International Journal of
Clinical Pharmacology & Pharmacotherapy
Mini Review Open Access

Bismuth-Containing Therapy for *Helicobacter pylori* Eradication

Huei-Mi Li[1], Jyh-Chin Yang[2*]
[1]*School of Pharmacy, National Taiwan University, Taipei, Taiwan*
[2]*Department of Internal Medicine, Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*

Introduction

Helicobacter pylori (*H. pylori*) was first identified in human and cultured by Marshall and Warren in 1982 [1]. More than 50% of the world's population are infected by *H. pylori* , which is etiologically associated with gastritis, gastric atrophy, peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer [2, 3]. Currently, triple therapy with combinations of a proton pump inhibitor (PPI) and two antibiotics (i.e., PPIs/clarithromycin/amoxicillin or metronidazole) are used as the treatment of choice for *H. pylori* infection [4-6]. However, resistance to antibiotics can be the major factor affecting the cure rate for *H. pylori* infection [7]. The prevalence of resistance to clarithromycin or metronidazole in different studies has been variously reported to be 2-25% or 9-76%, respectively, depending on the geographical areas, and the trend to antibiotic resistance is rising [8-12]. Consequently, the eradication rate of triple therapy for *H. pylori* infection has been rapidly falling to below 80% in most areas [13, 14]. This increase in antibiotic resistance has become a challenge to the eradication of *H. pylori* and alternative treatments are required.

Publication History:

Received: May 05, 2015
Accepted: July 02, 2016
Published: July 04, 2016

Keywords:

Phytotherapy, Natural anxiolytics, Active plant compounds, GABAA receptors

Guidelines	2016 Canada	2012 Europe	2009 Asia-Pacific Region	2007 USA
First-line	Guided by antimicrobial susceptibility testing BQT, 14 days CT, 14 days	**Low CLA-R** CLA-TT, 7-14 days **High CLA-R** BQT, 10-14 days	CLA-TT, 7-14 days	CLA-TT, 10-14 days BQT, 10-14 days
Alternative	**Low CLA-R** CLA-TT, 14 days	**Low CLA-R** BQT, 10-14 days **High CLA-R** ST, 10 days/CT	BQT, 7-14 days ST, 10 days (need more data)	ST, 10 days (need more data
Second-line	BQT, 14 days LEV-T, 14 days	**Low CLA-R** BQT, 10-14 days LEV-T, 10 days **High CLA-R** LEV-T, 10 days	BQT, 7-14 days LEV-T, 10 days RIF-T, 7-10 days	BQT, 10-14 days LEV-T, 10 days
Third-line		Guided by antimicrobial susceptibility testing		

Table :. International guidelines for the management of *H. pylori* infection.
CLA-R: clarithromycin-resistant; CLA-TT: clarithromycin-containing triple therapy; BQT: bismuth-containing quadruple therapy; LEV-T: levofloxacin-containing triple therapy; ST: sequential therapy; CT: concomitant therapy

Alternative regimens include sequential therapy (dual therapy with PPI and amoxicillin followed by triple therapy with PPI, clarithromycin and metronidazole) and quadruple therapy without bismuth compounds (concomitant therapy containing a PPI, amoxicillin, clarithromycin, and metronidazole). However, it remains challenging to these two regimens because of the rising trend in bacterial resistance to clarithromycin and metronidazole [14-16]. The failure of primary *H. pylori* therapy can then lead to substantial increase in post-treatment antimicrobial resistance [14, 17, 18]. On the other hand, levofloxacin-containing triple therapy has been recommended as the first-line, alternative, or rescue therapies [6, 13], but their eradication rates vary among studies and are usually below 90% by intention-to-treat (ITT) analysis [14]. Meanwhile, the failure of levofloxacin-containing therapy can significantly increase the development of antibiotic resistance [17-19], further limiting the efficacy of subsequent rescue therapies. These recommended treatments were summarized in Table 1.

Compared to clarithromycin, not only resistance to bismuth has not been reported but resistance to tetracycline is also uncommon, with a mean rate of 1-10%[9, 20, 21]. The aim of the present work is to briefly review the development of bismuth-containing therapy for *H. pylori* infection.

The Comeback of Bismuth in Treating *H. pylori* Infection

Bismuth compounds have been used for over two centuries in treatment of stomatitis, bowel dysfunction (flatulence, constipation,

***Corresponding Author:** Dr. Jyh-Chin Yang,, Department of Internal Medicine, Hospital and College of Medicine, National Taiwan University, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan; Tel: +886-2-937018088; E-mail: jcyang47@ntu.edu.tw

Citation: Li HM, Yang JC (2016) Bismuth-Containing Therapy for *Helicobacter pylori* Eradication. Int J Clin Pharmacol Pharmacother 1: 113. doi: http://dx.doi.org/10.15344/2016/ijccp/113

abdominal pain), and non-ulcer (functional) dyspepsia [22-24]. However, the use of the majority of bismuth compounds has become unpopular because of their potential adverse effects. Also, a number of drug-regulatory authorities are actively delisting bismuth-containing products from medical use [25]. Nonetheless, the development of colloidal bismuth subcitrate (CBS), bismuth subsalicylate (BSS), and ranitidine bismuth citrate (RBC) have attracted renewed interest because of their newly discovered activities for travellers' diarrhea, peptic ulcer disease, and *H. pylori*-related gastroduodenal disease.

Action Mechanism of Bismuth Salts

Bismuth is a trivalent heavy metal element used in many medical applications [26]. A number of different bismuth-based preparations are available, including BSS that is commonly used in the United States and CBS that is used in Europe [27], and RBC. BSS is water insoluble while CBS is water soluble, and both have low systemic absorption [28]. Despite a long history of being a medicinal agent for gastrointestinal disorders and duodenal ulcers, the mechanism of action of bismuth compounds against *H. pylori* is still controversial. Nevertheless, bismuth absorption is not required for its efficacy in *H. pylori* eradication, suggesting a local mechanism for action. An effective bismuth concentration approximating 1 mg/mL has been suggested at standard therapeutic dosing [29]. The minimal inhibitory concentration of bismuth to prevent the growth of 90% of *H. pylori* tested (MIC90) ranges from 4 to 32 mg/L [30, 31]. Potential mechanisms of action for bismuth may include: complexes of bismuth with the bacterial wall and periplasmic membrane are noted on electron microscopic studies [32]; inhibition of a number of the enzymes produced by *H. pylori* including urease, catalase and lipase are observed, which may affect the local environment for growth of the organism [33, 34]; an inhibition of adherence of *H. pylori* to surface epithelial cells can [35, 36]; impeded proton entry into the organisms potentially impairing their ability to respond to acid and enhancing the efficacy of growth-dependent antibiotics [37].

Bismuth Monotherapy and Bismuth-Containing Dual Therapy

Starting in the mid to late 1980s, numerous studies have attempted to cure *H. pylori* infections using CBS, BSS, and RBC. CBS and BSS were the first bismuth compounds shown to inhibit the growth of *H. pylori* in vitro. RBS is also active against *H. pylori* in vitro [28]. However, the eradication rate of bismuth monotherapy was low and was comparable to that of amoxicillin, which mainly suppresses the organism temporarily [38-39]. Bismuth-containing treatment combined with other antibacterial agents has been more successful in treating *H. pylori* infection than with monotherapy. Eradication rate with the combination of bismuth and metronidazole was better than bismuth plus amoxicillin (55.1% vs. 43.7%, p=0.049). The average eradication rate of other dual therapies was about 48.5% (Table 2).

Antibiotic agent	Regimen	Eradication rate (%)
Monotherapy		
CBS	120 mg QID for 4 weeks	10/27 (37)
CBS	120 mg QID for 4 weeks	2/26 (7.7)
CBS	120 mg QID for 4 weeks	12/67 (18)
CBS	120 mg QID for 4 weeks	14/43 (33)
CBS	480 mg QID for 8 weeks	6/22 (27)
CBS	120 mg QID for 4 weeks	5/20 (25)
CBS	120 mg QID for 4 weeks	14/101 (14)
CBS	120 mg QID for 8 weeks	6/20 (30)
CBS	240 mg BID for 8 weeks	3/20 (15)
BSS	900 mg TID for 4 weeks	1/17 (5.9)
BSS	600 mg TID for 6 weeks	3/24 (12)
Amoxicillin	375 mg TID for 4 weeks	5/22 (23)
Amoxicillin	750 mg BID for 2 weeks	1/7 (14)
Amoxicillin	375 mg TID for 4 weeks	11/45 (24)
Doxycycline	100 mg QD for 9 days	0/7 (0)
Tinidazole	1 g BID for 5 days	0/7 (0)
Dual therapy		
CBS + Amoxicillin	120 mg QID for 4 week + 375 mg TID for 4 week	8/20 (40)
CBS + Amoxicillin	120 mg QID for 4 week + 500 mg TID for 1 week	9/18 (50)
CBS + Amoxicillin	120 mg QID for 4 week + 500 mg TID for 2 week	12/60 (60)
CBS + Amoxicillin	120 mg QID for 2 week + 500 mg TID for 1 week	10/20 (50)
CBS + Amoxicillin	120 mg QID for 4 week + 375 mg TID for 4 week	8/23 (35)
BSS + Amoxicillin	600 mg TID for 6 week + 1 g BID for 2 week	11/23(49)
CBS + Metronidazole	120 mg QID for 4 week + 400 mg TID for 1st week	19/26 (73)
CBS + Metronidazole	120 mg QID for 1 week + 500 mg TID for 1 week	10/26 (38)
BSS + Metronidazole	524 mg QID for 3 week + 250 mg QID for 2 week	15/19 (79)
Amoxicillin + Metronidazole	500 mg TID for 1 week + 400 mg TID for 1 week	15/27 (56)
Amoxicillin + Tinidazole	500 mg QID for 8 days + 200 mg BID for 8 days	28/53 (53)
Amoxicillin + Ofloxacin	500 mg QID for 8 days + 200 mg BID for 8 days	3/15 (20)

Table 2: Monotherapy and dual therapy used in the treatment of *H. pylori* infection.

Bismuth-Containing Triple Therapy

Different from bismuth monotherapy and bismuth-containing dual therapy, bismuth-containing triple therapy, consisting of bismuth salt, metronidazole, and tetracycline, has been demonstrated to be effective in eradicating *H. pylori*. Giving a combination of CBS (108 mg four times daily) and tetracycline (500 mg four times daily) for 4 weeks along with metronidazole (200 mg four times daily) for the first 10 days, an eradication rate of at least 94% was achieved [40, 41]. This BMT (bismuth/metronidazole/tetracycline) therapy was shown to give a statistically higher eradication rate than the combination of bismuth, metronidazole, and amoxicillin (94.1% vs. 73.1%, p<0.0005) [39]. In this regard, the BMT therapy has been recommended at the NIH Consensus Conference on *H. pylori* in 1994 [42]. However, metronidazole resistance significantly reduced the effectiveness of the regimen. The eradication rate was 19/21 (90.5%) in patients with metronidazole-sensitive organisms, whereas it was only 6/19 (31.6%)

in patients with metronidazole-resistant strains [43]. Also, the complexity of these regimens has led to poor patient compliance in clinical practice. In this regard, BMT therapy was gradually replaced by the clarithromycin-containing triple therapy.

Bismuth-Containing Quadruple Therapy

Although bismuth-containing triple therapy provides high eradication rates, primary and acquired resistance to metronidazole in *H. pylori* has led to treatment failure [44,45]. In early 1990s, proton pump inhibitors (PPIs) were developed and have been concomitantly used with bismuth-containing triple therapy, showing increased treatment efficacy [46,47]. The combination had its supporters but remained a rescue treatment thereafter before the PPI-clarithromycin-containing triple therapy was recommended as the standard treatment [48,49]. However, the effectiveness of PPI-clarithromycin-containing triple therapy is decreasing due to the increase in antibiotic resistance to clarithromycin. Alternatively, bismuth-containing quadruple therapy (BQT) containing a PPI, bismuth, metronidazole, and tetracycline is effective even in the presence of resistance to metronidazole [50]. For the comparison of BQT and standard triple therapy, BQT achieved eradication in 83.4% of patients whereas standard triple therapy achieved an eradication rate of 70.4% [51,52]. There were no statistical differences in side effect and compliance. Starting from Maastricht III consensus report, in areas with high clarithromycin resistance, BQT is recommended instead of standard triple therapy as alternative first choice treatment for *H. pylori* eradication [53]. Currently, not only in Europe but in Toronto Consensus, BQT consisting of a PPI, bismuth, metronidazole, and tetracycline for 10-14 days has been recommended to be the standard or an alternative first-line treatment in areas with 15-20% prevalence of clarithromycin resistance [6, 54]. Also, BQT can eradicate the bacterium in 77.6% (range from 64.8% to 89.4%) of naïve patient by ITT analysis and its efficacy was not affected by metronidazole resistance [55]. However, it was difficult to get a good compliance because of the difference in the timetable of each medicine and the problems to get the bismuth salts in some countries. The development of a formulation of BMT three-in-one capsule (Pylera®, Aptalis, Mont St Hilaire, QC, Canada) may allow standardization of the treatment with a better compliance [52]. The combined formulation has shown to be effective in the treatment of *H. pylori* infection [56]. However, photosensitivity has been a major concern, which can be manifested by an exaggerated sunburn reaction in patients taking tetracycline. Bismuth subcitrate potassium may cause temporary and harmless darkening of the tongue and/or black stools, generally reversible within several days after treatment is stopped. Other adverse reactions include taste perversion, diarrhea, nausea, headache, and abdominal pain [57].

The comeback of BQT because it has the advantage of using the following compounds. First, the resistance of bismuth salts have not been described. Secondly, tetracycline is an antibiotic for which resistance is rarely encountered. The reason is that to reach a high level resistance, three adjacent point mutations are required. The change in the nucleotide triplet (AGA-926 to 928→TTC) has been associated with this resistance probably because of a lack of binding to the h1 loop, which is the binding site of tetracycline on the 30S subunit of the ribosome. For the third antimicrobial compound, metronidazole, it against *H. pylori* is also concentration-dependent [58,59]. Also, it has a post-antibiotic effect for more than 3 hours against anaerobes, but there is no available data against *H. pylori* [60]. Resistance in vitro exists at a high prevalence in most countries around the world, but the clinical impact of this resistance is limited and it can be overcome by increasing the dose and duration of treatment.

Prolong Treatment Duration to 14 Days

In light of the higher eradication rates compared to regimens of shorter durations, the consensus group strongly recommended that all *H. pylori* regimens (both first-line and rescue therapies) be administered for 14 days. This prolonged use of antibiotics for all patients is warranted because the increased failure with shorter regimens would result in resistant strains and less successful future treatments. It is best to achieve the maximum cure rates from the start [54].

Conclusion

The resistance to clarithromycin and metronidazole has limited the application of standard triple therapy. As the resistance to bismuth has not been reported, bismuth-containing therapy is worth an attention and BQT is currently a better bismuth-containing therapy used in the treatment of *H. pylori* infection. BQT has been recommended as an alternative first choice regimen to standard triple therapy, in areas with low clarithromycin resistance, and it is recommended as the first-line therapeutic option in areas with a high prevalence of clarithromycin resistance. Although the BQT is limited by the complex dosing schedule and side-effects, a formulation of BMT three-in-one capsule can be helpful to overcome this problem.

Competing Interest

The authors declare that they have no competing ointerests.

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