication were excluded. A total of 98 patients were included in the final study sample. Demographic information was obtained through a review of the patient's electronic medical records. Data collected included age, sex, race, ethnicity, past medical history, and medications. Survey questions included the doxycycline regimen (frequency and duration), indications for doxycycline treatment, and sensitivity to lactose (Table 1). Further details on the phone survey can be found in Table 2. This study was approved by the University of Southern California institutional review board (#UP-23-01187-AM002).

The primary outcome of this study is to determine if there is an association between GI AE and lactose intolerance among patients receiving doxycycline treatment for dermatologic conditions. We used a two-sided chi-square test to evaluate the relationship and calculated the risk using an OR. OR was computed from the data with 95% CI. Secondary outcomes included the incidence of GI AE, frequency of specific GI AE, and notable patterns in question answers. This data was then summarized using descriptive statistics, with the mean for continuous data and frequency for categorical data. The data was analyzed using IBM SPSS Statistics for Windows Version 29 (IBM Corp., Armonk, NY, USA).[25]

RESULTS

A total of 967 patients were called and invited to participate in a phone interview. Of those, 98 patients completed the survey and were included in the study. Baseline patient demographics are illustrated in Table 1. The average age of participants was 40 years old (SD 16); 59.2% were female, and most patients identified as either White (38%) or another race (38%). The most common conditions treated were acne (52%) and infection (16.3%).

The survey identified 46 patients had experienced GI AE with doxycycline treatment (Table 2). The most common AE were nausea (63%), abdominal pain (45.7%), and diarrhea (30.4%). Only one patient experienced pill-induced esophagitis during their course of treatment.

Of the 46 patients with GI AE, 21 patients further described the impact their experiences had on their ability to finish their course of treatment. There were 12 patients (57.1%) that reported that despite the GI effects, they were able to complete their course of treatment. Treatment discontinuation due to GI side effects occurred

in 6 patients (28.6%), and 3 patients (14.3%) experienced GI symptoms that prompted them to seek a medication change or dosage adjustment to mitigate GI side effects.

Of the 46 who reported GI AE, 21 (45.7%) actively altered their diets, either avoiding or incorporating specific foods to alleviate their symptoms. Notably, 7 of the 21 patients (33.3%) who modified their diets reported eliminating lactose-containing food. In contrast, 25 patients (54.3%) did not make any dietary changes despite experiencing GI discomfort.

Given the open-ended format of the survey, participants were encouraged to describe their treatment experiences based on recall. The most common additional comments made by participants are listed (Table 2).

The incidence of GI AE among doxycycline users is summarized in Table 3. In total, of the 46 doxycycline users who reported GI AE, 8 participants also experienced lactose intolerance. The odds ratio suggests that lactose-intolerant individuals have about 1.979 times the odds of experiencing GI AE compared to those without lactose intolerance.

However, the 95% confidence interval (0.598 to 6.547) and a p=0.257 indicate that this result is not statistically significant.

Table 1: Patients' demographics and indications for doxycycline treatment.

Parameters	Result[a] N (%)
Average age (in years), mean±SD	40±16
Sex	
Female	58 (59.2)
Male	40 (40.8)
Race	
White	38 (38.8)
Black	5 (5.1)
Asian	9 (9.2)
Other	38 (38.8)
Declined	7 (7.1)
Unknown	1 (1.0)
Ethnicity	
Hispanic	18 (18.4)
Non-Hispanic	70 (71.4)
Declined	10 (10.2)
Indication for treatment	
Acne	51 (52.0)
Infection	16 (16.3)
Rosacea	9 (9.2)
Folliculitis	7 (7.1)
Rash/dermatitis	6 (6.1)
Acne and rosacea	3 (3.1)
Wound healing	1 (1.0)
Pemphigus vulgaris	1 (1.0)
Migratory glossitis	1 (1.0)
Lichen planopilaris	1 (1.0)
Hidradenitis suppurativa	1 (1.0)
Unknown reason[b]	1 (1.0)

*a-Reported as total no. of patients. b-Patient unable to recall reason for treatment and limited documentation in EHR.

Table 2: Incidence, nature, and impact of GI AE with doxycycline treatment.

Parameters		Result, N (%)
Incidence of GI AE	Yes	46 (46.9)
	No	52 (53.1)
Reported GI AE (46)[a]	Nausea	29 (63.0)
	Abdominal pain	21 (45.7)
	Diarrhea	14 (30.4)
	Vomiting	7 (15.2)
	Bloating	6 (13.0)
	Constipation	2 (4.3)
	Acid reflux	2 (4.3)
	Weight changes	2 (4.3)
	Esophagitis	1 (2.2)

Continued.

Parameters		Result, N (%)
Impact of GI AE on treatment adherence (21)[a]	Continued treatment despite GI AE	12 (57.1)
	Discontinued treatment due to GI AE	6 (28.6)
	Change in medication or dosage was needed	3 (14.3)
Changes to diet to mitigate GI AE (46)[a]	Yes	21 (45.7)
	No	25 (54.3)
Specific adjustments by those that made dietary changes (21)[a]	Ensured consumption of a substantial meal	8 (38.1)
	Eliminated lactose products	7 (33.3)
	Avoided oily and heavy foods	4 (19.0)
	Took probiotics or dietary supplements	4 (19.0)
	Avoided spicy food	2 (9.5)
	Followed a specific dietary regimen	2 (9.5)
Additional comments regarding GI AE (46)[a]	Transient effect[b]	9 (19.6)
	Chronic effects after completion of course	7 (15.2)
	Effects due to empty stomach	10 (21.7)
	Effects due to sleeping after administration	1 (2.17)
	Effects led to avoidance of medication in future	4 (8.69)

*a-Represents the number of patients out of 98 for whom information regarding this parameter was provided; b-patients report symptoms resolved spontaneously within the hour.

Table 3: Incidence of lactose intolerance and GI AE in doxycycline users.

Parameters		Results
Incidence of GI AE	Yes	46
	No	52
Incidence of lactose intolerance	Yes	13
	No	87
GI AE among lactose intolerant individuals	Yes	8
	No	5
GI AE among non-lactose intolerant individuals	Yes	38
	No	47
Odds ratio		1.979; 95% CI: 0.598 to 6.547

DISCUSSION

Dermatologists lead the prescribing of oral antibiotics such as doxycycline among medical specialists for extended periods; understanding the underlying causes of side effects from doxycycline is crucial.[20,26] In an era of growing concern over antibiotic resistance, systemic agents like doxycycline have minimal potential for developing antibiotic resistance and remain one of the preferred therapeutic options.[27] As such, if there are modifiable factors, such as lactose intolerance, that play a role in its side effect profile, these factors need to be identified and mitigated when possible.

Of 98 survey participants, 46.9% (46/98) reported GI AE during treatment, which is consistent with prior studies.[9-11] 63% (29/46) of patients experienced nausea, 45.7% (21/46) abdominal pain, and 30.4% (14/46) diarrhea. These findings align with a systematic review by Waitayangkoon et al that found 43.2% (434/1004) of patients experienced some GI symptom; 29.1% (180/619) specifically reported nausea/vomiting, 14.8% (90/607) specifically reported diarrhea, and 14.9% (146/980) reported abdominal pain. Importantly, Waitayangkoon et al were able to appreciate that patients taking doxycycline were almost three times more likely to withdraw from treatment than those in the placebo group, with some participants choosing to withdraw despite mild side effects.[28] In our study, we observed 6 patients who explicitly recalled discontinuing their course of doxycycline, citing the impact of their GI AE as a reason for withdrawing from treatment.

Our study aimed to investigate whether symptoms of GI distress associated with doxycycline were more prevalent in patients with lactose intolerance. Although there was a higher observed incidence of GI AE among lactose-intolerant individuals, the association was not statistically significant (OR 1.979, 95% CI 0.598-6.547; chi-square test, p=0.257). Further research will be necessary to determine whether lactose intolerance is a contributing factor and whether mitigating factors, such as lactase enzyme supplement administration, may improve GI side effects in those individuals.

Despite our limited sample size, the review of patient responses reveals notable patterns in the subjective experiences of those with lactose intolerance. Of the 46 patients who experienced GI AE, 7 reported chronic GI distress even after completing their doxycycline course,

with 4 of these 7 also experiencing lactose intolerance. Among the 6 patients who discontinued doxycycline due to GI AE, 3 were lactose intolerant. Additionally, of the 3 patients who needed to change their medication or dosage, 1 was lactose intolerant. Notably, some rarer side effects, such as acid reflux (in 2 patients) and esophagitis (in 1 patient), were reported exclusively by lactose-intolerant individuals. Although no statistically significant association was found between GI AE and lactose intolerance, the experiences of these 8 lactose-intolerant patients warrant further exploration. The small sample size is a key limitation of this study, and larger future studies may be able to identify a significant association.

Previous studies have identified strategies to help prevent the side effects of doxycycline. Clinicians recommend that patients take doxycycline with water and avoid a supine position for at least 30-60 minutes after administration to prevent esophageal injury.[13,29,30] Further, clinicians advise patients to avoid dairy products within 2 hours of taking the medication, as significant data shows that dairy intake reduces absorption rates.[29,31,32] Though our study did not find a significant association between lactose intolerance and GI AE, clinicians should be aware that lactose-intolerant patients may report moderate to severe symptoms. For these patients, changing therapies should be considered if symptoms arise. Further, for patients with a known lactose sensitivity, alternative treatments may be considered from the start.

Our study has several limitations. The small sample size may have limited statistical power to detect a true association. The study relies on self-reported data from patients from a single medical center. This may have introduced recall bias. Further, recruitment of patients through phone-based surveys is subject to selection bias, as those with AE may have been more likely to participate.

Further investigation is needed to confirm our observations. Future prospective studies with larger sample sizes are needed to confirm these findings and better characterize the relationship between lactose intolerance and doxycycline-associated GI AE. Such research may also inform strategies, such as lactase enzyme supplementation, to mitigate side effects in affected patients.

CONCLUSION

This study found a high incidence of GI AEs among patients prescribed doxycycline, with nearly half reporting symptoms, highlighting GI intolerance as a barrier to medication adherence. Although lactose intolerance was associated with increased odds of GI AEs, the relationship was not statistically significant. Our findings suggest a possible trend that warrants further investigation. Larger prospective studies are needed to clarify the relationship between lactose intolerance and doxycycline-associated GI AEs and determine the clinical impact of lactose-containing doxycycline formulations. Clinicians should remain mindful of GI symptoms in lactose-intolerant patients taking doxycycline and consider strategies to improve tolerability and adherence when symptoms arise.

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