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High dose versus standard dose in triple therapy for *Helicobacter pylori* eradication?

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Summary

Empiric clarithromycin-containing (note: I believe that –based is slang as there is no rational reason for choosing one component of a multiple drug therapy) triple therapies for eradication of *Helicobacter pylori* do not reliably produce a $\geq 80\%$ success rate on an intention-to-treat basis. This lack of adequate treatment response is primarily due to clarithromycin resistance. This commentary discusses the findings of a meta-analysis by Villoria *et al.* that investigated whether a triple therapy containing a high-dose PPI and clarithromycin plus either amoxicillin or tinidazole improves the success rate of *H. pylori* eradication compared a triple therapy containing a standard-dose PPI. The mean intention-to-treat cure rates were greater in patients using the high-dose PPI regimen compared with the standard dose regimen (82% vs 74%, respectively). However, the actual cure rates of these studies were poor and the improvements were unlikely to be clinically significant. The prevalence of clarithromycin resistance in most of the world is such that clarithromycin-containing triple therapy should not be used empirically. Alternatives include sequential or concomitant therapy and bismuth-containing quadruple therapies.

Keywords

dose; eradication therapy; *Helicobacter pylori*; proton pump inhibitor; resistance

Commentary

Rates of *Helicobacter pylori* (NOTE: you skip back and forth between *Helicobacter pylori* and *H. pylori*) eradication using traditional clarithromycin-containing triple therapies have decreased because of increasing clarithromycin resistance.¹ Villoria *et al.* report the findings of a meta-analysis that compared the rates of *H. pylori* eradication using a twice daily triple therapy regimen consisting of either a standard or a high dose PPI plus clarithromycin and either amoxicillin or tinidazole administered for 7 days.² The authors included 6 studies and a total of 1,703 patients in their analysis—5 of these studies compared a high and a standard-dose PPI in a triple therapy regimen containing clarithromycin and amoxicillin, and one study compared a high and a standard dose PPI in a triple therapy regimen containing clarithromycin and tinidazole. The mean intention-to-treat success rate was 74% (734/992, 95%CI: 71–77% with a standard dose PPI and improved to 82% (587/711, 95%CI: 78–84%) with a high PPI dose. The authors' conclusion that triple therapy regimens containing a high-dose PPI are slightly more effective than regimens containing a standard PPI dose is consistent with another

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meta-analysis that compared once versus twice daily PPI dosing in triple therapy.³ Villoria *et al.* attributed the modest, and probably clinically insignificant improvement, to enhanced acid suppression.

Meta-analyses are extremely useful for comparing historical data and identifying topics that require further study. Villoria *et al.* appropriately recommend several additional analyses to be performed, for example, an analysis of the effect of treatment duration on *H. pylori* eradication.

The overall success of *H. pylori* eradication in the meta-analysis by Villoria and colleagues was poor, even with administration of a high dose PPI. Poor cure rates with triple therapy are largely because of clarithromycin resistance, which effectively transforms triple therapy into a dual therapy (e.g. PPI plus amoxicillin). The results noted in this meta-analysis are, therefore, probably related mostly to the PPI plus amoxicillin component of the triple therapy. Triple therapy could, therefore, be envisioned as the simultaneous administration of two dual therapies—a PPI plus clarithromycin and a PPI plus amoxicillin or tinidazole.¹ If the eradication rate expected for a 7-day course of treatment with a PPI plus clarithromycin would be approximately 80% for susceptible strains and 0% for clarithromycin-resistant strains, and these outcomes would not be greatly influenced by PPI dose, particularly for clarithromycin-resistant strains. By contrast, the results of treatment with a PPI plus amoxicillin are markedly influenced by PPI dose and duration. The success rate of *H. pylori* eradication using a dual therapy regimen consisting of a twice daily standard dose PPI plus amoxicillin for 7 days is approximately 35% and increases to approximately 50% with a 14-day regimen or with a double dose of PPI (1)[

From the poor success rate reported in the meta-analysis by Villoria *et al.* we estimate that approximately 20% of the patients investigated were clarithromycin-resistant [. If this assumption is correct, the rate of successful *H. pylori* eradication would theoretically be the sum of patients cured by using PPI plus clarithromycin (assuming that 80% of these patients have clarithromycin-susceptible strains) and those cured by using PPI plus amoxicillin. Thus, if 80% of patients have clarithromycin-susceptible strains and this value is multiplied by the eradication rate for clarithromycin-susceptible *H. pylori* (80%), 64% of patients should be cured. The amoxicillin component of the triple therapy would be beneficial to those patients who were not susceptible to the clarithromycin component (i.e. 36% of patients), and if this value is multiplied by the eradication rate achieved by using amoxicillin for 7 days (35%), an additional 12.6% of patients should be cured. Therefore, *H. pylori* eradication would be expected to cure a total of 76.6% of patients, and this percentage should increase to 82% if the eradication rate achieved by PPI plus amoxicillin was increased to 50% because of the increased PPI dose.¹ On the other hand, metronidazole and tinidazole are pH-independent antibiotics, and increasing the PPI dose would not be expected to offset the detrimental effects of clarithromycin-resistance. Accordingly, no significant improvement was seen with administration of a high-dose PPI versus a standard-dose PPI in combination therapy with tinidazole. In summary, the factors that determine the outcome of a PPI-containing *H. pylori* therapy include the effectiveness of each component in relation to the control of intragastric pH. Amoxicillin and clarithromycin require bacterial replication which only takes place at neutral or near-neutral pH. In contrast, metronidazole/tinidazole are prodrugs that are largely acid independent antibiotics. While both amoxicillin and clarithromycin would be expected to be more effective when intragastric pH is very well controlled, increasing clarithromycin resistance has led to most research focusing on improving the effectiveness of amoxicillin but controlling intragastric pH.

Villoria *et al.* noted that the greater success rate observed in patients receiving therapy with a high PPI dose might relate to findings from other studies that have shown an enhanced effectiveness of triple therapy in patients who are poor metabolizers of PPIs and who achieve

improved control of acidity.^{2,4,5} Among users of triple therapy, the benefit of improved pH control is independent of the presence of clarithromycin resistance—that is, the benefits of acid inhibition affect the results with the PPI plus amoxicillin component, and is consistent with the notion that replication-dependent antibiotics only effectively eradicate *H. pylori* between pH 6–8.⁶ Cure rates with administration of triple therapy are, in fact, closely related to the degree of acid suppression and this is exemplified by studies that have demonstrated a 100% cure rate in patients that have maintained a pH >4 for ≥90% of a 24-day treatment regimen, irrespective of clarithromycin susceptibility status.^{6,7}

The increased effectiveness of amoxicillin in patients who metabolize PPIs slowly suggests that eradication rates >90% should be obtainable by using optimal PPI and amoxicillin dosing.⁶ Studies, therefore, are needed to identify the PPI dose and dosing interval that will reliably achieve pH control similar to that achieved in slow PPI metabolizers. Alternatively, long-acting PPIs or a combination of PPIs and antacids (e.g. sodium bicarbonate) could be used,⁸ and theoretically, should produce cure rates that approach 100%, reducing any contribution made by clarithromycin-resistance. As *H. pylori* treatment studies notoriously destroy new theoretical strategies for *H. pylori* eradication, only clinical trials performed within different populations and regions will determine whether these goals can be achieved. The meta-analysis by Villoria *et al.* demonstrates how to improve eradication rates slightly, but these slight improvements still unacceptable clinically.² The prevalence of clarithromycin resistance in most of the world is such that the empiric triple therapy should be replaced by alternative treatments such as sequential or concomitant therapy, or bismuth-containing quadruple therapies. In areas in which clarithromycin and metronidazole resistance is particularly prevalent, empirical *H. pylori* treatment strategies containing either of these antibiotics should be avoided.^{1,6}

PRACTICE POINT

Although a triple therapy comprising a PPI, clarithromycin and amoxicillin results in a slightly increased rate of *Helicobacter pylori* eradication with a high PPI dose compared with a standard PPI dose, cure rates remain unacceptably low and further studies are required to determine alternative approaches to improve eradication rates.

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Biography

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