

Bismuth-based quadruple therapy with bismuth subcitrate, metronidazole, tetracycline and omeprazole in the eradication of *Helicobacter pylori*

Raymond Lahaie MD¹, Alain Farley MD², Chrystian Dallaire MD³, André Archambault MD⁴, Carlo A Fallone MD⁵, Terry Ponich MD⁶, Richard Hunt MD⁷, Michael Oravec MD⁸, Paul Whitsitt MD⁸, Sander Veldhuyzen Van Zanten MD⁹, Norman Marcon MD¹⁰, Robert Bailey MD¹¹, André Dumont MD¹, Bich Nguyen MD¹, Sylvain Desrochers PhD¹², Jean Spénard PhD^{13,14}

R Lahaie, A Farley, C Dallaire, et al. Bismuth-based quadruple therapy with bismuth subcitrate, metronidazole, tetracycline and omeprazole in the eradication of *Helicobacter pylori*. Can J Gastroenterol 2001;15(9):581-585.

BACKGROUND: A previous study showed that 14 days of qid bismuth-based triple therapy with tetracycline 500 mg, metronidazole 250 mg and colloidal bismuth subcitrate 120 mg resulted in excellent *Helicobacter pylori* eradication rates (89.5%). The present study looked at a shorter treatment period by adding omeprazole and by reducing the dose of tetracycline.

METHODS: One hundred sixty-one patients with *H pylori* confirmed by histology and ¹³carbon urea breath test were included in the study. They were treated for seven days with bismuth subcitrate 120 mg plus metronidazole 250 mg plus tetracycline 250 mg qid plus omeprazole 20 mg bid (OBMT). Patients were 18 to 75 years of age and had dyspepsia with or without a history of peptic ulcer. Patients with irritable bowel syndrome, active ulcer or previous attempt at eradication, or those who had used

antibiotics or antiulcer drugs in the previous 30 days were excluded. Eradication was determined by two ¹³carbon urea breath tests done one and three months, respectively, after treatment. Strains with minimal inhibitory concentrations of 8 µg/mL or higher were considered to be resistant to metronidazole.

RESULTS: The overall per protocol eradication rate was 84% – 89.5% in metronidazole-sensitive and 70.8% in metronidazole-resistant strains. Modified intent-to-treat analysis resulted in a 80% eradication rate – 82.5% in metronidazole-sensitive and 66.7% in metronidazole-resistant strains. Only one patient discontinued treatment because of adverse events.

CONCLUSIONS: The OBMT regimen used in this study is safe and effective against metronidazole-sensitive *H pylori* strains.

Key Words: Bismuth; *Helicobacter pylori*; Quadruple-therapy; Tetracycline; Treatment; Metronidazole

pour le résumé, voir page suivante

¹Centre Hospitalier de l'Université de Montréal, Hôpital St-Luc, Montréal; ²Centre de Gastro-Entérologie et d'Endoscopie de Montréal, Montréal; ³Centre Hospitalier St François d'Assise, Québec; ⁴Hôpital Maisonneuve-Rosemont, Montréal; and ⁵McGill University Health Center, Montreal, Quebec; ⁶London Health Science Centre, Victoria Campus, London; ⁷McMaster University, Hamilton; and ⁸Oshawa Clinic, Oshawa, Ontario; ⁹Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; ¹⁰Wellesley Hospital, Toronto, Ontario; ¹¹Hys Center, Edmonton, Alberta; ¹²Cirion Biopharma Research Inc, Laval; ¹³Axcan Pharma Inc, Mont-Saint-Hilaire; and ¹⁴Faculté de Médecine, Département de Pharmacologie, Université de Montréal, Montréal, Québec

Correspondance and reprints: Dr Raymond Lahaie, Division of Gastroenterology, Centre Hospitalier Université de Montréal, Hôpital St-Luc, 1058 St-Denis, Montréal, Québec H2X 3J4. Telephone 514-281-2121, fax 514-281-6135, e-mail lahaier@odyssee.net

Received for publication February 6, 2001. Accepted July 17, 2001

Quadrithérapie à base de bismuth avec subcitrate de bismuth, métronidazole, tétracycline et oméprazole pour l'éradication d'*Helicobacter pylori*

HISTORIQUE : Une étude a déjà montré que l'administration q.i.d. pendant 14 jours d'une trithérapie à base de bismuth composée de 500 mg de tétracycline, 250 mg de métronidazole et 120 mg de subcitrate de bismuth colloïdal donnait lieu à des taux d'éradication excellents d'*Helicobacter pylori* (89,5 %). L'étude actuelle s'est penchée sur un traitement de durée plus courte avec l'ajout d'oméprazole et une réduction de la dose de tétracycline.

MÉTHODES : Cent soixante-et-un patients porteurs de *H. pylori*, histologie et test d'urée respiratoire marquée au ¹³carbone à l'appui, ont participé à cette étude. Ils ont été traités pendant sept jours au moyen de 120 mg de subcitrate de bismuth, 250 mg de métronidazole, 250 mg de tétracycline q.i.d. et 20 mg d'oméprazole b.i.d. (OBMT). Les patients étaient âgés de 18 à 75 ans et souffraient de dyspepsie avec ou sans antécédents

d'ulcère gastroduodénal. Les patients souffrant du syndrome du côlon irritable, d'ulcère évolutif ou ayant déjà tenté un traitement d'éradication auparavant, ou ceux qui avaient utilisé des antibiotiques ou des médicaments contre les ulcères au cours des 30 jours précédant ont été exclus. L'éradication a été confirmée par deux tests d'urée respiratoire marquée au ¹³carbone, un, puis trois mois respectivement après le traitement. Les souches présentant des concentrations inhibitrices minimales de 8 µg/mL ou plus ont été jugées résistantes au métronidazole.

RÉSULTATS : Le taux d'éradication global selon le protocole a été de 84 – 89,5 % pour les souches sensibles au métronidazole et de 70,8 % pour les souches résistantes au métronidazole. L'analyse modifiée selon l'intention de traiter a donné un taux d'éradication de 80 % - 82,5 % pour les souches sensibles au métronidazole et de 66,7 % pour les souches résistantes au métronidazole. Un seul patient a cessé son traitement en raison de réactions indésirables.

CONCLUSION : Le schéma OBMT utilisé dans cette étude est sûr et efficace contre les souches de *H. pylori* résistantes au métronidazole.

Reports from the Canadian *Helicobacter pylori* Consensus Conference (1) and from the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology (2) advocate testing and eradicating *H. pylori* in patients presenting with gastroduodenal ulcers. However, results of a survey indicated that 43% to 66% of American physicians also eradicate *H. pylori* in patients with nonulcer dyspepsia (3). Over the years, many treatments have been tested for the eradication of *H. pylori*. Among them, the so-called bismuth-based triple-therapy with colloidal bismuth subcitrate, metronidazole and tetracycline (BMT) has been extensively tested with success (4).

In a previous trial (5), a 14-day treatment with colloidal bismuth subcitrate 120 mg qid plus metronidazole 250 mg qid plus tetracycline 500 mg qid gave very good eradication rates of 82% and 90% by modified intent-to-treat (MITT) and per protocol analyses, respectively. The influence of metronidazole sensitivity on the eradication rate was, however, not assessed.

In an effort to increase the efficacy of the regimen, a proton pump inhibitor was added (6-9). Also, the treatment duration was reduced to seven days, and the amount of tetracycline was lowered to 1 g daily to increase gastrointestinal tolerance. This study, therefore, was designed to assess the efficacy and safety of a seven-day treatment for the eradication of *H. pylori* with colloidal bismuth subcitrate 120 mg qid plus metronidazole 250 mg qid plus tetracycline 250 mg qid, all given 1 h before meals and at bedtime, in addition to omeprazole 20 mg bid with the morning and evening meals.

PATIENTS AND METHODS

This was an open-label, multicentre (10) study of *H. pylori*-positive patients with or without a history of peptic ulcer. The local ethics committee of each of the participating centres approved the study. Males and females, aged 18 to 75 years, found positive for *H. pylori* by both ¹³carbon urea breath test and histology at entry were eligible after giving informed written consent.

The following main exclusion criteria were applied: macroscopic esophagitis, previous gastric surgery, dysphagia, vomiting, hematemesis, melena, recent documented gastrointestinal bleeding, iron-deficiency anemia, inability to abstain from alcohol, significantly impaired renal or hepatic function, contraindication to the use of bismuth, metronidazole or tetracycline, chronic use of nonsteroidal anti-inflammatory drugs, use of antibiotics within 30 days before enrollment, regular use of bismuth compounds in the past 30 days, a previous attempt to eradicate *H. pylori* infection and use of antiulcer drugs (including H₂ receptor antagonists [seven days] or proton pump inhibitors [30 days]) preceding enrollment.

Upon confirmation of willingness to participate, routine assessment of health status and esophagogastroduodenoscopy were performed. The patient also underwent a ¹³carbon urea breath test (Dia-13 Helico, Dianatec-Iso, Canada).

During endoscopy, three biopsies were taken from the antrum and two from the body. One antrum biopsy was used on the site for rapid urease test. One antrum biopsy and one corpus biopsy were sent to the central study pathologists for the detection of *H. pylori* after staining with Wharthin-Starry solution. One antrum biopsy and one corpus biopsy were placed in Stuart's transportation medium and sent on dry ice to the central microbiologist for assessment of metronidazole sensitivity by E-test. A cutoff value of 8 µg/L was used for the minimum inhibitory concentration to classify sensitivity.

If *H. pylori* was detected at screening by rapid urease test, the patient was allowed to start the treatment immediately. This result had to be later confirmed both by ¹³carbon urea breath test and by histology (only four patients were later found to be *H. pylori* negative by ¹³carbon urea breath test and excluded from analysis). Patients self-administered the study drugs, provided in a blister pack. They were instructed not to take milk or other dairy products, or antacids within 2 h of taking the study medications.

Within four days following completion of the treatment, physical examination and clinical laboratory tests were

TABLE 1
Demographics of the modified intent-to-treat (MITT) and per protocol study populations

Variable	MITT (n=161)	Per protocol (n=146)
Age (years)	51.3±13.4	51.8±13.4
Height (cm)	166.5±13.5	166.2±13.8
Weight (kg)	73.8±16.4	73.7±16.2
Men/women (n)	84/77	74/72
History of gastric ulcer (n)*	21	18
History of duodenal ulcer (n) *	57	50
History of nonulcer dyspepsia (n)	105	99

Values are means ± SD. *A given patient may be in both groups

repeated and adverse events recorded. Not less than 28 and 84 days after the end of treatment, patients returned for ¹³carbon urea breath tests. Eradication was defined as two negative ¹³carbon urea breath test results at least one and three months after completion of therapy.

All medications for dyspepsia were prohibited throughout the study as well as nonsteroidal anti-inflammatory drugs and acetylsalicylic acid. The occasional use of acetaminophen was, however, permitted, and antacids were allowed as rescue medication if the dyspepsia symptoms were severe.

All patients were, a priori, advised to refrain from alcohol during the seven-day treatment period. Female patients using oral contraceptives were informed about the risk of interaction between tetracycline and oral contraceptives, and advised to use an additional means of contraception. Patients were also warned to avoid exposure to direct sunlight and/or ultraviolet light during the seven-day treatment period because of the photosensitizing effect of tetracycline.

The rate of eradication probability was estimated, and the 95% standard confidence interval was computed. The primary analysis was done on the MITT population comprising all patients with positive ¹³carbon urea breath test and histology at entry, who were entered in compliance with the inclusion and exclusion criteria, and had taken at least one dose of the study medication. A secondary analysis was done on the per protocol population comprising all patients in the MITT group for whom ¹³carbon urea breath test results at one and three months were available, and who did not have any major protocol violation.

Stratification was done a posteriori by sensitivity or resistance to metronidazole. Eradication rate and 95% confidence intervals were computed for each subgroup of patients. These subgroups were compared by the likelihood ratio test.

RESULTS

Two hundred thirty-eight patients were screened for the study. Sixty-eight were found to be *H pylori* negative at entry, four withdrew before starting the medication, one

TABLE 2
Helicobacter pylori eradication rates in the modified intent-to-treat (MITT) and per protocol study populations

Population	Overall	<i>H pylori</i> sensitive	<i>H pylori</i> resistant	P
MITT				
Eradication rate	128/161 (80%)	52/63 (82.5%)	18/27 (66.7%)	0.105
95% CI	73.3-85.7	73.2-91.9	48.9-84.4	
Per protocol				
Eradication rate	123/146 (84%)	51/57 (89.5%)	17/24 (70.8%)	0.045
95% CI	78.3-90.2	81.9-97.1	53.7-88.0	

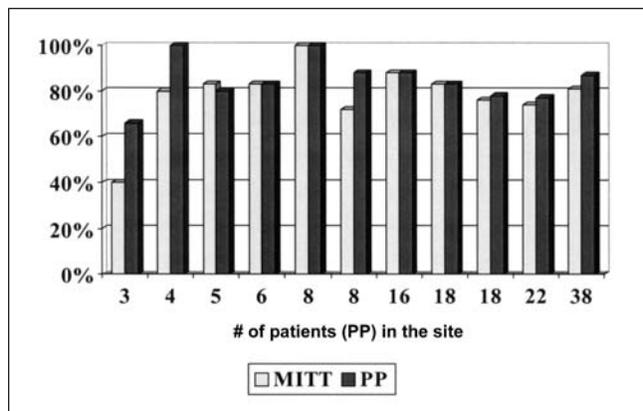


Figure 1) Individual *Helicobacter pylori* eradication rates in the modified intent-to-treat (MITT) and per protocol (PP) study populations

was included in violation of the upper age limit and was discontinued, and four were included despite the presence of a concomitant condition precluding participation (gastrointestinal bleeding, thyroid disease and elevated transaminase levels at baseline) and were discontinued, leaving 161 patients in the MITT population. Fifteen patients were subsequently withdrawn (six protocol violations, six lost to follow-up, one adverse event and two voluntary withdrawals), leaving 146 patients in the per protocol population. Their demographics are presented in Table 1.

H pylori was successfully eradicated in 128 patients in the MITT population, for a rate of 80%, and in 123 patients in the per protocol population, for a rate of 84% (Table 2). The individual eradication rates by study sites varied between 40% and 100%, and 67% and 100%, in the MITT and per protocol populations, respectively (Figure 1).

A sample size of 140 patients was estimated a priori for the 95% confidence interval based on the assumptions that expected eradication rate of BMT plus omeprazole (OBMT) would be 90%, alpha-error 5% and length of the confidence interval 95%. With an eradication rate of 80%, 161 patients give the power to compute the 94% confidence interval.

TABLE 3
Metronidazole sensitivity of *Helicobacter pylori* in the study population by city

City	Resistant/assessable	Rate
Halifax	0/3	0
Quebec	1/13	7.7
Montreal total	21/57	36.8
Site 1	9/22	40.9
Site 2	6/13	46.2
Site 3	2/14	14.3
Site 4	4/8	50.0
Oshawa	0/4	0
Toronto	0/3	0
Hamilton	0/1	0
London	2/6	33.3
Edmonton	3/3	100
Overall	27/90	30.0
95% CI	(20.5-39.5)	

The metronidazole sensitivity was successfully documented in strains from 90 patients and showed an average resistance rate of 30.0%. The results by city and site are presented in Table 3. Eighteen of 27 resistant strains (66.7%) and 52 of 63 sensitive strains (82.5%) were eradicated in the MITT population ($P=0.105$). Seventeen of 24 resistant strains (70.8%) and 51 of 57 sensitive strains (89.55%) were eradicated in the per protocol population ($P=0.045$). Detailed results are shown in Table 2.

One patient withdrew due to adverse events after four days of treatment. She complained of severe epigastric pain and moderate diarrhea that were classified as "possibly related" to study drugs by the investigator. She also complained of mild peridental bleeding that was classified as "unlikely related" to study drugs by the investigators. All events resolved.

Mild diarrhea (24%), nausea (12%), headache (10%), taste disturbance (9%), abdominal pain (7%), moderate diarrhea (6%) and dizziness (6%) were the adverse events most often reported and considered related to active study medications by open-label evaluation. Elevations of alanine aminotransferase and aspartate aminotransferase levels outside the normal ranges were seen in some patients (6%), but they were not clinically significant; mean \pm SD changes during treatment were as follows: $+10.9 \pm 14.15$ (range -33.0 to $+70.0$ IU/L) for alanine aminotransferase and $+7.7 \pm 9.6$ IU/L (range -23 to $+46$ IU/L) for aspartate aminotransferase.

DISCUSSION

The overall eradication rate by MITT analysis was 80%. The rates varied greatly from site to site, and this difference is likely explained, in part, by the small sample size seen in

some investigative sites. If the site where only three patients were included in the per protocol analysis is not considered, the range becomes 66% to 100%.

In the MITT population, the combination of colloidal bismuth subcitrate 120 mg plus metronidazole 250 mg plus tetracycline 250 mg qid given with omeprazole 20 mg bid successfully eradicated *H pylori* in 82.5% and 66.7% of metronidazole-sensitive and metronidazole-resistant strains, respectively. Compared with the previously reported values of 88.5% and 69% in a survey of 1639 patients treated with a bismuth-based regimen (11), the actual rates were a little lower in sensitive strains and as low as those in resistant ones. The regimen used in the present study is, therefore, effective and safe for the eradication of metronidazole-sensitive *H pylori* strains, but is less effective than the 14-day triple therapy with 2 g daily of tetracycline given without a proton pump inhibitor (5).

In the present study, the overall prevalence of resistance to metronidazole in Canada was 30%. It varies greatly from site to site, and part of this variation is likely explained by the small sample sizes in some of the investigative sites. Nonetheless, this 30% figure compares favourably with the previously reported prevalence of 33% (10). The differences between the eradication rates in metronidazole-sensitive and metronidazole-resistant strains were statistically significant for the per protocol population but not for the MITT protocol; this is likely due to a type 2 error in the latter group. Actually, these tests were exploratory, and the sample size was not estimated based on these comparisons.

Three of the most often reported adverse events were expected, because taste disturbance and nausea are known adverse effects of metronidazole, and diarrhea is a known adverse effect of tetracycline. Adverse event was the reason to discontinue treatment in only one patient. They were limited in time to the period of treatment. Moreover, no serious adverse event or clinically significant laboratory abnormalities were reported in the trial.

The efficacy of this regimen in metronidazole-resistant strains remains a limiting step to its use and should be improved. Published preliminary results have shown more promising efficacy with a new 10-day treatment with a single triple-capsule containing colloidal bismuth subcitrate 120 mg plus metronidazole 375 mg plus tetracycline 375 mg given qid with omeprazole 20 mg given with the morning and evening meals (12). Updated results (data on file) with this capsule have shown, in 125 patients with active or history of duodenal ulcer, an MITT eradication rate of 91.9% in metronidazole-sensitive and 80.4% in metronidazole-resistant strains respectively.

CONCLUSIONS

We conclude that the OBMT regimen used in the present study is effective against metronidazole-sensitive *H pylori* strains. However, longer duration of treatment (10 days) with higher doses of metronidazole and tetracycline (1.5 g daily each) seems better as suggested by the preliminary results of a more recently completed study (12).

REFERENCES

1. Hunt R, Thomson ABR, on behalf of the Consensus Conference Participants. Canadian *Helicobacter pylori* Consensus Conference. *Can J Gastroenterol* 1998;12:31-41.
2. Howden CW, Hunt RH. On behalf of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Guidelines for the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 1998;93:2330-8.
3. Breuer T, Goodman K, Malaty H, Sudhop T, Graham D. How do clinicians practicing in the U.S. manage *Helicobacter pylori*-related gastrointestinal diseases? A comparison of primary care and specialist physicians. *Am J Gastroenterol* 1998;93:553-61.
4. Borody TJ, Shortis NP, Reyes E. Eradication therapies for *Helicobacter pylori*. *J Gastroenterol* 1998;33(Suppl 10):53-6.
5. Veldhuyzen Van Zanten S, Farley A, Marcon N, et al. Bismuth subcitrate, metronidazole, and tetracycline HCl in eradication of *Helicobacter pylori*: A randomized, double-blind study. *Can J Gastroenterol* 2000;14:599-602.
6. Phull PS, Griffiths AE, Halliday D, Jacyna MR. One week treatment for *Helicobacter pylori* infection: A randomised study of quadruple therapy versus triple therapy. *J Antimicrob Chemother* 1995;36:1085-8.
7. Hosking SW, Ling TKW, Chung SCS, et al. Duodenal ulcer healing by eradication of *Helicobacter pylori* without anti-acid treatment: randomised controlled trial. *Lancet* 1994;343:508-10.
8. De Boer W, Driessen W, Jansz A, Tytgat G. Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. *Lancet* 1995;345:817-20.
9. Borody TJ, Andrews P, Fracchia G, Brandl S, Shortis NP, Bae H. Omeprazole enhances efficacy of triple therapy in eradicating *Helicobacter pylori*. *Gut* 1995;37:477-81.
10. Lahaie RG, Gaudreau C, Tremblay C, et al. In vitro evaluation of *Helicobacter pylori* pretreatment antibiotic resistance and evaluation of the diffusion test. *Digestive Disease Week Abstract Book*. Bethesda: American Gastroenterology Association, 1998;14:1017. (Abst)
11. Spénard J, Colin P. Efficacy of bismuth-based quadruple therapy for eradication of *Helicobacter pylori*: A survey of 1639 patients. *Gastroenterology* 2000;118(Suppl 2):A501. (Abst)
12. Loren L, Hunt R, Spénard J. Bismuth-based single capsule therapy: Interim analysis of omeprazole (O) + bismuth (B)-metronidazole (M)-tetracycline (T) 3-in-1 capsule vs. O + amoxicillin (A) + clarithromycin (C). *Gastroenterology* 2001;115(A):61A. (Abst)



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

