Editorial

Furazolidone in *Helicobacter Pylori* Therapy: Misunderstood and Often Unfairly Maligned Drug Told in A Story of French Bread

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INTRODUCTION

Helicobacter pylori is a common bacterial infectious disease. Clinical trialist's are generally gastroenterologists and often lump *H. pylori* intellectually with other gastrointestinal (GI) diseases such as constipation or inflammatory bowel disease.[1,2] It differs markedly as there is no placebo response and with the proper regimen in terms of dose, duration, frequency, etc., cure rates of 100%, or near 100%, are possible and expected.[2] Treatment failure can always be understood in terms of poor regimen design or antimicrobial resistance. As an analogy one could liken an excellent anti- *H. pylori* regimen to a recipe. Thus, if one wished to make French bread and not the Arabian *khobz*, one would select a proven recipe which would carefully describe the important details in terms of ingredients, amounts, handling, baking, etc.[3]

The authors of the furazolidone review in this issue of the Journal are experienced clinical investigators and provide a broad overview of the use of furazolidone in the treatment of *H. pylori*.[4] However, the audience of clinicians desires recipes (i.e., detailed proven and optimized protocols along with advice about when to and when not to use a particular regimen). The report fails in this regard. Continuing our French bread analogy, they inform us of some ingredients such as flour, water, sugar but not others (e.g., "another antibiotic") and few details. Just as the list of ingredients on a package of bread will not allow one to reproduce the contents, their failure to dissect and identify what works and why, and what does not and why, leaving us cooks unable to produce our desired product, reliable cures. In addition, we are cautioned that furazolidone may be a carcinogen. This warning is not completely accurate. The International Agency for Research on Cancer (IARC) categorizes agents in categories or groups: Group 1: Carcinogenic to humans. Group 2A: Probably carcinogenic to humans (substances for which there is a lesser degree of evidence in humans but sufficient evidence in animal studies, or degrees of evidence considered appropriate to this category, e.g., unequivocal evidence of mutagenicity in mammalian cells), Group 2B: Possibly carcinogenic to humans, (substances for which there is sufficient evidence in animal tests, or degrees of evidence considered appropriate to this category), Group 3: Unclassifiable as to carcinogenicity in humans, Group 4: Probably not carcinogenic to humans. Furazolidone is a category 3 agent. The IARC report states: "Furazolidone has been produced commercially since 1955. It is used in human and veterinary medicine as an antibacterial and antiprotozoal agent. No data were available to assess the teratogenicity or chromosomal effects of this compound in humans. No case report or epidemiological study of the carcinogenicity of furazolidone was available to the Working Group. Evaluation: No evaluation of the carcinogenicity of furazolidone to experimental animals could be made. In the absence of epidemiological data, no evaluation of the carcinogenicity of furazolidone to humans could be made."[5] Furazolidone was last updated in 1998 and group 3 drugs have been typically excluded from more recent complications of carcinogens. Drugs used in animals can easily enter the human food chain and are thus rigorously controlled. As they note, furazolidone was removed from animal use. Clinical usage of all drugs is dictated by risks and benefits. Clinical usage of most drugs is often short such that the benefits can easily outweigh possible but low risks.

The authors recommend counseling patients about furazolidone.[4] If carcinogenicity is a potential issue it would seem they should be more concerned about metronidazole which is used in sequential therapy. Metronidazole is listed as a definite carcinogen in animals and as a category agent 2B in humans. The package insert for metronidazole carries a "black box" warning from the Federal Drug Agency (FDA) stating "WARNING Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided." http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a2883ca1-5a9a-4259-9d80-46ab67274384.

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There is a similar warning for tinidazole. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a0d01539-8413-4703-94cc- d221918630a1. Furazolidone is no longer marketed in the United States because the Shire company decided the market was too small and informed the FDA that they would no longer market it. The FDA responded that they would "publish a notice in the Federal Register stating that (the company has) voluntarily requested withdrawal of approval of these applications because (it has) stopped marketing the drug products under the NDA". That notice was subsequently published (Federal Register / Vol.70, No. 42 / Friday, March 4, 2005 / Notices, pp 11652). Furazolidone can, however, be obtained cheaply in Latin America.

How to best use furazolidone for *H. pylori* eradication

Most regimens or "recipes" have never been optimized and furazolidone-containing regimens are no exception.[3,6-8] We recommend furazolidone combination therapy for areas with high rates of resistance and for patients with multiple prior treatment failures.[6] Our success has been essentially 100% despite many subjects not being able to complete the full 10 to 14 day regimen.[6] We hope that others in regions where it is available will optimize regimens as we suspect that a much lower dose should suffice (e.g., we found that 7 mg, 7 times a day one and 3 hours after meals and bedtime, was effective in dropping the UBT to normal).[9]

The optimal dose of furazolidone is unknown; we recommend 100 mg t.i.d. with meals as part of a 4 drug combination [Table 1].[6] A few caveats are necessary when using furazolidone. The drug is an monoamine oxidase inhibitor and thus interacts with many other drugs and foods (e.g., we provide patients with an information sheet that cautions against aged cheese, sausage including bologna, salami and pepperoni, lima beans, lentils, snow peas, and soybeans, canned figs and raisins, beer, ale and wines, licorice, soy sauce and any food product that is made with soy sauce, monamine oxidase inhibitors, phenylpropanolamine, ephedrine, and phenylephrine).

In summary, furazolidone is an underutilized drug especially useful in areas where resistance is widespread and multiple. To make excellent French bread requires a proven recipe; the ideal use of any anti-*H. pylori* therapy requires an optimized regimen. The lack of specifics by authors of the review limit its applicability for the clinician and their misunderstanding of the data about carcinogenicity unfairly maligns what should otherwise be a useful drug.

Table 1: Recommended furazolidone-containing *anti-Helicobacter pylori* therapy B

Furazolidone quadruple therapy: Bismuth subsalicy1ate or subcitrate 2 tabs q.i.d, tetracycline HC1 500 mg q.i.d.(with meals and bedtime), furazolidone 100 mg, t.i.d. (with meals) and a standard dose PPI b.i.d. for 10-14 days.

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