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Nitazoxanide as Salvage Treatment for Refractory *Helicobacter pylori* Infections

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Abstract

Background: Increasing resistance of *Helicobacter pylori* to metronidazole and clarithromycin has resulted in greater failure rates to standard treatments. For this reason, a salvage treatment becomes necessary. In this study, we report our findings with different regimens containing nitazoxanide, an antiprotozoal agent, in the treatment of refractory *H. pylori* infections.
Methods: Patients were treated consecutively and had to meet the following criteria: 1) proven symptomatic *H. pylori* gastritis via a stool antigen test or gastric biopsy and 2) failure of at least one course of treatment with a standard regimen. The sample size totaled twenty-five patients with thirty treatment episodes utilizing ten different nitazoxanide-containing regimens. A successful treatment was defined as a negative stool antigen test performed at least four weeks post-treatment.
Results: Overall, the eradication rate for all nitazoxanide-containing treatment regimens was 70%. Of note, the most frequently prescribed regimen, which consisted of nitazoxanide 500 mg twice per day, rifabutin 150 mg twice per day, omeprazole 20 mg twice per day, and one tablespoon (15 cc) of bismuth subsalicylate three times per day, had a 91% success rate.
Conclusions: For refractory *H. pylori* infections, we recommend a treatment regimen consisting of nitazoxanide 500 mg twice per day, rifabutin 150 mg twice per day, omeprazole 20 mg twice per day, and one tablespoon of bismuth subsalicylate three times per day for eight to ten days. Further evaluation of nitazoxanide-containing treatment regimens is warranted.

Keywords: *Helicobacter pylori;* Antibiotic Resistance; Nitazoxanide; Rifabutin

Introduction

Marshall and Warren first reported that *Helicobacter pylori* caused gastric and duodenal ulcers in 1982 [1]. *H. pylori* has been classified as a Class I carcinogen by the World Health Organization's (WHO) International Agency for Research on Cancer due to its strong association with the development of gastric adenocarcinoma and gastric-associated lymphoid tissue lymphoma [2]. Up to 95% of gastric cancers are attributed to *H. pylori* infections [3]. *H. pylori* is the most common chronic bacterial infection worldwide, with prevalence ranging between 85 to 95 percent in developing countries and between 30 to 50 percent in developed countries [4-6].

The recommended treatment for *H. pylori* infections consists of a proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole for fourteen days in areas where *H. pylori* resistance to clarithromycin or metronidazole is less than fifteen percent and in patients who have not had previous macrolide exposure [7]. A quadruple therapy with bismuth subsalicylate, a proton pump inhibitor, tetracycline, and metronidazole for ten to fourteen days is recommended for patients with a previous macrolide exposure, an allergy to penicillin, or where clarithromycin resistance exceeds fifteen percent [7]. If initial treatment fails, the American College of Gastroenterologists recommends that previously used antibiotics be avoided. Salvage treatments include bismuth subsalicylate quadruple therapy and levofloxacin triple therapy for fourteen days [7].

Resistance to standard treatments has increased in recent years. The WHO designated *H. pylori* a high priority subject for antibiotic resistance research and development in 2018 for this reason [8]. A meta-analysis involving 178 studies from 65 countries showed that primary resistance rates for clarithromycin, metronidazole, and levofloxacin were 15% or higher in nearly all regions investigated [8].

The rising prevalence of resistant *H. pylori* infections has been associated with failure of first line regimens. We define a refractory *H. pylori* infection as one which has failed to respond to one or more courses of standard treatment. Several studies have shown promising results for nitazoxanide in the treatment of *H. pylori* infections [9]. Nitazoxanide is currently approved by the U.S. Food and Drug Administration (FDA) for use to treat *Cryptosporidium* and *Giardia* infections [10]. In our practice we have evaluated patients with refractory *H. pylori* infections referred for management and treatment. A meta-analysis of ten studies that utilized a nitazoxanide-based treatment regimen for *H. pylori* found a cure rate of 80% or more in eight of the ten studies [9]. Based on these reports, we employed a variety of nitazoxanide-containing regimens to treat patients who had failed prior therapeutic trials.

We report our experience with nitazoxanide containing regimens in a group of patients with refractory *H. pylori* infections.

Methods

We collected all patients who were referred for refractory symptomatic *H. pylori* infection between 2015 and 2021. The patients met the following criteria: (1) proven symptomatic *H. pylori* gastritis or ulcer diagnosed with a stool antigen test (enzyme immunoassay via Quest or LabCorp) or gastric biopsy; (2) failure of at least one course of treatment with a standard regimen. The stool antigen test utilized had an overall sensitivity and specificity of greater than 95% [11]. The sample size totaled twenty-five patients, sixteen females and nine males with an average age of 60.4. (Table 1). Patients were treated using ten different nitazoxanide-containing treatment regimens for a total of thirty treatment episodes (Table 2). Some patients were given successive treatments with nitazoxanide, however in each case the supporting antibiotics were changed. All patients had a complete evaluation (history, physical, laboratory testing). Information collected from chart reviews included medical histories, date of evaluation, *H. pylori* test result, number and type of prior treatments, symptoms prior to treatment, type of nitazoxanide-containing salvage treatment prescribed, length of treatment measured in days, treatment outcome, and symptoms post-treatment. Four patients reported potential adverse effects: one instance of bloating, two instances of diarrhea, and one instance of nausea. We defined a successful treatment outcome as a negative *H. pylori* stool antigen test performed at least four weeks after the treatment regimen was completed. We report the percentage cure rates for the usage of nitazoxanide-containing regimens and for the individual treatment regimens themselves.

Table 1: Sample Characteristics

	N
Total Patients	25
Sex	
Male	9
Female	17
Mean Age (SD)	60.4 (16.6)

Table 2: Salvage Treatment Regimens

Regimen	**Medications**
1	Nitazoxanide 500 mg, clarithromycin 500 mg, omeprazole 20 mg, bismuth subsalicylate 1 tbsp
2	Nitazoxanide 500 mg, levofloxacin 500 mg, omeprazole 20 mg, bismuth subsalicylate 1 tbsp
3	Nitazoxanide 500 mg, ampicillin 1000 mg, omeprazole 20 mg, bismuth subsalicylate 1 tbsp
4	Nitazoxanide 500 mg, amoxicillin 1000 mg, tetracycline 500 mg, omeprazole 20 mg, bismuth subsalicylate 1 tbsp
5	Nitazoxanide 500 mg, rifabutin 150 mg, levofloxacin 500 mg, omeprazole 20 mg
6	Nitazoxanide 500 mg, rifabutin 150 mg, omeprazole 20 mg, bismuth subsalicylate 1 tbsp
7	Nitazoxanide 500 mg, amoxicillin 1000 mg, omeprazole 20 mg, bismuth subsalicylate 1 tbsp
8	Nitazoxanide 500 mg, rifabutin 150 mg, tetracycline 500 mg, omeprazole 20 mg, bismuth subsalicylate 1 tbsp
9	Nitazoxanide 500 mg, rifabutin 150 mg, tetracycline 500 mg, omeprazole 20 mg
10	Nitazoxanide 500 mg, doxycycline 100 mg, omeprazole 20 mg, bismuth subsalicylate 1 tbsp

Results

This study included twenty-five patients and a total of thirty treatment episodes. The average prior number of treatments was three (Table 5), with medications such as clarithromycin, levofloxacin, metronidazole, and amoxicillin (Table 3). The range in the length of salvage treatments was five to twelve days (Table 5). The most commonly reported symptom amongst the patients prior to treatment was abdominal pain. Overall, the eradication rate for nitazoxanide-containing treatment regimens was 70%, with twenty-one of the thirty treatment episodes resulting in *H. pylori* eradication (Table 4). Of those twenty-one successful treatment episodes, seventeen of the patients reported complete symptom resolution. The most commonly reported symptom amongst the remaining patients was abdominal pain. Upon further evaluation of the individual treatment regimens, it was noted that the regimens with the highest eradication rates, regimens 5, 6, 7, 8, 9, and 10, had a combined eradication rate of 85%, with seventeen out of the twenty treatment episodes classified as successful (Table 4). Additionally, the most frequently prescribed regimen, Treatment 6, which consisted of rifabutin 150 mg twice per day, nitazoxanide 500 mg twice per day, omeprazole 20 mg twice per day, and one tablespoon (15 cc) of bismuth subsalicylate three times per day, had a 91% success rate (Table 5).

Table 3: Previously Used Medications

Medication
Tetracycline
Amoxicillin-clavulanate
Levofloxacin
Omeprazole
Metronidazole
Ampicillin
Dicloxacillin
Clarithromycin
Esomeprazole
Pantoprazole
Bismuth subsalicylate
Garlic
Olive oil

Table 4: Treatment Outcome per Treatment Episode

Patient	Treatment Episode	Treatment Regimen	Length of Treatment (days)	Treatment Outcome
1	1	1	8	F[a]
2	2	2	12	F
2	3	3	7	F
2	4	1	7	F
2	5	4	10	F
3	6	2	8	C[b]
4	7	5	12	C
5	8	6	10	C
6	9	6	8	C
7	10	6	10	C
8	11	7	7	F
8	12	2	10	C
8	13	2	10	F
9	14	8	8	C
10	15	9	5	C
11	16	7	8	F
12	17	6	8	C
13	18	6	8	C
14	19	6	10	C
15	20	7	8	C
16	21	7	10	C
17	22	7	8	C
18	23	10	8	C
19	24	4	12	C
20	25	6	8	C
21	26	6	8	C
22	27	6	8	C
23	28	7	10	C
24	29	6	10	C
25	30	6	8	C

[a]F, treatment fail.
[b]C, treatment cure.

Discussion

Over time, increasing rates of resistance have been reported for clarithromycin, metronidazole, and levofloxacin. A retrospective study in the Netherlands showed significant increases in resistances to clarithromycin (9.8 to 18.1%), metronidazole (20.7 to 23.2%), and ampicillin (6.3 to 10%) over a period of ten years [12]. An analysis of primary antibiotic resistance in Asian-Pacific regions demonstrated resistance rates of 17% for clarithromycin, 44% for metronidazole, and 18% for levofloxacin [13]. Moreover, other studies indicate that even previous antibiotic use in general increases the risk of harboring resistant H. pylori strains [14-15]. Thus, it is imperative that salvage regimens be developed.

Nitazoxanide-containing regimens have been shown to be comparable or superior to standard regimens [16]. The regimens that demonstrated the highest eradication rates were regimens that contained nitazoxanide plus a proton pump inhibitor

and one or two antibiotics [9]. Furthermore, nitazoxanide has shown promise in patients who have failed previous treatment. An Egyptian study demonstrated an eradication rate of 83% in patients prescribed a quadruple therapy of nitazoxanide, levofloxacin, omeprazole, and doxycycline for fourteen days [17].

We sought to evaluate the efficacy of nitazoxanide-containing regimens for the treatment of refractory *Helicobacter pylori* infections. We defined refractory *H. pylori* infections as those which had failed one or more treatments with standard regimens. The overall cure rate for the various treatment combinations was 70% (Table 4). One treatment regimen had a remarkable success rate of 91% (Table 5). This treatment regimen consisted of nitazoxanide 500 mg twice per day, rifabutin 150 mg twice per day, omeprazole 20 mg twice per day, and one tablespoon (15 cc) of bismuth subsalicylate three times per day. The average length of treatment was nine days, with a range of eight to ten days (Table 4).

Table 5: Cure Rates for Individual Salvage Treatment Regimens

Treatment Regimen	Number of Uses	Number of Cures	Number of Fails	Cure Rate (%)
1	2	0	2	0
2	4	2	2	50
3	1	0	1	0
4	2	1	1	50
5	1	1	0	100
6	11	10	1	91
7	5	3	2	60
8	1	1	0	100
9	1	1	0	100
10	1	1	0	100

A study by Hoffman and colleagues in 2007 proposed that the mechanism for the action of nitazoxanide on *H. pylori* is through the noncompetitive inhibition of bacterial pyruvate: ferredoxin/flavodoxin oxidoreductases, which may bypass mutation-based drug resistance [18].

There are a few limitations of this study that must be considered when evaluating the results. We were only able to include twenty-five patients, which may affect the reliability of the results and increase the possibility of a type II statistical error. In addition, we did not have the ability to test antibiotic susceptibility in our patients, as gastroscopy was not repeated in the treatment process. A distinct advantage to the study is that we achieved symptomatic and clinical cures with a regimen lasting between eight to ten days. Other studies have achieved cures with treatments lasting fourteen days. Shorter treatment regimens are more advantageous because they decrease overall antibiotic exposure, lessen the risk of adverse effects, and reduce the risk of producing resistant organisms [19].

Our findings indicate that nitazoxanide may be used to treat refractory *H. pylori* infections. A treatment regimen of nitazoxanide 500 mg twice per day, rifabutin 150 mg twice per day, omeprazole 20 mg twice per day, and one tablespoon (15 cc) of bismuth subsalicylate three times per day for eight to ten days results in successful eradication of *H. pylori* infections. We believe further evaluation of nitazoxanide-containing treatment regimens is warranted, especially the nitazoxanide-rifabutin regimen in comparison to currently-recommended standard salvage regimens.

Addendum

Since the completion of this manuscript, four more patients have been successfully treated with the regimen of nitazoxanide 500 mg twice per day, rifabutin 150 mg twice per day, omeprazole 20 mg twice per day, and one tablespoon (15 cc) of bismuth subsalicylate three times per day for eight days with no reported adverse effects. This raises the cure rate to 93%. Additionally, the regimens with the highest eradication rates, regimens 5, 6, 7, 8, 9, and 10, now have a combined eradication rate of 88%.

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