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Furazolidone, an underutilized drug for *H. pylori* eradication: Lessons from Iran

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Abstract

Background—Treatment success of *H. pylori* eradication therapy has declined worldwide largely because of increased antimicrobial resistance. New therapeutic approaches are needed, especially for countries like Iran, where resistance to commonly used drugs is already widespread and traditional *H. pylori* therapies produce poor cure rates.

Aim—to review the results of quadruple therapy trials containing bismuth and furazolidone in Iran.

Methods—We searched PubMed, Google scholar as well as the references of all published papers for studies done in Iran, utilizing furazolidone in the treatment of *H. pylori* infections. The target population was 4 drug studies that utilized a combination of bismuth, furazolidone, amoxicillin, or tetracycline plus a proton pump inhibitor.

Results—Eighteen studies with 22 arms including 1713 subjects were found. The weighted mean cure rate for 14-day studies (6 studies) using 200 mg b.i.d. furazolidone was 80% intention-to-treat (ITT) and 87% per protocol (PP). Studies using 100 mg b.i.d (3 studies) were less effective (weighted mean ITT cure rate = 67%). One small 14 day study with furazolidone 100 mg q.i.d. achieved cure rates of 94.5% ITT and PP.

Conclusions—Although furazolidone-bismuth quadruple therapy proved relatively effective in Iran, furazolidone-containing regimens remain to be optimized. Based on these data and results from China, it appears likely that 14 day therapy containing furazolidone 100 mg t.i.d. or q.i.d. is likely to provide the highest cure rates with lowest side effects; this remains to be experimentally

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tested. Detailed suggestions for further development of furazolidone-containing regimens are provided.

Keywords

H. pylori; therapy; furazolidone; amoxicillin; tetracycline; proton pump inhibitors; review

Introduction

Furazolidone is a broad spectrum nitrofuran antimicrobial which has primarily been used in humans for the treatment of diarrheal diseases. In the pre-*Helicobacter pylori* era, furazolidone was successfully used in the treatment of peptic ulcer disease in China [1]. The subsequent discovery that peptic ulcer disease was caused by infection with *H. pylori* led to the search for effective antimicrobial therapies [2] which included testing of furazolidone and other nitrofurans for *H. pylori* eradication therapy. Furazolidone proved to be the only successful anti-*H. pylori* nitrofuran. Furazolidone, when used as a component of the multidrug regimens, particularly in association with bismuth has been shown to be highly effective for *H. pylori* eradication [3;4]. However, its use is frequently associated with side effects and a reduction in regimen-adherence [5].

The widespread increase in resistance to antibiotics most commonly used for *H. pylori* therapy (eg, clarithromycin, metronidazole, fluoroquinolones) has resulted in the search for new antimicrobial regimens. *H. pylori* resistance has remained rare to tetracycline, amoxicillin and furazolidone making them potentially useful in regions where antimicrobial resistance to other commonly used anti-*H. pylori* antimicrobials has become a problem. However, in many countries tetracycline is no longer available, in part because its low market price has made it unprofitable to manufacture and market.

Prior to 2002 furazolidone's largest use was in agriculture. In 2002, the United States Food and Drug Administration prohibited the use of all nitrofuran drugs (eg, dimetridazole; ipronidazole; other nitroimidazoles, furazolidone, nitrofurazone, and other nitrofurans) in food-producing animals due to evidence that the nitrofurans could produce carcinogenic residues in animal tissues. This prohibition also included topical use in agriculture and also in aquaculture (fish, shrimp, etc) so even products of bees such as imported honey are currently tested for the presence of nitrofuran antibiotics. This issue resulted in furazolidone becoming unavailable in many western countries. By 1980 furazolidone was considered an outdated clinical drug, in the United States and because the market was small and declining, the single manufacturer stopped production of the drug and voluntarily gave up its FDA approval [6].

China and Iran both experience high *H. pylori* prevalence and high burdens of *H. pylori*-related gastric cancer. In both countries, antimicrobial resistance in *H. pylori* is common and furazolidone is available [7–14]. In China, a 14 day combination of a proton pump inhibitor, a bismuth salt, plus combinations of furazolidone, tetracycline, metronidazole, or amoxicillin have proven reliably effective for *H. pylori* eradication [3;4]. The widespread use of antibiotics in Iran has also resulted in a high prevalence of antimicrobial resistance among *H. pylori* isolates, thus making reliable *H. pylori* eradication therapy difficult [10–

12;15–19]. Furazolidone is clinically available in Iran. Accordingly a number of clinical trials have been done using various combinations of anti-*H. pylori* antimicrobials comprising of this drug. While triple therapies consisting of a proton pump inhibitor, furazolidone, and amoxicillin proved relatively ineffective, the results were considerably improved by the addition of bismuth (eg, 54% with triple furazolidone (100 mg b.i.d) -containing therapy for 14 days vs. 72% with 100 mg furazolidone b.i.d. plus bismuth, and 92% for 200 mg furazolidone b.i.d. plus bismuth [13;20;21].

In Iran, furazolidone is locally available and considered a cost-effective therapy [13;19;22]. As a result, the current recommended first line *H. pylori* eradication therapy in Iran is a two week course of b.i.d. therapy consisting of furazolidone 200 mg b.i.d., amoxicillin 1 gm, bismuth 240 mg and a PPI [19;22]. Here, we review the experience with furazolidone-bismuth quadruple therapy in Iran based on the concept that the review of these studies will help identify reliably effective treatment strategies for multidrug resistant *H. pylori* infections in any region.

Methods

We searched PubMed, Google scholar as well as the references of all published papers, and any papers published from Iran utilizing furazolidone in the treatment of *H. pylori* infections. The target population was 4 drug studies that utilized the combination of bismuth, furazolidone, amoxicillin, or tetracycline. Each paper was obtained, read and the data extracted by MM, BA and DYG. For each study the intention to treat and per protocol results are presented.

Results

Nineteen papers from Iran with 23 arms were identified that described bismuth, PPI, furazolidone-containing quadruple therapies [21;23–40] (Tables 1–3). One study was excluded because the cure rate was tested after two weeks and while the subjects were still receiving PPIs [39] resulting in 18 studies, with 22 arms including a total of 1713 subjects. In these studies the furazolidone doses were 100 mg b.i.d. or q.i.d, and 200 mg b.i.d. Most studies used bismuth citrate 200 or 240 mg b.i.d., amoxicillin 1000 mg b.i.d, furazolidone, and either omeprazole 20 mg once or b.i.d. or pantoprazole 40 mg b.i.d. The studies were grouped in relation to furazolidone dosage, duration and combination of drugs into the following tables: Table-1: bismuth, furazolidone, amoxicillin, PPI quadruple therapies; Table-2: bismuth, furazolidone, tetracycline, PPI quadruple therapy; Table-3: novel sequential therapies containing bismuth, the PPI, and amoxicillin was give for 10 days and either metronidazole or clarithromycin given for the first 5 days and 200 mg b.i.d. furazolidone given for the second 5 days.

Table 1 (bismuth, furazolidone, amoxicillin, PPI quadruple therapies) presents studies which used furazolidone doses of 100 mg or 200 mg b.i.d. for 7 to 14 days. Fourteen day therapy with furazolidone 100 mg b.i.d (3 studies[21;28;40]). achieved relatively poor results with PP ranging from 56% to 85.7% (weighted mean for PP and ITT were 71% and 67%, respectively, Table 1). There were 4 studies [32;37;41;42] using a sequential therapy with

furazolidone 200 mg b.i.d. given for the first week of a two week therapy. The weighted mean cure rates of these studies were 89 and 81% for PP and ITT, respectively. Only one 10 day regimen was studied and achieved cure rates of 86.6% and 83.7% for PP and ITT, respectively [38]. Fourteen day therapy (6 studies[21;24–26;29;43]) all with 200 mg b.i.d. furazolidone (Table 1b) did somewhat better with 3 of the studies [21;24;43] having PP cure rates of 90% or greater. The weighted mean cure rates for the six 14 day- studies[21;24–26;29;43] were 87% and 80%, PP and ITT, respectively.

Table 2 shows the 5 studies with bismuth, furazolidone, tetracycline, PPI quadruple therapy. Studies with furazolidone 200 mg b.i.d. for 7 day [33] or 100 mg b.i.d. for 14 days [35] produced poor results (eg, 71% [33] and 68.4% [35] ITT, respectively). One 14 day study [33] with 200 mg b.i.d. gave poor results (65% ITT, 69.7% PP) and one that gave omeprazole only once a day[27], surprisingly did better with 90% ITT and PP results. The best result was obtained with furazolidone 100 mg q.i.d. for 14 days [31] which achieved 94.5% ITT and PP results.

Table 3 shows 1 study (two trials) [30] with novel sequential therapies, where either 200 mg b.i.d metronidazole or clarithromycin was given for 5 days followed by 200 mg b.i.d. furazolidone for the second 5 days along with bismuth, the PPI, and 1000 mg amoxicillin for the full 10 days. These two trials had a PP cure rate of 91.3% and 88.7% respectively (Table-3). The problem with interpreting these results include the lack of susceptibility data for metronidazole and clarithromycin, which would likely influence the outcome to a great extent.

Discussion

Furazolidone is a monoamine oxidase inhibitor (MAO) which interacts with a number of other drugs and especially with commonly used foods such as soy sauce and aged cheese [6]. Successful ITT results require patients to be educated regarding food and drug avoidances. Most find that a description of the symptoms likely to occur is useful to prepare the patient and to encourage them to complete the therapy [44]. There has also been confusion in the literature based on some authors' erroneous description of furazolidone as a human carcinogen [45]. The carcinogenicity of furazolidone was examined by the World Health Organization and and was listed as Class III (i.e., there was no evidence for its carcinogenicity in man) [6]. It should be noted, however, that one of the most commonly used antimicrobials for *H. pylori*, metronidazole, is classified as a Class I (definite) human carcinogen [6].

Successful *H. pylori* eradication has been defined as one that will reliably achieve an ITT cure rate of at least 90% and/or a 95% or greater PP cure rate in regimen-adherent patients with susceptible infections [46]. In Iran, *H. pylori* therapy consisting of omeprazole 20 mg, amoxicillin 1,000 mg, and bismuth citrate 240 mg with either 100 or 200 mg of furazolidone, all twice a day failed to reliably achieve this objective. Fourteen day full dose b.i.d. therapy provided ITT cure rates between 67% and 92% (weighted mean of 80%). In Iran, the dose of furazolidone is generally limited to a maximum of 200 mg b.i.d, because of the concern regarding the possible high rates of severe adverse drug reactions [25]. On the

other hand, doses of less than 400 mg/day were locally considered ineffective for *H. pylori* eradication [21;21;47].

In this review, the best cure rate (i.e., 94.5%) for furazolidone quadruple therapy was achieved in a small study (55 subjects) using tetracycline and furazolidone 100 mg q.i.d. along with bismuth (q.i.d) and omeprazole twice daily [31]. Review of these studies helps provide a basis to develop a strategy to identify reliably effective furazolidone-bismuth containing regimens for Iran and possibly other countries where furazolidone is available.

Recommendations for future studies

The components of a successful *H. pylori* therapy include the different drugs, formulations, doses, frequency of administration, and duration of therapy. The list of drugs includes anti-secretory agents, bismuth, amoxicillin or tetracycline, and furazolidone. Studies from China showed that doses, dosing intervals and duration are all important [3]. In China the best results were achieved with furazolidone 100 mg t.i.d. for 14 days. In this review, 100 mg furazolidone q.i.d. was best, although it was reported by only one study and t.i.d. furazolidone therapy was not tested [31]. Future studies comparing lower individual furazolidone doses such as 100 mg t.i.d. vs. q.i.d. appear worthwhile.

Recent guidelines show improved cure rates with both standard triple therapy and bismuth quadruple therapy when using double dose PPI, (eg, 40 mg omeprazole or an equivalent b.i.d.) [48]. Most current studies from Iran used 20 mg of omeprazole b.i.d and it would be interesting to compare the effects of using higher doses of PPIs as well as those which are resistant to CYP2C19 metabolism (rabeprazole or esomeprazole). In other trials of bismuth quadruple therapies, bismuth dosing has most often ranged from 2 to 4 times daily [49]. Although it appears that the doses used here (240 mg of bismuth citrate b.i.d.) are most likely adequate, comparisons with more frequent administration should be considered.

Recent studies with amoxicillin-containing bismuth quadruple therapies have suggested increasing the dose of amoxicillin to 1 gram t.i.d., which has resulted in improved outcome [50;51]. Studies examining and comparing amoxicillin 1000 mg t.i.d. and lower doses such as 500 or 750 mg t.i.d. should also be carried out. Finally, when tetracycline is used, the dose has varied from 500 mg q.i.d. to 250 mg q.i.d.. Overall 500 mg b.i.d. appears to be successful, but it is interesting that the most successful trial in Iran used 250 mg q.i.d. [31]. Further examination of tetracycline dosing seems warranted. Overall, if a reduced dose of both furazolidone and tetracycline results in a reduction in side effects and/or improved regimen-adherence, they would be worth considering, provided the cure rates are not adversely affected.

Since resistance to amoxicillin, tetracycline, and furazolidone have been reported from Iran [17;18;52–55], one cannot assume that all infections are susceptible. Future studies should include collection and storage of biopsies for culture and susceptibility testing so that the results can be interpreted in relation to the susceptibility patterns. Gastric biopsies placed in transport media and stored at −70C remain viable indefinitely and thus allow susceptibility

testing to be done when and where convenient [56]. Agar dilution methods are recommended as they are considered reliable and common standard worldwide.

The World Health Organization recently listed *H. pylori* among the high priority group of the infections, where resistance has become an issue [57]. Their publication was designed to guide research companies and scientists to develop new drugs, overcoming current anti-microbial resistance. Currently, resistance in *H. pylori* is still rare against furazolidone, amoxicillin, tetracycline, and rifabutin. While new drugs are being developed, it behooves us to learn to better use these drugs, which we have available.

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Table 1

Furazolidone-Amoxicillin–bismuth quadruple therapy

Year	City	Treatment Protocol						Treatment Success				Assays	Reasons for non-compliance	Ref
		Bismuth (BPC)	Furazolidone	Amoxicillin	PPI		Days	ITT		PP%				
					O/P	Dose		N	%	N	%			
2004	Tehran	240 b.i.d	100 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	50	72	49	73.4	UBT	Side effect (n=1)	[21]
2009	Shiraz	240 b.i.d.	100 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	69	49	60	56	UBT	Lost (n=9)	[28]
2009	Zaheda n	200 q.i.d.	100 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	49	85.7	49	85.7	stool antigen test	–	40
2007	Isfahan	200 b.i.d.	200 b.i.d.	1000 b.i.d.	O	20 b.i.d.	7	78	71.8	66	84.8	UBT	No UBT (n=12) Poor Adherence (n=1)	[25]
2012	Sari	240 b.i.d. 14 days	200 b.i.d. 7 day (1st wk)	1000 b.i.d. 14 day	p	40 b.i.d. 14 day	7	36	80.6	35	82.9	UBT	No UBT (n=1)	[36]
2012	Sari	240 b.i.d. 14days	200 b.i.d. 7 day (1st wk)	1000 b.i.d. 14 day	p	40 b.i.d. 14 day	7*	148	80.4	124	89.7	UBT	No adherence (n=12) No UBT (n=11)	[37]
2010	Yazd	120 q.i.d. 14 days	200 b.i.d. 7 day (1st wk)	1000 b.i.d 14 day.	O	20 b.i.d. 14 day	7*	92	79.3	82	89	RUT/His tology	Lost (n=8) Side effect (n=2)	[34]
2011	Sari	240 b.i.d.	200 b.i.d. 7 day (1st wk)	1000 b.i.d.	O	20 b.i.d.	7*	80	86.3	72	90.3	UBT	No UBT (n=4) Side effect (n=1) Poor Adherence (n=3)	[32]
2015	Sari	200 b.i.d.	200 b.i.d.	1000 b.i.d.	O	20 b.i.d.	10	124	83.7	104	86.6	UBT	Poor Adherence (n=4) Side effect (n=3)	[38]

Furazolidone-Amoxicillin–bismuth quadruple therapy (14 day- treatment studies with 200 mg furazolidone b.i.d)														
Year	City	Treatment Protocol						Treatment Success				Assays	Reasons for non-compliance	Ref
		Bismuth (BPC)	Furazolidone	Amoxicillin	PPI		Days	ITT		PP%				
					O/P	Dose		N	%	N	%			
2001	Tehran	240 b.i.d	200 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	63	84	59	90	UBT	Lost (n=2) Side effect (n=11)	[23]
2003	Rasht/Tehran	240 b.i.d	200 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	90	78.9	89	78	UBT	Side effect (n=1)	[26]
2004	Tehran	240 b.i.d	200 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	50	92	49	93.8	UBT	Side effect (n=1)	[21]
2007	Tehran	240 b.i.d	200 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	104	83.6	84	95.2	UBT	Side effect (n=7) Poor Adherance (n=2) No UBT (n=7) Lost (n=4)	[24]
2007	Isfahan	200 b.i.d	200 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	78	73.1	66	82.6	UBT	No UBT (n=5) Poor Adherance (n=3)	[25]

Furazolidone-Amoxicillin–bismuth quadruple therapy (14 day- treatment studies with 200 mg furazolidone b.i.d)														
Year	City	Treatment Protocol						Treatment Success				Assays	Reasons for non-compliance	Ref
		Bismuth (BPC)	Furazolidone	Amoxicillin	PPI		Days	ITT		PP%				
					O/P	Dose		N	%	N	%			
2011	Qum	240 b.i.d	200 b.i.d.	1000 b.i.d.	O	20 b.i.d.	14	43	67.4	34	85.3	UBT	Side effect (n=3) No UBT (n=4) Poor Adherance (n=2)	[29]

PPI, proton pump inhibitor; PP, per protocol; q.i.d., four times daily; b.i.d., twice daily; q.i.d., four times daily; q.d. daily; ITT, intention to treat; BPC, bismuth potassium citrate; O, omeprazole; P, pantoprazole.

* = sequential type therapy.

Table 2

Furazolidone-Tetracycline–bismuth quadruple therapy

Yea r	City	Treatment Protocol						Treatment Success				Assays	Reasons for non-compliance	Ref
		Bismuth (BPC)	Furazolidone	Tetracycline	PPI		Days	ITT		PP%				
					O/P	Dose		N	%	N	%			
2009	Rasht	240 b.i.d	200 b.i.d.	500 b.i.d.	O	20 b.i.d.	7	61	71	–	–	UBT	rare	[33]
2005	Tehran	120 b.i.d	100 b.i.d.	500 b.i.d.	O	20 b.i.d.	14	76	68.4	–	–	UBT	Poor Adherance	[35]
2014	Jahrom	120 b.i.d	100 q.i.d.	250 q.i.d.	O	20 b.i.d.	14	55	94.5	55	94.5	UBT	rare	[31]
2001	Tehran	240 b.i.d	200 b.i.d.	500 b.i.d.	O	20 once	14	80	90	80	90	UBT	rare	[27]
2009	Rasht	240b.i.d	200 b.i.d.	500 b.i.d.	O	20 b.i.d.	14	74	65	69	69.7	UBT	Side effect (n=5)	[33]

PPI, proton pump inhibitor; PP, per protocol; q.i.d., four times daily; b.i.d., twice daily; q.i.d., four times daily; q.d. daily; ITT, intention to treat; BPC, bismuth potassium citrate; O, omeprazole; P, pantoprazole.

Table 3

Novel Furazolidone-containing sequential therapy

Yea r	City	Treatment Protocol						Treatment Success				Assays	Reasons for non-compliance	Ref
		Bismuth (BPC)	Furazolidone (mg) plus Other (mg)	Amoxicillin	PPI		Days	ITT		PP%				
					O/P	Dose		N	%	N	%			
2010	Tehran	240 b.i.d.	200 b.i.d. (received metronidazole (M) (500 mg bid) rst 5 days, followed by furazolidone for the second 5 days.	1000 b.i.d.	O	20 b.i.d.	10	107	78.5	92	91.3	UBT	Lost (n=3) Side effect (n=2) No UBT (n=10)	[30]
2010	Tehran	240 b.i.d.	200 b.i.d. (received clarithromycin (500 mg bid) first 5 days, followed by furazolidone (F) for the second 5 days.	1000 b.i.d.	O	20 b.i.d.	10	106	82	98	88.7	UBT	Lost (n=1) Side effect (n=1) No UBT (n=6)	[30]

PPI, proton pump inhibitor; PP, per protocol; q.i.d., four times daily; b.i.d., twice daily; q.i.d., four times daily; q.d. daily; ITT, intention to treat; BPC, bismuth potassium citrate; O, omeprazole; P, pantoprazole.