Bismuth-based triple therapy with bismuth subcitrate, metronidazole and tetracycline in the eradication of *Helicobacter pylori*: A randomized, placebo controlled, double-blind study

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OBJECTIVE: To determine the rate of *Helicobacter pylori* eradication following bismuth-based triple therapy with colloidal bismuth subcitrate, tetracycline hydrochloride and metronidazole.

PATIENTS AND METHODS: One hundred and eleven patients were randomly assigned, in a two to one ratio, to colloidal bismuth subcitrate 120 mg qid plus metronidazole 250 mg qid plus tetracycline 500 mg qid (Gastrostat), or matching placebo tablets and capsules for 14 days. Presence or absence of *H pylori* was documented by histology at entry and at least 28 days after treatment. Patients had dyspeptic symptoms with or without a history of peptic ulcer. Patients with any previous attempt(s) at eradication of *H pylori*, who used bismuth, antibiotics, H_2 receptor antagonists or proton pump inhibitors in the previous four weeks were excluded.

RESULTS: Fifty-three of 59 (90%) patients on bismuth-based treatment and only one of 35 (3%) on placebo achieved eradication by per protocol analysis. Fifty-three of 65 (82%) patients on bismuth-based treatment achieved eradication, while only two of 34 (5%) achieved eradication on placebo by intention to treat analysis. Eradication rates for bismuth-based treatment across sites ranged from 83% to 100%. Only two patients in the bismuth-based treatment group (4%) and one in the placebo group (3%) discontinued treatment because of adverse events.

CONCLUSIONS: Colloidal bismuth subcitrate plus metronidazole plus tetracycline, given in the doses studied for 14 days, is safe and highly effective against *H pylori* infection and would be appropriate as a first-line therapy for eradication.

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

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Thérapie triple à base de bismuth avec du sous-citrate de bismuth, du métronidazole et de la tétracycline pour l'éradication de *Helicobacter pylori* : une étude à double insu, comparative avec placebo et randomisée

OBJECTIF : Déterminer le taux d'éradication de *Helicobacter pylori* après une triple thérapie à base de bismuth avec du sous-citrate de bismuth, du chlorhydrate de tétracycline et du métronidazole.

PATIENTS ET MÉTHODES : Cent onze patients ont été assignés au hasard dans une proportion de 2 contre 1 à un groupe de traitement avec 120 mg de sous-citrate de bismuth colloïdal quatre fois par jour plus 250 mg de métronidazole quatre fois par jour plus 500 mg de tétracycline (Gastrostat) ou dans un groupe de traitement placebo par comprimés et capsules appariés pendant 14 jours. La présence ou l'absence de *Helicobacter pylori* a été documentée par un examen histologique à l'inclusion des patients dans l'étude et au moins 28 jours après le traitement. Les patients souffraient de dyspepsie avec ou sans ulcère gastro-duodénal. Les patients qui avaient fait l'objet d'une ou plusieurs tentatives d'éradication de *Helicobacter pylori* antérieurement, qui avaient utilisé du bismuth, des antibiotiques, des antagonistes des récepteurs H_2 ou des inhibiteurs de la pompe à protons dans les quatre semaines précédentes ont été exclus de l'étude.

RÉSULTATS : Cinquante-trois des 59 (90 %) patients du groupe de traitement à base de bismuth, et seulement un des 34 (3 %) sont parvenus à une éradication par placebo selon une analyse par protocole. Cinquante-trois des 65 (82 %) patients du groupe de traitement à base de bismuth sont parvenus à une éradication, alors que deux patients seulement sur 34 (5 %) sont parvenus à une éradication par placebo selon une analyse avec intention de traiter. Les taux d'éradication pour le traitement à base de bismuth à travers les sites allait de 83 % à 100 %. Seulement deux patients du groupe de traitement à base de bismuth (4 %) et un du groupe placebo (3 %) ont cessé le traitement à cause d'effets indésirables.

CONCLUSIONS : Une thérapie triple avec du sous-citrate de bismuth colloïdal, du métronidazole et de la tétracycline, administrés aux doses étudiées pendant 14 jours, est sûre et très efficace contre *Helicobacter pylori* et serait appropriée comme traitement de première ligne pour son éradication.

There is conclusive evidence that *Helicobacter pylori* is associated with duodenal ulcer, gastric ulcer and gastric cancer (1-3).

A meta-analysis of *H pylori* eradication studies indicated that bismuth-based triple therapy regimens comprising bismuth, a nitroimidazole and a second antibiotic achieved eradication rates of up to 80%, and that the most effective combination in this class is colloidal bismuth subcitrate, metronidazole and tetracycline (4). However, many of the studies included in that meta-analysis suffered from methodological weaknesses (5).

The primary objective of the present study was to determine the rate of *H pylori* eradication following therapy with colloidal bismuth subcitrate 120 mg (as bismuth oxide) qid, metronidazole 250 mg qid and tetracycline hydrochloride 500 mg qid for 14 days in *H pylori*-positive dyspeptic patients with or without a history of peptic ulcer.

PATIENTS AND METHODS

This randomized, double-blind, placebo controlled, parallel group, multicentre study comprised *H pylori*-positive patients with dyspepsia. The local Ethics Committee of each of the participating centres approved the study.

Subjects were selected from patients scheduled to undergo gastroscopy. Males or females, aged 18 to 75 years, positive for *H pylori* by histology at entry and presenting with symptoms of dyspepsia were eligible after giving informed written consent.

Exclusion criteria were macroscopic esophagitis; active duodenal or gastric ulcer within three months of enrollment; previous gastric surgery; dysphagia; vomiting; hematemesis; melena; recent documented gastrointestinal bleeding; iron-deficiency anemia; pregnancy; 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 (NSAIDs); use of antibiotics in the 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 H_2 receptor antagonists or proton pump inhibitors) during the seven days preceding enrollment.

During endoscopy, two biopsies were taken from the antrum and two from the body. They were placed in 10% formalin in individual containers and sent to the central study pathologist, who was blinded to the treatment received by the patients. All sections were stained using a special silver stain for *Helicobacter* organisms as well as the routine hematoxylin and eosin stain (6).

If *H pylori* was detected on site by rapid urease test, the patient was randomly assigned to active or matching placebo treatment by using a two to one ratio of active drugs or placebo. This result had to be confirmed by the presence of *H pylori* on at least one of the four histology slides to confirm the patient's validity. Active treatment comprised colloidal bismuth subcitrate 120 mg qid, metronidazole 250 mg qid and tetracycline hydrochloride 500 mg (Gastrostat, Axcan Pharma, Canada) qid for 14 days. Subjects self-administered the study drugs, provided in a blister pack, four times daily on an empty stomach, 1 h before meals and at bedtime for 14 days. Subjects were instructed not to take milk or other dairy products, or antacids within 2 h of taking the study medications.

Within four days of completion of therapy, physical examination and clinical laboratory tests were repeated and adverse events recorded. Not less than 28 days after the end of treatment, patients returned for a repeat endoscopy and four biopsies were taken to verify the presence or absence of *H pylori*. Eradication was defined as the absence of *H pylori* on all histology slides taken at least four weeks after the end of treatment.

All medications for dyspepsia were prohibited throughout the study, as were NSAIDs and acetylsalicylic acid. The oc-

casional use of acetaminophen was, however, permitted. The use of antacids was allowed as rescue medication if the dyspepsia symptoms were severe.

Patients enrolled in this study were a priori advised to refrain from alcohol during the two-week treatment period. Female patients using oral contraceptives were informed about the risk of interaction between tetracyline 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 two-week treatment period because of the photosensitivity effect of tetracycline.

The sample size of 62 subjects in the active treatment group was based on the following assumptions: expected eradication rate of BMT 80% and of placebo 0%, alpha error 5% and length of the confidence interval 95%.

The primary analysis was a per protocol (PP) analysis and included all patients with positive histology at entry and evaluable histology four weeks later. The intention to treat (ITT) analysis included all patients with positive histology at entry who met the inclusion/exclusion criteria, except for three patients who completed the study with all procedures performed successfully but whose final histology slides were lost by the carrier between the study site and the central laboratory. These three patients were not considered in any analysis.

A posteriori exploratory analysis was done on the influence of ulcer type on eradication rate.

RESULTS

One hundred and eleven patients were randomly assigned to the study medication. Four were found to be *H pylori*-negative at entry, the poststudy slides were lost during transportation for two patients, the prestudy slides were lost during transportation for one patient and one patient was entered in violation of the inclusion criteria (found to be pregnant) and her treatment was interrupted after one dose, leaving 103 patients evaluable by ITT analysis. Three more patients withdrew because of adverse events, five were lost to follow-up and one withdrew voluntarily, leaving 94 patients evaluable by PP analysis.

Of the 103 patients evaluable by ITT analysis, 65 received BMT therapy and 38 received placebo. Fifty-three (81.5%) patients on BMT achieved *H pylori* eradication. The 95% confidence interval of the rate of eradication ranged from 76.7% to 86.4% by ITT analysis.

Of the 94 patients evaluable by PP analysis, 59 received the BMT therapy and 35 received placebo. Their demographics are presented in Table 1. Fifty-three of 59 patients (90%) receiving BMT achieved eradication of *H pylori* infection, while only one of the 35 patients (3%) receiving placebo did ($P<0.0001$). The 95% confidence interval of the rate of eradication by BMT ranged from 82% to 98%. The individual eradication rates by study centre were 83%, 89%, 91%, 100%, 100%, 100% and 100%.

Thirty-six patients (63%) receiving active BMT and twenty-four (69%) receiving placebo had a history of previous ulcer or showed deformity of the duodenal cap in keeping with previous ulcer. In patients receiving BMT, there was no statistically significant difference in eradication rates between patients with a history of ulcer (91.7%) and those without (85.7%) (either gastric, duodenal or unspecified; $P=0.659$) or between site of ulcer (gastric [87.5%] versus duodenal [92.3%]; $P=1.000$).

TABLE 1
Demographics for the efficacy analysis of *Helicobacter pylori* eradication

Variable	Active drug (n=59)	Placebo (n=35)	P
Age (years), mean ± SE	49.8±1.8	47.5±1.9	NS
Height (cm), mean ± SE	167.9±1.4	169.7±1.7	NS
Weight (kg), mean ± SE	72.3±2.1	75.3±2.6	NS
Men/women	28/29	25/10	0.0503
History of ulcer			
Yes	36	24	
No	21	11	NS
Type of ulcer			
Gastric	16	9	
Duodenal	13	7	
Unspecified	7	8	NS

NS Not significant

Three patients violated the protocol. One stopped treatment after 13 days but was reported as completing the study by the investigator. The infection was successfully eradicated in this patient. One took a single dose of diclofenac on day 9 of treatment; the infection was successfully eradicated in this patient. The third patient received ketoprofen during the whole 14-day period of BMT. The infection was not cured in this patient, who showed presence of an active ulcer at the last visit. All three patients were included in both analyses.

Three patients discontinued study drugs because of adverse events: two (4%) in the BMT group and one (3%) in the placebo group. One patient withdrew after 2.5 days (10 doses) of treatment with BMT because of nausea and lightheadedness; another withdrew after 4.5 days (18 doses) of treatment with BMT because of bloating and tiredness; and the third withdrew after three days (12 doses) of treatment with placebo because of heartburn, diarrhea, abdominal pain and dizziness.

Nausea (26%), taste disturbance (18%), heartburn (17%), headache (15%) and diarrhea (11%) were the adverse events most often reported and considered related to active study medications. Dark stools (35%) and loose stools (18%) also were frequently reported. Elevations of alanine aminotransferase and aspartate aminotransferase were seen in some patients but were not clinically important.

DISCUSSION

The results of this study, which reports a mean, PP, overall rate of *H pylori* eradication of 90%, compare favourably with those published using the same bismuth-based treatment or a similar BMT treatment.

TABLE 2
Eradication rate of *Helicobacter pylori* by type of analysis

	Intention to treat	Per protocol
BMT therapy		
Number evaluable	65	59
Number eradicated	53	53
Percentage eradicated	81.5%	89.8%
95% CI	76.7-86.4%	85.9-93.8%
Placebo		
Number evaluable	38	35
Number eradicated	2	1
Percentage eradicated	5.3%	2.9%
95% CI	1.6-8.9%	0-5.8%

BMT Bismuth subcitrate plus metronidazole plus tetracycline

In a multicentre, randomized trial, Thijs et al (7) compared the efficacy and safety of bismuth-based triple therapy (bismuth subcitrate 120 mg, metronidazole 250 mg and tetracycline 250 mg qid) versus omeprazole 40 mg bid plus amoxicillin 1000 mg bid – both treatments given for 14 days. Fifty-five patients (40 with peptic ulcer disease, 15 with nonulcer dyspepsia) received BMT. *H pylori* was eradicated in 96% (52 of 54) of patients by PP and 95% (52 of 55) of patients by ITT analysis. The dropout rate due to poor compliance was only 4% (two of 55) in the BMT group, a rate similar to that in our study. Bell et al (8) reported the results of a nonrandomized cohort study involving five different combination regimens, one of which was colloidal bismuth subcitrate 120 mg qid, metronidazole 400 mg tid and tetracycline 500 mg qid given for 14 days. *H pylori* infection was eradicated in 89% (23 of 26) of patients. Kung et al (9) reported an 80% (28 of 35) eradication rate (ITT) following a one-week only treatment with colloidal bismuth subcitrate 120 mg qid, metronidazole 400 mg qid and tetracycline 500 mg qid. Yang et al (10) reported an 83% (55 of 66) eradication rate (ITT) after a two-week treatment with bismuth subcitrate qid, metronidazole 250 mg qid and tetracycline 500 mg qid. Kim et al (11) reported an 88% (45 of 51) eradication rate (ITT) after a one-week treatment with colloidal bismuth subcitrate 120 mg qid, metronidazole 250 mg qid and tetracycline 500 mg qid.

If the results of these five trials are pooled, the overall ITT eradication rate is 88% (203 of 232).

Unge (12) reported a meta-analysis on 56 treatment arms involving 2956 patients treated with bismuth-based therapy using bismuth (any salt), tetracycline and a nitroimidazole. *H pylori* infection was cured in 2326 (79%) patients. This result, which was slightly lower than ours, likely occurred because different doses and treatment durations were included in the analysis.

In this study, resistance to metronidazole was not assessed. The reported prevalence of metronidazole resistance in Canada is about 33% (13). Our results demonstrated that, with the limitation of not having assessed metronidazole resistance, BMT achieved a 90% cure rate.

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 events were rarely a reason to discontinue treatment and were limited in time to the period of treatment. Moreover, no serious adverse event or clinically significant laboratory abnormalities were reported in the trial.

CONCLUSIONS

BMT treatment for 14 days at the doses described here is highly effective against *H pylori*, with an overall PP eradication rate of 89.5% (95% CI 81.5% to 97.5%) when metronidazole resistance is not assessed. Moreover, patients with gastric ulcer, duodenal ulcer or nonulcer dyspepsia did not respond differently to treatment with BMT. Finally, the BMT treatment was safe, and the withdrawal rate due to adverse events was very low.

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