

A. INGREDIENT NAME:

BISMUTH CITRATE

B. Chemical Name:

C. Common Name:

Bismuthi et Ammonii Citras

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	<i>(Results)</i>	<i>(Specifications)</i>
Bismuth oxide content on dry basis	57.3%	55.0-59.0%

E. Information about how the ingredient is supplied:

A white, amorphous or micro-crystalline powder, odorless and tasteless, and permanent in the air.

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Hopkins, R. J. Current FDA-approved treatments for *Helicobacter pylori* and the FDA approval process. *Gastroenterology*, 1997; 113(6Suppl): S126-130.

Stanescu, A., Mayer, D., and Gabard, B. *Helicobacter pylori* eradication therapy with bismuth citrate/amoxicillin combination therapy. *Leber, Magen, Darm*, 1996; 26(1): 32-36.

Tillman, L. A., Drake, F.M., and Dixon, J. S. Review article: safety of bismuth in the treatment of gastrointestinal diseases. *Alimentary Pharmacology & Therapeutics*, 1996; 10(4): 459-467.

1998-345431-62-16-BDL03

H. Information about dosage forms used:

Tablets

I. Information about strength:

120 mg, 2 tablets-3 times a day/ or Ranitidine bismuth citrate (RBC) 200, 400, 800mg bid.

J. Information about route of administration:

Orally

K. Stability data:

Melts at decomposition or with mineral acids
Stable

L. Formulations:

Bismuth Subnitrate.....100gms
Citric Acid.....70gms
Distilled water, a significant quantity
See file for compounding formulation

M. Miscellaneous Information:

Database: Medline <1966 to present>

Set	Search	Results
1	exp bismuth/	2126
2	bismuth citrate.tw.	53
3	efficacy.tw.	108250
4	safety.tw.	44957
5	exp drug therapy/	115501
6	2 and 3	11
7	2 and 4	4
8	2 and 5	13
9	from 6 keep 3-5,7-8,10	6
10	from 7 keep 3-4	2
11	from 8 keep 12-13	2

<1>

Unique Identifier

98060676

Authors

Laine L. Estrada R. Trujillo M. Emami S.

Title

Randomized comparison of ranitidine bismuth citrate-based triple therapies for Helicobacter pylori.

Source

American Journal of Gastroenterology. 92(12):2213-5, 1997 Dec.

Abstract

OBJECTIVES: In an attempt to increase the efficacy and simplicity of FDA-approved regimens for Helicobacter pylori, we studied (1) addition of an inexpensive antibiotic (amoxicillin) to twice-daily ranitidine bismuth citrate (RBC)-clarithromycin dual therapy, and (2) substitution of RBC for bismuth subsalicylate + H₂-receptor antagonist in bismuth-based triple therapy. METHODS: Subjects with previously untreated Helicobacter pylori infection documented by ¹³C-urea breath test plus either endoscopic biopsy or serology were randomly assigned to a 2-wk course of (1) RBC 400 mg b.i.d., amoxicillin 1 g b.i.d., and clarithromycin 500 mg b.i.d. (RAC), or (2) RBC 400 mg b.i.d., metronidazole 250 mg t.i.d., and tetracycline 500 mg t.i.d. (RMT). Repeat breath test was performed 4 wk after the completion of therapy. RESULTS: Intent-to-treat and per-protocol cure rates for RAC were 46 of 50 patients (92%) and 45 of 47 patients (96%); for RMT they were 40 of 50 patients (80%) and 37 of 42 patients

(88%). Study drugs were stopped due to side effects in three patients (6%) taking RAC and six patients (12%) taking RMT. CONCLUSIONS: Twice-daily RBC-based triple therapy with clarithromycin and amoxicillin produces *Helicobacter pylori* eradication rates over 90%, which is comparable to rates seen with proton pump inhibitor-based triple therapies. RBC also may be substituted for bismuth subsalicylate and an H₂-receptor antagonist in standard bismuth-based triple therapy.

<2>

Unique Identifier

98056756

Authors

Hopkins RJ.

Title

Current FDA-approved treatments for *Helicobacter pylori* and the FDA approval process.

Source

Gastroenterology. 113(6 Suppl):S126-30, 1997 Dec.

Abstract

U.S. Food and Drug Administration (FDA) approval of new drugs expands treatment options and serves as a "safety net" of well-documented efficacy and safety. The information provided in the package insert facilitates physician education and provides some assurance that marketing information is accurate. As of February 1997, three *Helicobacter pylori* regimens have been FDA-approved for eradication of *H. pylori* in infected patients with active duodenal ulcers. Regimen 1, omeprazole + clarithromycin (O/C), was supported by two multicenter, controlled studies with a 6-month follow-up. Eradication rates were 74% (n = 53; 95% confidence interval [CI], 62-85) and 64% (n = 61; 95% CI, 52-76). Twenty-five of 26 patients with failed eradication therapy who were taking O/C with clarithromycin-susceptible strains before treatment and who had pretreatment and posttreatment susceptibility tests performed developed clarithromycin resistance after treatment. Regimen 2, ranitidine-bismuth-citrate + clarithromycin, was supported by two multicenter, placebo-controlled studies with a 6-month follow-up. Eradication rates were 84% (n = 19; 95% CI, 60-96) and 73% (n = 22; 95% CI, 50-88). Insufficient pretreatment and posttreatment susceptibility data were collected to assess antimicrobial resistance. Regimen 3, bismuth subsalicylate + metronidazole + tetracycline + an H₂-receptor antagonist, was supported by two pivotal literature-based studies. Eradication rates in patients

with duodenal ulcer were 82% (n = 51; 95% CI, 70-92) and 77% (n = 39; 95% CI, 61-89), respectively. When extrapolating the results of these three FDA-approved regimens to the clinical setting, particular aspects of the clinical trial should be kept in mind. These include the type of controls, primary end points used, population studied, and number and type of dropouts.

<3>

Unique Identifier

97450491

Authors

Williams MP. Hamilton MR. Sercombe JC. Pounder RE.

Title

Seven-day treatment for Helicobacter pylori infection: ranitidine bismuth citrate plus clarithromycin and tetracycline hydrochloride.

Source

Alimentary Pharmacology & Therapeutics. 11(4):705-10, 1997 Aug.

Abstract

BACKGROUND: Dual therapy with ranitidine bismuth citrate plus clarithromycin twice daily for 14 days is an effective regimen for eradicating Helicobacter pylori infection. AIM: To determine whether this regimen can be improved by the addition of a second antibiotic, tetracycline hydrochloride, whilst reducing the duration of treatment to 7 days. METHODS: Sixty-one out-patients were enrolled to this open treatment study. All had H. pylori infection, as determined by 13C-urea breath test and, for those undergoing endoscopy, by rapid urease test. Patients were treated with ranitidine bismuth citrate 400 mg, clarithromycin 500 mg and tetracycline hydrochloride 500 mg all twice daily for 7 days. Eradication of H. pylori was assessed by two separate 13C-urea breath tests, the first 28-68 days after the completion of treatment, the second 28-162 days later. H. pylori infection was considered cured if both tests were negative. RESULTS: All 61 patients were included in the intention-to-treat efficacy analysis. Successful eradication of H. pylori was achieved in 55/61 patients (90%; 95% CI; 82-98%). Fifty-nine out of sixty-one patients reported 100% compliance; one patient missed a single dose of medication and the other withdrew at 48 h due to nausea and vomiting. Minor adverse events were reported by 30/61 patients. CONCLUSION: One-week triple therapy with ranitidine bismuth citrate, clarithromycin and tetracycline, all twice daily, is a safe and well-tolerated regimen which eradicates H. pylori in 90% of infected

patients.

<4>

Unique Identifier

96384043

Authors

Peterson WL. Ciociola AA. Sykes DL. McSorley DJ. Webb DD.

Title

Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating H. pylori and reducing ulcer recurrence. RBC H. pylori Study Group [see comments].

Comments

Comment in: Aliment Pharmacol Ther 1996 Dec;10(6):1035

Source

Alimentary Pharmacology & Therapeutics. 10(3):251-61, 1996 Jun.

Abstract

AIM: To compare the efficacy of the coadministration of ranitidine bismuth citrate plus the antibiotic clarithromycin, with ranitidine bismuth citrate alone or clarithromycin alone for the healing of duodenal ulcers, eradication of H. pylori and the reduction of ulcer recurrence. METHODS: This two-phase, randomized, double-blind, placebo-controlled, multicentre study consisted of a 4-week treatment phase followed by a 24-week post-treatment observation phase. Patients with an active duodenal ulcer were treated with either ranitidine bismuth citrate 400 mg b.d. for 4 weeks plus clarithromycin 500 mg t.d.s. for the first 2 weeks; ranitidine bismuth citrate 400 mg b.d. for 4 weeks plus placebo t.d.s. for first 2 weeks; placebo b.d. for 4 weeks plus clarithromycin 500 mg t.d.s. for the first 2 weeks; or placebo b.d. for 4 weeks plus placebo t.d.s. for the first 2 weeks. RESULTS: Ulcer healing rates after 4 weeks of treatment were highest with ranitidine bismuth citrate plus clarithromycin (82%) followed by ranitidine bismuth citrate alone (74%; P = 0.373), clarithromycin alone (73%; P = 0.33) and placebo (52%; P = 0.007). Ranitidine bismuth citrate plus clarithromycin provided significantly better ulcer symptom relief compared with clarithromycin alone or placebo (P < 0.05). The coadministration of ranitidine bismuth citrate plus clarithromycin resulted in significantly higher H. pylori eradication rates 4 weeks post-treatment (82%) than did treatment with either ranitidine bismuth citrate alone (0%; P < 0.001), clarithromycin alone (36%; P = 0.008) or placebo (0%; P < 0.001). Ulcer recurrence rates 24 weeks

post-treatment were lower following treatment with ranitidine bismuth citrate plus clarithromycin (21% compared with ranitidine bismuth citrate alone (86%; $P < 0.001$), clarithromycin alone (40%; $P = 0.062$) or placebo (88%; $P = 0.006$). All treatments were well tolerated.

CONCLUSIONS: The coadministration of ranitidine bismuth citrate plus clarithromycin is a simple, well-tolerated and effective treatment for active *H. pylori*-associated duodenal ulcer disease. This treatment regimen effectively heals duodenal ulcers, provides effective symptom relief, eradicates *H. pylori* infection and reduces the rate of ulcer recurrence. The eradication of *H. pylori* infection in patients with recently healed duodenal ulcers is associated with a significant reduction in the rate of ulcer recurrence.

<5>

Unique Identifier

97006475

Authors

Wyeth JW. Pounder RE. Duggan AE. O'Morain CA.
 Schaufelberger HD. De Koster EH. Rauws EA. Bardhan KD.
 Gilvarry J. Buckley MJ. Gummett PA. Logan RP.

Title

The safety and efficacy of ranitidine bismuth citrate in combination with antibiotics for the eradication of *Helicobacter pylori*.

Source

Alimentary Pharmacology & Therapeutics. 10(4):623-30, 1996 Aug.

Abstract

BACKGROUND: Ranitidine bismuth citrate is a novel salt of ranitidine and a bismuth citrate complex. It has intrinsic antisecretory and anti-*Helicobacter pylori* activity, but monotherapy rarely eradicates *H. pylori* infection in man. **AIM:** A pilot study to investigate rates of *H. pylori* eradication achieved by co-prescription of ranitidine bismuth citrate with antibiotics, and to identify several regimens which would merit further investigation. **METHOD:** One hundred dyspeptic patients infected with *H. pylori* were randomly allocated to treatment with ranitidine bismuth citrate 800 mg b.d. plus either amoxicillin, metronidazole, clarithromycin, cefuroxime axetil, tetracycline, tetracycline plus metronidazole or clarithromycin plus tetracycline for 14 days. Eradication of infection was assessed using the ¹³C-urea breath test 4 weeks after the end of treatment. **RESULTS:** In a per protocol analysis eradication of *H. pylori* ranged between 22 and 100%; the

intention-to-treat eradication rates ranged between 15 and 92%. No adverse events were specifically attributed to ranitidine bismuth citrate. CONCLUSION: Co-prescription therapy, using ranitidine bismuth citrate and one or more antibiotics, is suitable for further investigation in large-scale clinical trials in patients infected with H. pylori.

<6>

Unique Identifier

97004564

Authors

Stanescu A. Mayer D. Gabard B. Jost G. Baczako K.
Dragici A. Malfertheiner P.

Title

[Helicobacter pylori eradication therapy with bismuth citrate/amoxicillin combination therapy]. [German]

Source

Leber, Magen, Darm. 26(1):32-6, 1996 Jan.

Abstract

The efficacy of a new combination preparation containing bismuth citrate and amoxicillin in one tablet was compared with the efficacy of bismuth citrate monotherapy in a randomised double-blind study on the eradication of Helicobacter pylori. The study involved 70 H. pylori positive (antrum biopsies showing a positive urease test) patients with non-ulcer dyspepsia and chronic gastritis. The treatment period was 14 days; 35 patients in group 1 received 2 tablets tid containing the bismuth citrate amoxicillin combination (BIAM tablet; 250 mg amoxicillin base and 120 mg bismuth); 35 patients in group 2 were treated with 2 (tablets) tid containing bismuth citrate (BI tablet; 120 mg bismuth). Total daily dose was therefore 1500 mg amoxicillin + 720 mg bismuth in group 1 patients resp. 720 mg bismuth in group 2 patients. 4 weeks after therapy H. pylori could not be histologically detected in the antrum of 22 patients (63%) in group 1 and 8 patients (24%) in group 2. Thus in group 1 (BIAM) a significantly higher eradication rate ($p < 0.001$) was shown than in group 2 (BI). Inflammation characterized by the infiltration of polymorphonuclear cells was significantly ($p < 0.01$) less pronounced in group 1 (BIAM) than in group 2 (BI) 4 weeks after the end of treatment. Gastrointestinal distress was quantified by evaluation of 13 different symptoms using a fourpoints scale at the beginning of the study and after 2 and 6 weeks. The sum of scores decreased by 81% in group 1 (BIAM) and 71% in group 2 (BI) after 6 weeks.

BISMUTH CITRATE

Dose is 120 mg, 2-3 times daily for H. pylori ulcer disease.

Bismuth toxicities in humans are well known. Acute effects reported are eye and skin irritation and kidney damage on repeated exposures. While chronic toxicities have not been investigated, effects seen have been weakness, dermatitis, diarrhea, fever, rheumatic pain, metal line on gums, halitosis and neuropathy.

REFERENCES

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3. Williams MP, Hamilton MR, Sercombe JC, et al. Seven-day treatment for *Helicobacter pylori* infection: ranitidine bismuth citrate plus clarithromycin and tetracycline hydrochloride. *Alimentary Pharmacology & Therapeutics* 1997; 11(4):705-10.
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6. Stanescu A, Mayer D, Gabard B, et al. [*Helicobacter pylori* eradication therapy with bismuth citrate/amoxicillin combination therapy]. [German] *Leber, Magen, Darm* 1996; 26(1):32-6.
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8. Pounder RE. Treatment of peptic ulcers from now to the millennium. [Review] [61 refs] *Baillieres Clinical Gastroenterology* 1994; 8(2):339-50.
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