How to Effectively Use Bismuth Quadruple Therapy: The Good, the Bad, and the Ugly

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KEYWORDS

• *Helicobacter pylori* • Therapy • Bismuth • Tetracycline • Metronidazole
• Proton pump inhibitors • Side effects • Adherence

KEY POINTS

- Bismuth quadruple therapy, consisting of a proton pump inhibitor, bismuth, metronidazole, and tetracycline, is a good alternative first-line therapy and is especially useful when penicillin cannot be used or when clarithromycin and metronidazole resistance is common.
- The literature is confusing because bismuth quadruple therapy is used to denote regimens that differ greatly in terms of duration, doses, and administration in relation to meals.
- Proton pump inhibitors can help negate the deleterious effects of metronidazole resistance in bismuth quadruple therapy. The optimum dose of proton pump inhibitor is unclear. A double dose twice a day is recommended.
- In the presence of metronidazole resistance, the optimum duration is 14 days along with 1500 to 1600 mg of metronidazole in divided dosages. The optimum doses and dosing intervals for tetracycline and bismuth are as yet unclear.

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- Poor patient adherence is a major issue with bismuth quadruple therapy. Patient education and counseling regarding the goals of therapy, the side effects, and the necessity to complete the full 14 days should be provided.
- As with all therapies, the decision to use bismuth quadruple therapy should be guided by the regional, local, and patient-specific antimicrobial resistance patterns and knowledge about effectiveness locally.
- Twice-a-day dosing may provide a high cure rate with fewer side effects, accomplishes a reduction in total antibiotic dose, and improves adherence. However, its effectiveness in relation to metronidazole resistance remains unclear.

BACKGROUND

Eberle, in 1834, noted that bismuth, primarily as the white oxide, was introduced into medicine in 1697 by Jacobi and that its use was later popularized by Drs Odier of Geneva and De la Roche, of Paris.[1] Throughout the nineteenth century, bismuth salts were widely and successfully used in gastroenterology.[2] Bismuth continued to be used as a primary or adjuvant therapy for dyspepsia and peptic ulcer until being replaced successively by antacids, histamine-2 receptor antagonists, and proton pump inhibitors (PPIs). Bismuth also had a long history of use as an antimicrobial especially for the treatment of syphilis.[3] In the United States, bismuth subsalicylate (eg, as Pepto-Bismol) was also used for dyspepsia and diarrhea and later to treat and prevent travelers' diarrhea.[4] In travelers' diarrhea, bismuth was shown to function as a topical antimicrobial, thus linking its use as an anti-infective to its subsequent use for treatment of *Helicobacter pylori*-related peptic ulcer disease.[5–7]

The most widely used forms of bismuth in use for gastroenterology at the time of the discovery of *H pylori* were bismuth subnitrate, subsalicylate, and subcitrate. In the 1970s, Gist-Brocades introduced a proprietary preparation of colloidal bismuth subcitrate (De-Nol) as an antiulcer therapy. The original De-Nol formulation was a colloidal suspension in ammonia water and had the very pungent odor of ammonia. The 1970s were also a time of great interest in ulcer pathogenesis and ulcer treatments. Many groups were also active in the study of ulcer in experimental animals. Colloidal bismuth subcitrate was shown to be able to coat and thus potentially protect the ulcer base, a property not seen with other bismuth preparations.[8–11] Over time, the list of its properties potentially important in the treatment of peptic ulcer grew large (**Box 1**).[12]

BISMUTH IN THE ERA OF NEW CONCEPTS REGARDING PATHOGENESIS AND TREATMENT OF PEPTIC ULCER

In the mid-twentieth century, peptic ulcer and its complications were a major medical problem in western countries. The importance of peptic ulcer was illustrated by the awarding of a Nobel prize to James Black in 1988 for the discovery of the histamine-2 receptor antagonists (in 1972) and for β-blockers (in 1964). The late 1970s and early 1980s saw the introduction of many new antiulcer agents (eg, sucralfate, histamine-2 receptor antagonists, synthetic prostaglandins, a tablet formulation of De-Nol, and finally, the PPIs). An epidemic of bismuth neurotoxicity occurred in France, which led to the removal of bismuth from many countries.[3,13] However, in