Effects of in vitro antibiotic resistance on treatment: Bismuth-containing regimens

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N Chiba. Effects of in vitro antibiotic resistance on treatment: bismuth-containing regimens. *Can J Gastroenterol* 2000;14(10): 885-889. Bismuth compounds remain useful for *Helicobacter pylori* eradication therapy. These include colloidal bismuth subcitrate (CBS), bismuth subsalicylate (BSS) and, most recently, ranitidine bismuth citrate (RBC). CBS appears to prevent the development of imidazole resistance when coadministered with nitroimidazoles. Traditional triple therapy with bismuth, metronidazole and tetracycline or amoxicillin (BMT/A) only partially overcomes metronidazole resistance. However, the addition of a PPI to bismuth triple therapy largely overcomes established metronidazole resistance if treatment is given for at least one week or more. When RBC rather than PPI is used with clarithromycin, this dual regimen appears to be more effective in preventing the development of secondary clarithromycin resistance. The triple combination of RBC, metronidazole and clarithromycin appears to be effective against metronidazole resistant strains of *H. pylori*. Thus, overall, there is some evidence that bismuth compounds may prevent the development of antibiotic resistance and that existing antibiotic resistance may at least be partially overcome in vitro and in vivo. With the growing emergence of *H. pylori* resistance to metronidazole and clarithromycin, further research to clarify the role of bismuth compounds is required.

Key Words: Antimicrobial susceptibility; Bismuth; Clarithromycin; Eradication; *Helicobacter pylori*; Metronidazole

Effets de la résistance aux antibiotiques *in vitro* sur le traitement : Schémas à base de bismuth

RÉSUMÉ : Les composés à base de bismuth restent utiles pour le traitement d'éradication d'*Helicobacter pylori*. On y retrouve le subcitrate de bismuth colloïdal (SBC), le subsalicylate de bismuth (SSB), et plus récemment, le citrate de bismuth-ranitidine (CBR). Le SBC semble apte à prévenir le développement de la résistance à l'imidazole lorsqu'on l'administre avec des nitro-imidazoles. La trithérapie habituelle à base de bismuth, métronidazole et tétracycline ou amoxicilline (BMT/A), ne vient que partiellement à bout de la résistance au métronidazole. Par contre, l'ajout d'un IPP à la trithérapie à base de bismuth abolit pour une bonne part la résistance au métronidazole avérée si le traitement dure au moins une semaine. Lorsqu'on utilise le CBR plutôt qu'un IPP avec la clarithromycine, ce double traitement semble plus efficace à prévenir le développement de la résistance secondaire à la clarithromycine. La trithérapie à base de CBR, métronidazole et clarithromycine semble efficace contre les souches d'*H. pylori* résistantes au métronidazole. Donc, dans l'ensemble, les composés de bismuth peuvent prévenir le développement d'une résistance aux antibiotiques et la résistance aux antibiotiques déjà établie peut être au moins partiellement vaincue *in vitro* et *in vivo*. Compte tenu de la résistance croissante de *H. pylori* au métronidazole et à la clarithromycine, il faudra approfondir la recherche pour clarifier le rôle des composés de bismuth.

The discovery of *Helicobacter pylori* (1) has revolutionized the ability to cure the approximately 15% of infected people who develop peptic ulcer disease and the rare patient with mucosa-associated lymphoid tissue lymphoma caused by this infection (2). Although causal associations between this infection and gastric carcinoma (3) have been identified, it still remains to be seen whether early eradication of

this infection can prevent subsequent development of cancer.

While the importance of *H. pylori* is well established, the ideal treatment regimen(s) remains somewhat elusive. The key antimicrobial agents, bismuth, amoxicillin, nitroimidazoles and clarithromycin, are commonly used in combination therapy. The gold standard triple therapies are one-

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Received for publication May 9, 2000. Accepted June 13, 2000

TABLE 1
Eradication of metronidazole-sensitive (MS) and -resistant (MR) strains of *Helicobacter pylori*

Author (reference)	Drugs	Eradication (%)	
		MS	MR
Chiba and Hunt (17)	BMT	89 (n=350)	50.6 (81/160)
Penston and McColl (18)	BMT/A	86 (n=787)	58 (n=322)
Tytgat (19)	BMT	85-98	32-87
	BMA	91-97	19-68

A Amoxicillin; BMT Bismuth plus metronidazole plus tetracycline

week, twice daily treatment with proton pump inhibitors (PPIs) plus clarithromycin and amoxicillin or a nitroimidazole (metronidazole or tinidazole), as recommended by numerous worldwide consensus conferences (4-7). Major factors affecting treatment success are lack of compliance due to either drug-induced side effects or the many pills consumed, and antibiotic resistance. The development of *H pylori* resistance to nitroimidazoles and clarithromycin is emerging as an important factor that adversely affects treatment success.

The available literature of the effects of in vitro antibiotic resistance on treatment are reviewed, with particular focus on bismuth-containing regimens. Surprisingly few data were identified in the literature to address this topic.

RATIONALE FOR BISMUTH COMPOUNDS IN THE TREATMENT OF *H PYLORI*

Bismuth compounds have been used for centuries to treat gastrointestinal disorders such as dyspeptic symptoms and diarrheal disorders (8). In particular, compounds such as colloidal bismuth subcitrate (CBS) have been used to heal duodenal ulcers (9,10). Bismuth compounds are topically active and have bactericidal effects against *H pylori*, possibly by disrupting its adhesion to epithelial cells or by inhibiting enzymes secreted by *H pylori*, such as proteases, lipases, glycosidases and phospholipases (11), ultimately leading to structural degeneration of *H pylori*.

Less than 1% of the oral dose of commonly used bismuth compounds such as CBS, bismuth subsalicylate (BSS) and ranitidine bismuth citrate (RBC) is absorbed (8). Although bismuth neurotoxicity is a potential concern, this occurs only when doses far in excess of those used for *H pylori* eradication are used (8).

BISMUTH MAY PARTLY PREVENT NITROIMIDAZOLE RESISTANCE

Early on, it was observed that when nitroimidazoles such as tinidazole were given alone, *H pylori* resistance developed readily. In one study, the coadministration of CBS with tinidazole reduced the development of *H pylori* resistance to tinidazole from 70% to 10% (12).

In another study, when tinidazole was given with CBS, resistance to tinidazole developed in 40%; when tinidazole

was given with amoxicillin, resistance developed in 35% (13). It was only when the three drugs were used together for 10 days that the rate of development of imidazole resistance dropped to only 3% (13). Thus, combinations of various antimicrobials appear to be important in preventing nitroimidazole resistance.

In treating patients with established nitroimidazole resistance, can the addition of a bismuth compound eradicate even resistant organisms? Two studies using dual therapy have reported such data. In the first study, CBS was used with tinidazole for 10 days and eradicated 91% of metronidazole-sensitive strains, while only 20% of resistant strains were eradicated (12). In the other study, BSS was used with metronidazole for 10 days, eradicating 82% of metronidazole-sensitive and 17% of metronidazole-resistant strains (14). The eradication rate in the metronidazole-resistant strains was no better than if bismuth compounds were given alone (15). Thus, the simple addition of a bismuth compound to a nitroimidazole does not overcome established imidazole resistance.

The first recommended gold standard, triple therapy was bismuth, metronidazole and tetracycline or amoxicillin (15,16). The effectiveness of these triple therapies for eradicating metronidazole-sensitive and -resistant strains of *H pylori* has been summarized in several reviews (17-19) (Table 1). While the efficacy is much reduced in resistant strains, the 50% or greater success is better than that of dual therapy.

The addition of a PPI to traditional bismuth triple therapy improves eradication efficacy (20). In a one-week, randomized, controlled trial comparing omeprazole, bismuth, metronidazole and tetracycline (OBMT) with bismuth, metronidazole and tetracycline (BMT), the eradication rate was 98% with OBMT and 83% with BMT ($P=0.02$) (21). Only five of the 100 strains had baseline metronidazole resistance. Of these strains, all three were eradicated with OBMT, but none of two were eradicated with BMT.

Both omeprazole and lansoprazole have been studied with BMT. Much of the available data for PPI-BMT in metronidazole-sensitive and -resistant strains have come from de Boer (21-28) in the Netherlands, who pretreated patients for three days with a PPI, then co-administered BMT for various durations. He has studied BMT for one to seven days (21-28). The one-day study used eight times daily dosing (22), while for two to seven days, the drugs were given four times daily. While the data are sparse, Figure 1, incorporating data from these studies, shows that the longer the duration of bismuth triple therapy with the PPI, the greater the improvement in efficacy in metronidazole-resistant strains, such that by one week, eradication efficacy appears unaffected by metronidazole resistance. In the one American study of lansoprazole with BMT, eradication in metronidazole-sensitive strains was 90% (26 of 29), while in resistant strains, the efficacy was reduced to 41% (seven of 17) (29). However, in this study, the drugs were given only twice daily compared with the more conventional four times daily, which may explain the reduced efficacy.

Overall, the PPI-BMT regimen for one week has been recommended as an alternative treatment after initial treatment failures and when *H pylori* metronidazole resistance is either known or suspected.

RBC MAY PREVENT THE EMERGENCE OF RESISTANCE

RBC is a unique, soluble salt that combines the gastric anti-secretory activity of ranitidine with the mucosal protective, antipepsin and anti-*H pylori* properties of bismuth (30,31). It is not simply an admixture of bismuth citrate with ranitidine.

One study specifically addressed whether the emergence of resistance to *H pylori* could be reduced when antibiotics were coadministered with RBC (32). Organisms were subcultured on media with RBC or no drug, and the rate of emergence of spontaneous resistance of *H pylori* to antibiotics was determined. When subcultured with RBC, the emergence of metronidazole resistance was significantly reduced, even in the one strain particularly prone to metronidazole resistance. The emergence of resistance to clarithromycin was reduced in one of two *H pylori* strains tested (32). An interesting observation was that *H pylori* was surrounded by bismuth oxychloride, with a greater number of bismuth molecules around the strain that showed a larger reduction in resistance. It was hypothesized that the coating of *H pylori* with bismuth molecules led to greater *H pylori* killing when metronidazole was added.

RBC DUAL THERAPY IN VITRO MAY BE EFFECTIVE AGAINST CLARITHROMYCIN-RESISTANT STRAINS

In vitro (33-35) and in mouse models (34), the combination of RBC with clarithromycin results in synergistic increases in the activity against *H pylori*, even in those resistant to clarithromycin (33,35). Using a two-dimensional checkerboard array, Osato et al (36) assessed the interaction of RBC and clarithromycin. In 10 of 11 *H pylori* isolates, the clarithromycin minimum inhibitory concentration (MIC)₉₀ was reduced an average of ninefold when combined with RBC to still achieve microbial killing, and one clarithromycin-resistant isolate (MIC₉₀ greater than 256 µg/mL) became sensitive to clarithromycin when combined with RBC. In a separate report using the same methodology, eight of 10 clarithromycin-resistant isolates became susceptible to clarithromycin (35).

RBC combined with metronidazole in vitro also demonstrated either total or partial synergy against metronidazole-resistant strains, as determined by a fractional inhibitory index of 0.5 or less (37). Dual therapy with RBC and clarithromycin may be effective against metronidazole-resistant *H pylori* strains, with eradication reported in 11 of 11 strains (38).

IN VIVO DATA

Whether RBC added to clarithromycin is effective in treating clarithromycin-resistant *H pylori* strains in vivo remains unclear, with opposing study results published.

Figure 1) Proton pump inhibitor plus bismuth, metronidazole and tetracycline triple therapy: de Boer eradication rates versus treatment duration. The numbers adjacent to the points are the number of strains evaluated. MR Metronidazole resistant; MS Metronidazole sensitive. Data from references 21-28

In an American duodenal ulcer study, patients infected with *H pylori* were treated with RBC plus clarithromycin dual therapy (39). The RBC combination did not overcome clarithromycin resistance (defined by MIC greater than 4 µg/mL), with an eradication rate of only 8% (three of 38) in resistant strains; in those with susceptible and intermediate strains, the eradication rate was 82% (208 of 254). The higher dose of clarithromycin 1.5 g/day was not more effective than the standard 1 g daily dose.

Mégraud et al (40) reported from an international study that a 14-day treatment with RBC plus clarithromycin dual therapy overcame clarithromycin resistance in 11 of 12 (92%) *H pylori* strains, while an omeprazole and clarithromycin regimen was less effective (three of eight [38%] eradicated) (40). Thus, with these opposing results, the role of dual therapy in eradicating clarithromycin-resistant *H pylori* remains to be clarified.

IN VIVO EMERGENCE OF ANTIBIOTIC RESISTANCE

Acquired clarithromycin resistance by *H pylori* after treatment with RBC and clarithromycin appeared to be reduced in two in vivo studies. In the Mégraud study reported above (40), one of 39 patients (3%) treated with RBC and eight of 44 (18%) of those treated with omeprazole acquired resistance to clarithromycin after treatment failure ($P=0.046$). Similarly, Osato et al (41), in a study of 466 patients with clarithromycin-susceptible *H pylori*, reported that, of those with treatment failure, 8% of those treated with RBC and clarithromycin and 17% of those treated with omeprazole and clarithromycin developed clarithromycin resistance ($P<0.01$). These data suggest that RBC cotherapy may reduce the emergence of antibiotic resistance.

IN VIVO RBC TRIPLE THERAPIES

RBC, tetracycline and clarithromycin triple therapy: Graham et al (42) used RBC 400 mg bid, tetracycline 500 mg bid and clarithromycin 500 mg bid for 14 days in an open study of 63 patients with clarithromycin-susceptible *H pylori* at

baseline and reported a 94% eradication success. Of the treatment failures, two of three became resistant to clarithromycin. While the sample size is small, it is unclear why there appeared to be such a large proportion of strains that became resistant compared with the 3% to 8% that became resistant compared with RBC-clarithromycin dual therapy (40,41).

RBC, metronidazole and tetracycline triple therapy: Triple therapy with RBC, metronidazole and tetracycline is a combination regimen similar to the traditional bismuth triple therapy. In one study, baseline metronidazole resistance significantly ($P=0.026$) reduced eradication efficacy from 97% in patients with a metronidazole-sensitive strain of *H pylori* compared with 57% in those with a resistant strain (43). These data are similar to those of traditional bismuth triple therapy, as discussed above, with reduced efficacy in resistant strains (Table 1). A Chinese study directly compared RBC or CBS with metronidazole and tetracycline triple therapy (RBC plus metronidazole plus tetracycline compared with BMT) and reported contrasting results, with 25 of 25 (100%) metronidazole-resistant strains eradicated with the RBC-MT regimen compared with 12 of 16 (75%, $P=0.018$) eradicated with traditional BMT triple therapy (44). Reasons for the contrasting results between these studies are unknown, and the true effect of metronidazole resistance on treatment efficacy remains to be elucidated. However, it is probable that there is a deleterious effect of resistance on efficacy because overall reported results with this regimen are more variable, ranging from 60% (45) to 92% (44).

RBC, metronidazole and clarithromycin triple therapy: PPI triple therapy, when combined with clarithromycin and metronidazole, is less effective when *H pylori* resistance to metronidazole is present (46). Triple therapy with RBC, clarithromycin and metronidazole overcame metronidazole resistance in nine of 10 strains in each of two studies (38,47).

Another clinical trial evaluated the effects of two different RBC triple therapies on resistant strains (48). With metronidazole resistance defined as an MIC greater than 8 µg/mL by the E-test, and clarithromycin resistance as an MIC greater than 2 µg/mL, the 20 patients with a metronidazole-resistant strain of *H pylori* treated for one week with RBC 400 mg bid, metronidazole 500 mg bid and clarithromycin 500 mg bid had 95% *H pylori* eradication. *H pylori* was also eradicated in three patients with baseline clarithromycin-resistant strains and in the one patient infected with a strain resistant to both antibiotics. In the patients who received amoxicillin 1 g bid in place of clarithromycin, eradication was 87% in metronidazole-susceptible strains but only 22% in metronidazole-resistant strains, suggesting that RBC triple therapy containing clarithromycin is more effective than amoxicillin in eradicating metronidazole-resistant *H pylori*.

SUMMARY

Bismuth compounds most commonly used in *H pylori* eradication include CBS, BSS and the newer RBC. With the recent focus on antibiotic resistance, the newer RBC has more

resistance data available. Overall, however, there are surprisingly few published data on this important topic.

CBS appears to prevent the development of imidazole resistance when coadministered with nitroimidazoles (12). If amoxicillin is added to the dual therapy, metronidazole resistance may be reduced further (13).

If imidazole resistance is present at baseline, neither the bismuth and imidazole dual therapy (12,14) nor the bismuth, metronidazole and tetracycline or amoxicillin (BMT/A) triple therapy (Table 1) effectively overcomes metronidazole resistance. However, the BMT/A triple therapy partially overcomes metronidazole resistance, with better results than with dual therapy. The newer RBC has been studied in an analogous regimen, and because results are discrepant (43,44), the efficacy of the RBC with metronidazole and tetracycline triple regimen remains unclear.

The addition of a PPI to traditional bismuth therapy (PPI-BMT) helps to overcome established metronidazole resistance; this effect is dependent on the duration of treatment (Figure 1).

In vitro, RBC combined with metronidazole may prevent the emergence of metronidazole resistance, and RBC combined with clarithromycin may also prevent the emergence of clarithromycin resistance (32). Also in vitro, these dual therapies may be effective against metronidazole- (37) and clarithromycin-resistant (33,35) *H pylori* strains. However, in vivo, conflicting study results of the efficacy of RBC with clarithromycin in eradicating clarithromycin-resistant strains have been reported (39,40). A regimen comprising RBC and clarithromycin appears to be more effective than a regimen comprising a PPI with clarithromycin in preventing clarithromycin resistance in treatment failure (40,41).

The triple combination of RBC, metronidazole and clarithromycin appears to be effective against metronidazole-resistant strains of *H pylori*, with consistent results reported in three studies (38,47,48).

Overall, there is some evidence that bismuth compounds may prevent the development of antibiotic resistance and that existing antibiotic resistance may at least be partially overcome in vitro and in vivo. Further data on this important topic are hopefully forthcoming.

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