Ranitidine bismuth citrate

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N Chiba, RH Hunt, ABR Thomson. Ranitidine bismuth citrate. Can J Gastroenterol 2001;15(6):389-398. Recognition of the relationship between *Helicobacter pylori* infection and the development of gastroduodenal disease has increased greatly in recent years. To avoid complications of *H pylori* infection, such as the development of recurrent duodenal and gastric ulcers, effective therapies are required for eradication of the infection. This article reviews ranitidine bismuth citrate (RBC), a novel complex of ranitidine, bismuth and citrate, which was developed specifically for the purpose of eradicating *H pylori*. Dual therapy with RBC in combination with clarithromycin for 14 days yields eradication rates of 76%. Triple therapy bid for one week with a proton pump inhibitor, clarithromycin and either amoxicillin or a nitroimidazole (tinidazole or metronidazole) is advocated as the treatment of choice for *H pylori* eradication. Analogous regimens with RBC in place of proton pump inhibitors show effective eradication rates in comparative studies and with pooled data. RBC, used alone or in combination with other antibiotics, appears to be a safe and effective drug for the treatment of *H pylori* infection. Bismuth levels do not appear to rise to toxic levels.

Key Words: Helicobacter pylori *treatment*

L'association ranitidine-bismuth-citrate

RÉSUMÉ : Depuis quelques années, on admet de plus en plus l'existence d'un lien entre l'infection à *Helicobacter pylori* et le développement de la maladie gastro-duodénale. Pour éviter les complications de l'infection à *H. pylori*, par exemple les récidives d'ulcères duodénaux et gastriques, il faut éradiquer l'infection au moyen de traitements efficaces. Cet article fait le point sur un traitement associatif de ranitidine-bismuth citrate (RBC), un nouveau complexe mis au point précisément dans le but d'éradiquer *H. pylori*. Le double traitement par RBC avec clarithromycine pendant 14 jours, donne lieu à des taux d'éradication de 76 %. Une trithérapie b.i.d. d'une durée d'une semaine avec un inhibiteur de la pompe à protons, de la clarithromycine et soit de l'amoxicilline ou du nitro-imidazole (tinidazole ou métronidazole) est préconisé comme traitement de choix pour l'éradication de *H. pylori*. Des schémas analogues par RBC au lieu des inhibiteurs de la pompe à protons donnent lieu à des taux d'éradication efficaces selon des études comparatives avec données regroupées. Le RBC utilisé seul ou en association avec d'autres antibiotiques semble sûr et efficace pour le traitement de l'infection à *H. pylori*. Les taux de bismuth ne semblent pas atteindre des taux toxiques.

About 15% of those infected with *Helicobacter pylori* will eventually develop peptic ulcer disease (1), and, according to global statistics, approximately 2% will develop gastric cancer (2). *H pylori* infection is responsible for up to 95% of duodenal ulcers (DU) and 80% of gastric ulcers, although *H pylori*-negative ulcers are increasing in North America as a proportion of ulcers diagnosed (1). A confirmed cure of the infection reduces the ulcer recurrence rate from between 60% and 80% to less than 5% the year after treatment (3). Because of the relationship between *H pylori* and the development of gastric cancer, eradicating the bacteria is anticipated, but not yet proven, to reduce the risk of this disease. Strategies for the management of *H pylori* infection have been proposed in Canada by the Canadian *H pylori* Study Group (4).

Although *H pylori* is susceptible to a wide variety of antibiotics in vitro, the organism has proved to be difficult to eradicate in vivo. The eradication rate for any monotherapy is usually less than 20% (5). Clarithromycin is the only treatment that has been shown to achieve higher rates of eradication (6,7), but the use of a single drug is not recommended because of the high rate of developing antibiotic resistance (6).

The determination of an ideal *H pylori* eradication regi-

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men has been elusive. The first gold standard triple therapy of bismuth, metronidazole and tetracycline (BMT) (3,5) remains effective. However, the large number of pills that must be consumed and the reduced efficacy in metronidazole-resistant *H pylori* infections are problematic (8). Dual therapy with a proton pump inhibitor (PPI) and either amoxicillin or clarithromycin has fewer side effects, but lower efficacy (8). These treatments evolved to the present gold standard triple therapies of a PPI with clarithromycin and either amoxicillin or a nitroimidazole (metronidazole or tinidazole) bid for one week, as recommended by numerous worldwide consensus conferences (9-12). However, these therapies are not uniformly effective, with somewhat variable efficacies in the presence of resistant *H pylori* strains.

There is still a need for the development of new drugs against *H pylori*. This paper reviews the clinical data regarding the efficacy and safety of a new agent, ranitidine bismuth citrate (RBC), developed specifically to eradicate *H pylori* infection.

RBC

Pharmacology: RBC is a novel complex of ranitidine (162 mg), bismuth (128 mg) and citrate (110 mg). It is an amorphous salt with consistent composition as shown by x-ray powder photography. RBC gives no characteristic diffractions and has no melting point, with decomposition beginning at about 150°C (13). There are clear structural differences between RBC and the admixture of ranitidine and bismuth citrate, as shown through infrared and nuclear magnetic resonance spectroscopy (13). The 400 mg dose of RBC is as effective as a 150 mg dose of ranitidine in inhibiting both daytime and nocturnal intragastric acidity (14), as well as meal-stimulated gastric acid secretion (14,15). Inhibition of gastric acid output by RBC is both time- and dose-dependent, and is independent of *H pylori* status (15). A single dose of RBC does not affect plasma gastrin levels (15), and RBC does not attenuate the rise in meal-stimulated gastrin levels compared with ranitidine (16).

RBC dissolves freely in water, particularly above pH 4, compared with an equimolar admixture of ranitidine and bismuth citrate, which forms an almost insoluble suspension (13). This solubility confers an increased activity against *H pylori* (17). Because the bismuth derived from RBC is far more soluble than bismuth subsalicylate, a lower dose of bismuth is needed for a therapeutic effect. For example, treatment with an RBC-based regimen includes a total of 258 mg of bismuth per day, compared with 2098 mg of bismuth (two tablets qid) when using bismuth subsalicylate. Absorption of bismuth is modest and increases in a dose-dependent fashion (14).

RBC is also more potent than its individual components for protection against indomethacin-induced gastric mucosal damage in the antrum and ethanol-induced fundic damage in a rat model (17). In addition, RBC inhibits human pepsin isoenzymes, while the admixture is inactive (13,17).

Thus, RBC is a novel molecule and new chemical entity that combines the gastric antisecretory activity of ranitidine with mucosal protective, antipepsin and anti-*H pylori* properties of bismuth. It is not simply an admixture of bismuth citrate with ranitidine.

ERADICATION OF *H PYLORI* INFECTION

A large, dose-finding, randomized, controlled trial (RCT) reported that RBC 200 mg bid, 400 mg bid and 800 mg bid healed DU as effectively and safely as ranitidine 150 mg bid (18). RBC is more effective than bismuth citrate and/or ranitidine against *H pylori*, and the bactericidal effect is more rapid (13,17). RBC suppresses but does not successfully eradicate *H pylori* infection by itself (18-21) and enhances the efficacy of a combination of antibiotics against *H pylori*.

Analysis of eradication rates in clinical trials: The efficacy of RBC combined with antibiotics has been evaluated in well designed clinical RCTs. Eradication rates from these studies have been calculated by three types of analyses: intention-to-treat (ITT), per-protocol and observed. ITT analysis includes all patients who were infected with *H pylori* at the time of random assignment. Those who are not evaluated at least four weeks after the end of therapy and those whose test results are otherwise unevaluable are counted as treatment failures or as *H pylori*-positive. These patients are included in the denominator of the eradication equation, but not in the numerator. Per protocol analysis excludes patients with missing or unevaluable post-therapy results and those who did not comply with the study protocol from the denominator. The observed rate includes those who did not comply with therapy but excludes those with missing or unevaluable results. Other investigators have used the more familiar term of 'all patients treated', which appears to be essentially the same analysis. A criticism is that when studies are reported as the unfamiliar term 'observed' ITT, readers may be confused into thinking that this is the traditional ITT.

The eradication rates presented in the tables of this review are all ITT rates from fully published RCTs. All patients who were randomly assigned to treatment have been included in the denominator. If a patient had a negative *H pylori* test result at least four weeks after the end of therapy and no positive results at any time after treatment, the patient was included in the numerator as a treatment success. Ninety-five per cent confidence intervals are given where available.

RBC plus one antibiotic: As an alternative to triple therapy with two antibiotics, dual therapy of RBC in combination with amoxicillin is ineffective, and data remain in abstract form only (22,23). However, RBC in combination with clarithromycin shows improved efficacy (Table 1) (23,24). Two studies have shown a synergistic effect when RBC and clarithromycin are used together, with the eradication rate being much greater than when the drugs are administered individually (19,25). Study designs, doses, scheduling and ITT eradication rates from 12 studies and 18 study arms of RBC and clarithromycin are shown in Table 1. The dose of RBC used in these studies was usually 400 mg bid for 14 to 28 days. Increasing the dose of RBC from 400 mg to 800 mg bid did not improve *H pylori* eradication rates (20,21).

The clarithromycin dose ranged from 250 mg qid to 500 mg tid for 14 days. Compared within the same studies, two weeks of RBC with clarithromycin either 250 mg qid or 500 mg bid gave equivalent results (26,27). No differences in adverse events were seen. However, the bid therapy would be pre-

TABLE 1
Summary of dual therapy of ranitidine bismuth citrate (RBC) in combination with clarithromycin

						Helicobacter pylori tests	
Author (reference)	**Patient conditions**	**Study design**	**Drugs, dosages and durations**	**Eradication (%) with ITT analysis**	**95% CI with ITT analysis**	**Pre-treatment**	**Post-treatment**
Pozzato et al (29)	Active duodenal ulcer	Open, randomized, multicentre	RBC 400 mg bid for 28 days plus clarithromycin 500 mg bid for seven days	42/56 (75)	62% to 86%	At least two of: CLO (A and C) plus H (A and C) plus ^{13}CUBT	CLO (A and C) plus H (A and C) plus ^{13}CUBT
			RBC 400 mg bid for 28 days plus clarithromycin 500 mg bid for 14 days	45/56 (80)	68% to 90%		
Cestari (34)	Dyspepsia	Open, randomized, multicentre	RBC 400 mg bid for 14 days plus clarithromycin 500 mg bid for 14 days	78/116 (67)	58% to 76%	RUT (A) plus H (A and C) plus ^{13}CUBT	^{13}CUBT
Lanza et al (25)	Active duodenal ulcer	Double-blind, randomized, multicentre	RBC 400 mg bid for 28 days plus clarithromycin 500 mg tid for 14 days	18/21 (86)		Culture plus H plus CLO (A)	Culture plus H plus CLO (A)
Bardhan et al (26)	Active duodenal ulcer	Double-blind, randomized, multicentre	RBC 400 mg bid for 28 days plus clarithromycin 250 mg qid for 14 days	187/255 (73)		CLO plus H (A) plus ^{13}CUBT	H (A and C) plus ^{13}CUBT
			RBC 400 mg bid for 28 days plus clarithromycin 500 mg bid for 14 days	202/253 (80)			
Bardhan et al (20)	Active duodenal ulcer	Double-blind, randomized, multicentre	RBC 400 mg bid for 28 days plus clarithromycin 250 mg qid for 14 days	57/69 (83)	72% to 91%	CLO (A and C) plus ^{13}CUBT	CLO (A and C) plus ^{13}CUBT
			RBC 800 mg bid for 14 days plus clarithromycin 250 mg qid for 14 days plus RBC 400 mg bid for 14 more days	51/72 (71)	59% to 81%		
Pounder et al (21)	Active duodenal ulcer	Double-blind, randomized, multicentre	RBC 400 mg bid for 28 days plus clarithromycin 250 mg qid for 14 days	18/30 (60)	72% to 91%	CLO (A and C) plus H (A and C) or ^{13}CUBT	CLO (A and C) plus H (A and C) plus ^{13}CUBT
			RBC 800 mg bid for 14 days plus clarithromycin 250 mg qid for 14 days plus RBC 400 mg bid for 14 more days	17/31 (55)	59% to 81%		
van der Wouden et al (36)	Peptic ulcer disease or dyspepsia	Open, randomized, two-centre	RBC 400 mg bid for 28 days plus clarithromycin 500 mg bid for 14 days	50/52 (96)	87% to 100%	RUT plus culture (A) plus histology (A and C)	RUT (A) plus culture plus histology (A and C) plus ^{13}CUBT
Dobrilla et al (28)	Active duodenal ulcer	Double-blind, randomized, double blind	RBC 400 mg bid for 28 days plus clarithromycin 500 mg bid for 14 days	104/136 (76)	68% to 83%	CLO plus H (A and C)	CLO plus H (A and C)
			RBC 400 mg bid for 28 days plus clarithromycin 500 mg tid for 14 days	107/137 (78)	70% to 85%		
Kolkman et al (65)	Duodenal ulcer history	Double-blind, randomized, multicentre	RBC 400 mg bid for 28 days plus clarithromycin 500 mg bid for 14 days	51/61 (84)	74% to 93%	CLO plus histology plus culture (all A and C)	CLO plus histology plus culture (all A and C)
Axon et al (27)	Active duodenal ulcer	Double-blind, randomized, multicentre	RBC 400 mg bid for 28 days plus clarithromycin 250 mg qid for 14 days	89/125 (71)		CLO (A) plus ^{13}CUBT	^{13}CUBT
			RBC 400 mg bid for 28 days plus clarithromycin 500 mg bid for 14 days	76/111 (69)			
Gudjonsson et al (37)	Dyspepsia	Double-blind, randomized, multicentre	RBC 400 mg bid for 14 days clarithromycin 500 mg bid for 14 days	133/171 (78)	72% to 84%	RUT (A) plus ^{13}CUBT	^{13}CUBT (two tests)
De Boer et al (35)	*H pylori*-positive	Open, randomized, multicentre	RBC 400 mg bid for 14 days plus clarithromycin 500 mg bid for 14 days	53/56 (95)	85% to 99%	CLO plus H plus culture (A and C)	CLO plus H plus culture (A and C)

A Antrum; C Corpus; ^{13}CUBT ^{13}Carbon urea breath test; H Histology; ITT Intention-to-treat; RUT Rapid urease test

TABLE 2
Ranitidine bismuth citrate (RBC) plus clarithromycin versus omeprazole plus clarithromycin in the eradication of resistant and susceptible strains of *Helicobacter pylori*

Strains of *H pylori*	Eradication for RBC plus clarithromycin (%)	Eradication for omeprazole plus clarithromycin (%)
Susceptible (<0.5 mg/L)	38/39 (97%)	32/44 (73%)
Intermediate (0.5mg/L to 2 mg/L)	4/4 (100%)	1/3 (33%)
Resistant (>2 mg/L)	11/12 (92%)	3/8 (38%)
Unevaluable	7/7 (100%)	6/9 (67%)
Total intention-to-treat	60/69 (87%)	42/72 (58%)

Data taken from reference 31

ferred due to its simplicity. Increasing the dose of clarithromycin to 500 mg tid is as effective as 500 mg bid for *H pylori* eradication and DU healing (28). Adverse events and dropout rates due to side effects (3% to 4%) were comparable between groups. Thus, the optimal dose of clarithromycin RBC in dual therapy is 500 mg bid. The ITT eradication rate ranges from 55% to 96%, and pooled results from the 1752 patients treated with RBC plus clarithromycin for 14 days in these studies is 76% (95% CI 70% to 82%).

RBC dual therapy for one week has also been studied in one published study (29). Pozzato et al (29) compared RBC 400 mg bid plus clarithromycin 500 mg bid for seven or 14 days in DU patients. There were comparable ITT eradication rates of 75% for patients given the seven-day regimen compared with 80% for patients assigned to the 14-day regimen, and compliance was excellent for both treatment durations (29). Another study (only in abstract form) compared one-week dual therapy using RBC and clarithromycin with triple therapy using RBC, clarithromycin and metronidazole. ITT eradication rates were 87% (48 of 55 patients; 95% CI 76% to 95%) for the dual therapy and 98% (54 of 55 patients; 95% CI 90% to 100%) for the triple regimen (30). Further data are required to determine whether the duration of RBC and clarithromycin dual therapy can be reduced to one week.

The efficacy of 14-day, RBC plus clarithromycin dual therapy in the eradication of *H pylori* infections shown to be resistant to clarithromycin is shown in Table 2 (31). In this study, the RBC and clarithromycin regimen appeared to be able to overcome the clarithromycin resistance, while the omeprazole and clarithromycin regimen did not (31). However, in a different American study, the same dual therapy was not effective against clarithromycin-resistant *H pylori* infections (32). Thus, the role of dual therapy in overcoming clarithromycin-resistant *H pylori* strains remains to be clarified.

The development of antibiotic resistance by *H pylori* strains during treatment with RBC and antibiotics has been evaluated in vivo in two studies. Mégraud et al (31) evaluated the antibiotic sensitivities of *H pylori* strains before dual therapy with either RBC or omeprazole and clarithromycin 500 mg bid for 14 days. After treatment, one of 39 patients (3%) treated with RBC and eight of 44 patients (18%) treated with omeprazole acquired resistance to clarithromycin (P=0.046). Similarly, Osato et al (33), in a study of 466 patients with initially clarithromycin-susceptible *H pylori*, found that of those patients with treatment failures, 8% of those treated with RBC and clarithromycin, and 17% of those treated with omeprazole and clarithromycin had developed clarithromycin resistance (P<0.01). Thus, these data suggest that the emergence of antibiotic resistance may be less with RBC-based therapy. Further studies are important and are awaited with interest.

Dual compared with triple therapy: RBC triple therapy for one week has been compared with dual therapy combining RBC and clarithromycin for two weeks (Tables 1, 3 and 4) (34-37). One study (34) found one-week triple therapy with RBC 400 mg bid, clarithromycin 250 mg bid and tinidazole 500 mg bid to be significantly better (P=0.001) than two-week dual therapy with RBC 400 mg bid and clarithromycin 500 mg bid (34). However, in other studies using RBC and clarithromycin dual therapy for two weeks, the proportion of patients cured was equivalent to those using RBC, clarithromycin and metronidazole triple therapy for one (36) or two weeks (26,37). It is thus unclear whether triple therapy is superior to dual therapy.

RBC TRIPLE THERAPIES

Eradication of *H pylori* with RBC plus clarithromycin and a nitroimidazole: The designs, doses, scheduling, testing details and ITT eradication rates from nine studies and 12 study arms of RBC in combination with clarithromycin and a nitroimidazole (metronidazole or tinidazole) are shown in Table 3. The dose of RBC in these trials was 400 mg bid for seven to 14 days. No RBC was given after the end of the seven-day eradication regimens.

With RBC, clarithromycin and metronidazole, a treatment duration of seven days was as effective as 10 days (38) or 14 days (26). A short, four-day therapy was not an effective treatment, having a suboptimal 60% eradication rate (38). There was a trend toward more side effects with the longer duration of treatment; three of 55 patients dropped out because of drug side effects in the 10-day arm, compared with one of 55 patients in the seven-day arm and none in the four-day arm (38). In comparing studies, there does not appear to be any differences between the regimens that used clarithromycin 250 mg bid (38,39) and the regimens that used clarithromycin 500 mg bid (26,36,37). The dose of metronidazole ranged from 800 mg to 100 mg daily.

For seven-day regimens, the ITT eradication rate ranged from 80% to 94%, and pooled results in 357 patients gave a mean eradication rate of 84% (95% CI 77% to 90%). For all treatment durations pooled together in 540 patients, the mean ITT eradication rate was 82% (95% CI 77% to 87%). For RBC, clarithromycin and tinidazole, all four studies (34,40-42) used the same doses of clarithromycin (250 mg bid) and tinidazole (500 mg bid). The ITT eradication rate ranged from 73% to 91%, and the pooled result in 264 patients was 82% (95% CI 69% to 94%). Pooled results are the same when metronidazole is used. Thus, either nitroimidazole can be used, depending on availability.

TABLE 3
Summary of triple therapy of ranitidine bismuth citrate (RBC) plus clarithromycin and a nitroimidazole (metronidazole or tinidazole)

						Helicobacter pylori tests	
Author (reference)	**Patient conditions**	**Study design**	**Drugs, dosages and durations**	**Eradication (%) with ITT analysis**	**95% CI with ITT analysis**	**Pre-treatment**	**Post-treatment**
Gudjonsson et al (37)	Healed duodenal ulcer or dyspepsia	Double blind, randomized, multicentre	RBC 400 mg bid for 7 days plus clarithromycin 500 mg bid for 7 days plus metronidazole 400 mg bid for 7 days	144 /179 (80)	75% to 86%	RUT (A) plus ^{13}CUBT	^{13}CUBT (two tests)
van der Wouden et al (36)	*H pylori*-positive	Open, randomized, two-centre	RBC 400 mg bid for 7 days plus clarithromycin 500 mg bid for 7 days plus metronidazole 500 mg bid for 7 days	49/52 (94)	84% to 99%	RUT plus culture (A) plus H (A and C)	RUT (A) plus culture plus histology (A and C) plus ^{13}CUBT
Savarino et al (39)	Dyspepsia	Open, randomized, three-centre	RBC 400 mg bid for 7 days plus clarithromycin 250 mg bid for 7 days plus metronidazole 500 mg bid for 7 days	31/36 (86)	71% to 95%	CLO plus H (A and C)	CLO plus H (A and C)
			RBC 400 mg bid for 7 days plus clarithromycin 250 mg bid for 7 days plus metronidazole 250 mg qid for 7 days	29/35 (83)	66% to 93%		
Bardhan et al (26)	Active duodenal ulcer	Double-blind, randomized, multicentre	RBC 400 mg bid for 28 days plus clarithromycin 500 mg bid for 14 days plus metronidazole 400 mg bid for 14 days	98/128 (77)		CLO plus H (A) plus ^{13}CUBT	H (A and C) plus ^{13}CUBT
Savarino et al (38)	Dyspepsia	Open, randomized, single-centre	RBC 400 mg bid plus clarithromycin 250 mg bid plus metronidazole 500 mg bid for			RUT plus H using Geimsa stain	^{13}CUBT after four weeks
			4 days	33/55 (60)	46% to 73%		
			7 days	46/55 (84)	71% to 92%		
			10 days	47/55 (85)	73% to 93%		
Cestari (34)	Dyspepsia	Open, randomized, multicentre	RBC 400 mg bid for 7 days plus clarithromycin 250 mg bid for 7 days plus tinidazole 500 mg bid for 7 days	104/123 (85)	77% to 90%	RUT (A) plus histology (A and C) plus ^{13}CUBT	^{13}CUBT
Ricciardiello et al (40)	Nonulcer dyspepsia	Open, randomized, multicentre	RBC 400 mg bid for 7 days plus clarithromycin 250 mg bid for 7 days plus tinidazole 500 mg bid for 7 days	39/50 (78)	64% to 89%	CLO (A) plus H (A and C) or ^{13}CUBT	^{13}CUBT
Spadaccini et al (41)	Peptic ulcer and gastritis	Open, randomized	RBC 400 mg bid for 7 days plus clarithromycin 250 mg bid for 7 days plus tinidazole 500 mg bid for 7 days	41/56 (73)	60% to 84%	RUT plus H using Geimsa stain	
Cammarota et al (42)	Dyspepsia	Open, randomized	RBC 400 mg bid for 7 days plus clarithromycin 250 mg tid for 7 days plus tinidazole 500 mg bid for 7 days	32/35 (91)	77% to 98%	RUT plus H (A)	^{13}CUBT

A Antrum; C Corpus; ^{13}CUBT ^{13}Carbon urea breath test; H Histology; ITT Intention-to-treat; RUT Rapid urease test

Eradication of *H pylori* with RBC plus clarithromycin and amoxicillin: Triple therapy with RBC, clarithromycin and amoxicillin omits metronidazole, possibly important in situations where infection with metronidazole-resistant strains of *H pylori* are suspected or documented. Table 4 shows the designs, dose, scheduling, testing details and ITT eradication rates from six studies. The dose of RBC in these trials was 400 mg bid for seven days in five of the six trials and for 14 days in one American study (43). The antibiotics were given for seven days; the dose of clarithromycin was usually 500 mg bid and amoxicillin was given as 1000 mg bid.

For seven-day regimens, the ITT eradication rate ranged from 71% to 94%, and pooled results in 229 patients gave a mean eradication rate of 84% (95% CI 71% to 96%). The eradication rate with 14-day therapy was similar. Results were very similar to the RBC, clarithromycin and nitroimidazole triple therapy eradication rates.

One Italian randomized trial (40) directly compared RBC, clarithromycin and either tinidazole or amoxicillin. The tinidazole arm showed a trend toward better eradication with a smaller (250 mg compared with 500 mg bid) clarithromycin dose and better tolerability, with no dropouts, compared

TABLE 4
Summary of triple therapy of ranitidine bismuth citrate (RBC) plus clarithromycin and amoxicillin

						Helicobacter pylori tests	
Study (reference)	**Patient conditions**	**Study design**	**Drugs, dosages and durations**	**Eradication (%) by ITT analysis**	**95% CI by ITT analysis**	**Pre-treatment**	**Post-treatment**
Laine et al (43)	Positive urea breath test	Open, randomized	RBC 400 mg bid for 14 days plus clarithromycin 500 mg bid for 14 days plus amoxicillin 1 g bid for 14 days	46/50 (92)	81% to 98%	Serology or H plus ^{13}CUBT	^{13}CUBT
Cammarota et al (42)	Dyspepsia	Open, randomized	RBC 400 mg bid for 7 days plus clarithromycin 250 mg tid for 7 days plus amoxicillin 1 g bid for 7 days	31/35 (89)	73% to 97%	RUT plus H (A)	^{13}CUBT
Catalano et al (45)	Duodenal ulcer	Single blind, randomized	RBC 400 mg bid for 14 days plus clarithromycin 500 mg bid for 7 days plus amoxicillin 1 g bid for 7 days	32/42 (76)		RUT plus H with or without culture (A and C)	RUT plus H with or without culture (A and C)
Sung et al (44)	Duodenal ulcer	Single blind, randomized, single centre	RBC 400 mg bid for 7 days plus clarithromycin 500 mg bid for 7 days plus amoxicillin 1 g bid for 7 days	47/50 (94)	87% to 100%	RUT (A) plus H (A and C) with or without ^{13}CUBT	RUT (A) plus H (A and C) with or without ^{13}CUBT
Ricciardiello et al (40)	Nonulcer dyspepsia	Open, randomized, multicentre	RBC 400 mg bid for 7 days plus clarithromycin 500 mg bid for 7 days plus amoxicillin 1 g bid for 7 days	39/55 (71)	57% to 82%	CLO (A) plus H (A and C) or ^{13}CUBT	^{13}CUBT
De Boer et al (35)	Any *H pylori*-positive	Open, randomized, multicentre	RBC 400 mg bid for 7 days plus clarithromycin 400 mg bid for 7 days plus amoxicillin 1 g bid for 7 days	43/47 (92)	80% to 98%	CLO plus H plus culture (A and C)	CLO plus H plus culture (A and C)

A Antrum; C Corpus; ^{13}CUBT ^{13}Carbon urea breath test; H Histology; ITT Intention-to-treat; RUT Rapid urease test

with a 7% dropout rate due to side effects with the amoxicillin triple therapy. Another similar study, using clarithromycin 250 mg tid in both arms, showed that RBC, clarithromycin and either tinidazole or amoxicillin were equally effective (42).

RBC plus two antibiotics compared with PPI plus two antibiotics: RBC triple therapy has been compared with PPI triple therapy. Designs, dose, scheduling, testing details and ITT eradication rates from three studies are listed in Table 5. In all studies, there was no significant difference in eradication rates between the treatment groups. In one study, there was no difference between the RBC and the lansoprazole triple therapy arms, but because a low dose of lansoprazole (15 mg bid) was used, a difference may have been missed (41). Using either RBC or omeprazole with clarithromycin and amoxicillin, DU healing was similar (44) and regimens were equally well-tolerated (45). This suggests that either RBC or a PPI triple combination can be used as first-line therapy; such a recommendation was made in a recent Canadian consensus update (9).

RBC triple therapy in PPI triple therapy failures: In one Italian study, patients were initially treated for one week with a PPI (omeprazole, pantoprazole or lansoprazole), amoxicillin and clarithromycin triple therapy (46). The overall ITT eradication rate was 78% (95% CI 73% to 83%). The 38 treatment failures were then treated openly with RBC 400 mg bid, tetracycline 500 mg tid and tinidazole 500 mg bid for two weeks, and for which the ITT eradication rate was 82% (95% CI 75% to 97%). *H pylori* resistance data were not collected. This RBC regimen may be useful for patients who experienced eradication failures without doing sensitivity testing.

Other RBC triple combinations: Traditional bismuth, metronidazole and tetracycline (BMT) triple therapy was the best early treatment regimen for *H pylori* infections (5), and efficacy was enhanced by coadministration of an antisecretory drug (47). RBC combines two of these four components and simplifies administration of the drugs. In one four-arm study, RBC (either 400 mg bid or 200 mg qid) was given with either oxytetracycline 500 mg qid or spiramycin 500 mg qid and metronidazole 400 mg qid for 10 days (48). The ITT eradication rates ranged from 88.6% to 93.6%, and results were equivalent whether RBC was given two or four times daily and whether spiramycin or oxytetracycline was used. The authors suggested that spiramycin, which is less expensive than clarithromycin, deserves further study.

Triple therapy with RBC, metronidazole and tetracycline is less effective, and results are more variable, with an ITT eradication rate of 86% (35) to 92% (49) after seven days of therapy, 60% after 10 days of therapy (50), and 72% (51) to 80% (43) with 14 days of treatment. The best eradication rate was achieved in the studies that used the highest doses of metronidazole (1.5 g to 1.6 g daily) and tetracycline (500 mg qid) (35,49) rather than smaller doses of metronidazole (250 mg tid [43] to 500 mg bid [50,51]) or tetracycline (500 mg bid

TABLE 5
Comparisons of ranitidine bismuth citrate (RBC) triple therapy and proton pump inhibitor triple therapy

Author (reference)	Patient conditions	Study design	Drugs, dosages and durations	Eradication (%) with ITT analysis	95% CI with ITT analysis	*H pylori* tests: Pre-treatment	*H pylori* tests: Post-treatment
Spadaccini et al (41)	Peptic ulcer disease or gastritis	Open, randomized, single-centre	RBC 400 mg bid for 7 days plus clarithromycin 250 mg bid for 7 days plus tinidazole 500 mg bid for 7 days (plus RBC 400 mg bid for 21 days if active ulcer)	41/56 (73)	60% to 84%	CLO plus H (A and C)	CLO plus H (A and C)
			Lansoprazole 15 mg bid for 7 days plus clarithromycin 250 mg bid for 7 days plus tinidazole 500 mg bid for 7 days (plus lansoprazole 30 mg od for 21 days if active ulcer)	43/56 (77)	64% to 87%		
Catalano et al (45)	Active duodenal ulcer	Single-blind, randomized, multicentre	RBC 400 mg bid for 14 days plus clarithromycin 500 mg bid for 7 days plus amoxicillin 1 g bid for 7 days	32/42 (76)		Culture with or without H plus RUT	Culture with or without H plus RUT (H with A and C biopsies, Geimsa stain)
			Omeprazole 20 mg bid for 14 days plus clarithromycin 500 mg bid for 7 days plus amoxicillin 1 g bid for 7 days	30/39 (77)			
Sung et al (44)	Active duodenal ulcer	Single blind, randomized, single-centre	RBC 400 mg bid for 7 days plus clarithromycin 500 mg bid for 7 days plus amoxicillin 1 g bid for 7 days	47/50 (94)	87% to 100%	RUT (A) plus H (A and C) with or without ^{13}CUBT	RUT (A) plus H (A and C) with or without ^{13}CUBT
			Omeprazole 20 mg bid for 7 days plus clarithromycin 500 mg bid for 7 days plus amoxicillin 1 g bid for 7 days	42/48 (88)	78% to 97%		

A Antrum; C Corpus; ^{13}CUBT ^{13}Carbon urea breath test; H Histology; ITT Intention-to-treat; RUT Rapid urease test

[50,51] or tid [43]). Furthermore, baseline metronidazole resistance significantly (P=0.026) reduced eradication efficacy from 97% in patients with a metronidazole-sensitive strain to 57% in those with a resistant strain of *H pylori* (35). A Chinese study compared RBC or colloidal bismuth citrate with metronidazole and tetracycline triple therapy (RBC-metronidazole tetracycline [RBC-MT] compared with BMT) and reported contrasting results (49). The RBC-MT combination showed a trend toward a better eradication rate (46 of 50 patients, 92%) than with traditional BMT triple therapy (41 of 50 patients, 82%, P=0.23). Metronidazole resistance was defined as a minimal inhibitory concentration (MIC) greater than or equal to 32 mg/L using the E-test. In this study, 25 of 25 (100%) metronidazole-resistant strains were eradicated with the RBC-MT regimen, compared with 12 of 16 (75%, P=0.018) with traditional bismuth triple therapy. Reasons for the conflicting results between the different studies are unknown.

Treatment with RBC, tetracycline and clarithromycin for one to two weeks has been reported by two authors, with ITT eradication rates of over 90% in more than 100 patients (52,53).

One study compared RBC and amoxicillin for one week combined with azithromycin 500 mg od or 1 g od for three days (54). The higher dose of azithromycin was more successful, with ITT eradication in 27 of 36 patients (75%), compared with only 14 of 32 patients (44%) using the lower, 500 mg daily dose. The higher dose was associated with a trend toward more side effects, and two patients stopped treatment because of side effects, but the difference was not significant.

RBC AND ANTIMICROBIAL RESISTANCE

In vitro effects of RBC against *H pylori*: Resistant strains of *H pylori* are increasingly recognized (55). In vitro data have shown that RBC is effective in killing 14 different strains of *H pylori*. The MIC_{90} of RBC against *H pylori* is 15 µg/mL to 16 µg/mL (55,56). Both in vitro (57,58) and in a mouse model (57), the combination of RBC with clarithromycin resulted in a synergistic increase in the activity against *H pylori* strains, even in those resistant to clarithromycin (58). Osato et al (55), demonstrated in 10 of 11 *H pylori* isolates that clarithromycin MIC_{90} values could be reduced by ninefold, on average, when combined with RBC, and still achieve microbial killing. Thus, RBC and clarithromycin acted synergistically to overcome resistance to clarithromycin (55). In another in vitro study (59), RBC showed synergy with clarithromycin and tetracycline against both sensitive and resistant strains of the bacterium. The mechanism of synergy remains

TABLE 6
Most commonly reported adverse events with ranitidine bismuth citrate (RBC) (percentage of patients)

Adverse event	Placebo (n=502)	RBC (n=3548)	Ranitidine (n=1740)	RBC plus amoxicillin (n=372)	RBC plus clarithromycin (n=348)
Headache	8.0	4.5	6.0	5.6	6.9
Diarrhea	4.6	1.9	2.0	7.0	8.0
Constipation	1.8	1.5	0.6	0	0.3
Nausea and vomiting	3.4	1.5	1.1	3.0	3.2
Dizziness	0.8	1.5	1.0	0.8	1.1
Upper respiratory tract infection	1.6	1.3	1.5	1.6	0.9

Data from references 63 and 64

unknown (59). RBC combined with metronidazole in vitro also demonstrated either total or partial synergy against metronidazole-resistant strains (60).

In vitro emergence of antibiotic resistance: An in vitro study analyzed the emergence of resistance in *H pylori* strains subcultured with metronidazole and clarithromycin (56). Coculturing *H pylori* with RBC was found to reduce significantly the rate of emergence of resistance to metronidazole, more than clarithromycin; resistance to spiramycin was unaltered. Why this occurs is unknown; however, the authors observed that in the strain that showed a larger reduction in resistance, there was a higher density of bismuth molecules surrounding the *H pylori* organisms (56).

RBC triple therapy in metronidazole- and clarithromycin-resistant *H pylori*: Antibiotic resistance, particularly to metronidazole, can reduce the efficacy of *H pylori* treatment regimens containing metronidazole. However, dual therapy with RBC and clarithromycin may be effective, with reported eradication in 11 of 11 metronidazole-resistant *H pylori* strains (36). In this study, metronidazole resistance was defined as an MIC greater than 8 μg/mL by the E-test. In the same study, triple therapy with RBC, clarithromycin and metronidazole overcame metronidazole resistance in nine of 10 strains. Similar results were reported by Bardhan et al (30), who reported that triple therapy with RBC, clarithromycin 500 mg bid and metronidazole 400 mg bid for seven days successfully eradicated baseline metronidazole-resistant *H pylori* strains in nine of 10 patients (30).

In another clinical trial, the effects of two different RBC triple therapies on resistant *H pylori* strains were evaluated (61). Patients were treated for one week with RBC 400 mg bid, metronidazole 500 mg bid and clarithromycin 500 mg bid (RMC) or RBC 400 mg bid, metronidazole 500 mg bid and amoxicillin 1 g bid (RMA). In this study, metronidazole resistance was defined as an MIC greater than 8 g/mL by the E-test, and clarithromycin resistance was defined as an MIC greater than 2 g/mL. With RMC, the overall eradication rate was 96% (107 of 111 patients) and was unaffected by prestudy metronidazole resistance (95% eradication in 20 patients). *H pylori* was also eradicated in three patients with baseline clarithromycin-resistant strains and in a patient infected by a strain resistant to both metronidazole and clarithromycin. For RMA, the overall eradication rate was 79% – 87% in metronidazole-susceptible strains but only 22% in resistant strains. This suggests that RMC triple therapy may overcome the in vitro metronidazole or clarithromycin resistance to eradicate *H pylori*. However, substituting clarithromycin with amoxicillin was not successful.

With RBC, clarithromycin and amoxicillin (35) triple therapy, efficacy was not reduced by baseline metronidazole resistance. Further studies will be important to substantiate these observations and to help identify the role of RBC-based treatments in patients who have failed initial therapy.

Side effects and safety: Side effects reported with RBC are few and generally mild. Less than 1% of bismuth administered orally is absorbed systemically, and after repeated dosing with RBC 200 mg, 400 mg or 800 mg bid, trough bismuth concentrations do rise in a dose-dependent fashion in patients with and without renal impairment. However, levels remained below 50 μg/L (14,18,62), which is considered the upper limit of safety. Peak bismuth levels do not appear to rise as high as with tripotassium dicitrato bismuthate, another commonly used bismuth compound (62).

A randomized, double-blind, parallel group study compared the safety of RBC 400 mg bid with that of ranitidine 150 mg bid for up to one year (63). Adverse events were few and comparable between the two groups. Of patients treated with RBC, 29% reported drug-related adverse events, compared with 35% of those treated with ranitidine. Three per cent of RBC-treated patients experienced a serious event, compared with 2% of those treated with ranitidine. Trough plasma levels of bismuth increased slightly over time in patients treated with RBC (63). However, these levels returned to pretreatment values within three months after the end of treatment, and no patient had a plasma bismuth level of more than 50 ng/mL (63).

Pipkin and colleagues (64) summarized the adverse events reported in studies of RBC alone or in combination with antibiotics (Table 6). The adverse events associated with RBC are few and comparable with those associated with ranitidine hydrochloric acid, which has a well established safety record. The only effects directly attributable to the bismuth

component of RBC were dark stools and discoloration of the tongue. The addition of either clarithromycin or amoxicillin increased the frequency of diarrhea marginally. Serious adverse events were seen in less than 1% to 2% of all study arms. The presence of renal failure and pregnancy are considered contraindications for the use of RBC.

CONCLUSIONS

In Canada, the approved dose of RBC is 400 mg twice daily with clarithromycin 250 mg four times daily (dual therapy) for two weeks for the treatment of patients with duodenal and gastric ulcer disease associated with *H pylori* infection. This may be followed by two weeks of RBC alone to facilitate ulcer healing. Adverse events are generally mild, treatment is well tolerated and bismuth toxicity is unlikely to arise. Studies to date of RBC triple therapy bid for one week show that when RBC is administered with clarithromycin and metronidazole or amoxicillin, eradication results are as effective as those achieved with the current first-line PPI-based triple therapy regimens. There is some suggestion that RBC combination treatments may overcome metronidazole resistance and possibly even clarithromycin resistance. Additionally, there appears to be a relatively low rate of acquired antibiotic resistance. Further data on the role of RBC combination therapies in antibiotic resistance and in the treatment of eradication failures are awaited with interest.

In the Canadian *H pylori* Consensus Conference update (9), recommended therapies include a regimen of a PPI (omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 400 mg) or RBC 400 mg, clarithromycin 500 mg and amoxicillin 1000 mg bid for seven days; or a regimen of a PPI or RBC, clarithromycin 500 mg or 250 mg, and metronidazole 500 mg bid for seven days.

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