

CLINICAL INFORMATION ON FURAZOLIDONE

Introduction:

Furazolidone (FZD) is a synthetic nitrofurantoin derivative that is an antibacterial and antiprotozoal agent.¹ FZD occurs as a yellow odorless crystalline powder with a bitter aftertaste. The drug is practically insoluble in water and alcohol. FZD is decomposed by alkali. The drug should be protected by light because it darkens on exposure to strong light and thus should be stored in light resistant containers.¹

Uses & Indications:

FZD is active against the protozoan *Giardia lamblia* (*Giardia intestinalis*) and against a range of bacteria in vitro including staphylococci, enterococci, *Escherichia coli*, *Salmonella* spp., *Shigella* spp., and *Vibrio cholerae*. FZD is bactericidal and appears to act by interfering with bacterial enzyme systems. Resistance is reported to be limited. It is used in the treatment of giardiasis, trichomoniasis, cholera and other vibrio infections¹. It has been suggested for other bacterial gastrointestinal infections but antibacterial therapy with FZD is regarded as unnecessary in mild & self-limiting gastro-enteritis.¹ However, FZD has been reported to possess anti-*Helicobacter* activity² and to have some ulcer-healing properties^{3,4,5}

Clinical experience has demonstrated that cure of *H.pylori* infection is difficult due to lack of compliance with drug regimens and development of antibiotic resistant *H.pylori*⁶ FZD and nitrofurantoin have been recommended as alternative agents for the treatment of *H.pylori* due to the high rate of metronidazole resistance. When multiple treatment regimens fail, it has been suggested that salvage therapy regimens such as bismuth or FZD quadruple therapy should be used.⁷ In a recent study Kwon et al., (2000) assessed the prevalence of FZD, nitrofurantoin & metronidazole resistance among *H.pylori* strains in 431 clinical isolates. 52% were metronidazole resistant compared to 2% (7 of 431) with resistance to FZD & nitrofurantoin.⁸ All seven FZD and nitrofurantoin resistant isolates were also resistant to metronidazole.⁸

Dosage & Administration.

For the treatment of giardiasis and for the adjunctive treatment of cholera, the usual adult dosage of FZD is 100mg (or 1.25mg/kg) four times daily. Children 5 years of age or older may receive 17-25 mg four times daily. FZD dosage probably should not exceed 8.8 mg/kg daily because of the possibility of producing nausea and vomiting. Diarrhea usually responds to FZD therapy within 2-5 days. If satisfactory clinical response is not attained within 7 days, the manufacturer recommends that FZD be discontinued; however, for the treatment of giardiasis most clinicians recommend 7-10 days of FZD therapy.¹

In the treatment of *H.pylori* infection, one-week triple therapy, consisting of tripotassium dicitrato bismuth (TDB), 240mg b.d., low-dose FZD (100mg b.d.) and clarithromycin (250mg b.d.) achieved high cure rate of *H.pylori*.⁹ Liu et al.¹⁰, (2000) reported that quadruple therapy with TDB 240mg b.d., FZD 100mg b.d., josamycin 1000mg b.d. and famotidine 20mg b.d. produced eradication rates (intention-to-treat/per protocol) of 90/95%, and duodenal ulcer healing rate of 94% (refer Table 1)¹¹.

| One-week regimens containing furazolidone for eradication of <i>Helicobacter pylori</i> (courtesy of Professor S-D. Xiao et al.) ¹¹ | | | | |
|--|--|--|---|---------------|
| Regimen | Drug combination | Dosage | <i>H.pylori</i> eradication rate | 95% CI |
| FCB | Furazolidone Clarithromycin TDB | 100mg b.i.d. 250mg b.i.d. 240mg b.i.d. | 91% | 82-99% |
| FCL | Furazolidone Clarithromycin Lansoprazole | 100mg b.i.d. 250mg b.i.d. 30mg b.i.d. | 91% | 82-99% |
| FCO | Furazolidone Clarithromycin Omeprazole | 100mg b.i.d. 250mg b.i.d. 20mg b.i.d. | 86% | 74-95% |
| FJB | Furazolidone Josamycin TDB | 100mg b.i.d. 1000mg b.i.d. 240mg b.i.d. | 77% | 66-87% |
| FBJFa | Furazolidone TDB Josamycin Famotidine | 100mg b.i.d. 240mg b.i.d. 1000mg.b.i.d. 20mg b.i.d. | 94.7% | 88.9-99.6% |
| FAO | Furazolidone Amoxicillin Omeprazole | 100mg b.i.d. 1000mg b.i.d. 20mg b.i.d. | 87% | 82-91% |
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Mild side effects occurred in only 18% of those receiving therapy.¹⁰ In a study conducted in Brazil, forty *H.pylori*-positive patients with duodenal ulcer were randomized to receive 20mg omeprazole o.m. or b.d. for one month plus 500mg clarithromycin (b.d.) and 200mg FZD (b.d.) for one week. Three months after the end of the treatment the eradication rates were 90% by intention-to-treat analysis, and 97% by per protocol analysis.¹² Mild side effects were observed in 25 patients, none of who abandoned the protocol. No difference was observed between 20mg and 40mg omeprazole daily doses.¹¹

Mechanism of Action & Pharmacokinetics.

FZD is bactericidal due to its interference with several bacterial enzyme systems, possibly including prevention of acetylation of coenzyme A. FZD also acts as a monoamine oxidase (MAO) inhibitor.

Following oral administration, FZD is poorly absorbed and is inactivated in the intestine. About 5% of an oral dose of FZD is excreted in the urine as unchanged drug and metabolites, which may tint the urine brown. The concentration of FZD in human breast milk has not been determined.

Cautions.

GI Effects

Nausea and vomiting are the most common adverse effects of oral FZD therapy; abdominal pain and diarrhea occasionally occur. These effects can be minimized or eliminated by reducing the dosage or discontinuing the drug.

Sensitivity Reactions

Hypersensitivity reactions to oral FZD occur in a small number of patients and generally subside with discontinuance of the drug. Hypersensitivity reactions include a fall in blood pressure, angioedema, fever, arthralgia, urticaria, and a vesicular or morbilliform rash. Erythema multiforme, pulmonary infiltration, and pulmonary eosinophilia also have been reported and may be due to hypersensitivity.

Other Adverse Effects

Headache and malaise occur occasionally with oral furazolidone therapy and can be minimized or eliminated by reducing dosage or discontinuing the drug. Following oral furazolidone administration, hypoglycemia, agranulocytosis, and, in one patient, partial deafness and dizziness have also been reported. Rarely, some patients receiving oral furazolidone experience a disulfiram-like reaction to alcohol. Polyneuritis and hemolytic anemia (in patients with glucose-6-phosphate dehydrogenase deficiency and in neonates) also have been reported rarely.

Precautions and Contraindications

Oral furazolidone may cause mild, reversible intravascular hemolysis in patients with a genetic deficiency of glucose-6-phosphate dehydrogenase. Such patients should be observed closely while receiving the drug, and furazolidone should be discontinued if any evidence of hemolysis occurs.

Although there have been no reports of adverse effects, the possibility of drug interactions characteristic of MAO inhibitors should be considered in patients receiving oral furazolidone, especially if the drug is administered in large doses or for prolonged periods. Because of a potential risk of hypertensive crisis, MAO inhibitors should be used with caution, if at all, in patients receiving indirectly acting

sympathomimetic amines (e.g., amphetamines, cyclopentamin, dopamine, ephedrine, metaraminol, methylphenidate, phenylephrine, psuedoephedrine) or tyramine-containing foods (e.g. broad beans, yeast extracts, strong unpasteurised cheeses, beer, wine, pickled herring, chicken livers, and fermented products). MAO inhibitors should also be used cautiously, if at all, in patients receiving other MAO inhibitors, sedatives, antihistamines, tranquilizers, opiates, or chocolate.

Oral furazolidone is contraindicated in patients who have exhibited hypersensitivity to the drug.

Pediatric Precautions

Furazolidone should not be administered to infants younger than 1 month of age (who have immature enzyme systems and glutathione instability) because of the possibility of producing hemolytic anemia.

Carcinogenicity

Animal studies have demonstrated that oral furazolidone is tumorigenic when administered chronically.

Pregnancy, Fertility, and Lactation

Safe use of oral furazolidone in women who are or may become pregnant has not been established, but there have been no reports of adverse effects of the drug on the fetus or neonate. Use of furazolidone during pregnancy should be restricted to those cases where the possible benefits outweigh the potential risks.

Large oral doses of furazolidone appear to depress spermatogenesis by action on the seminiferous tubules, but usual doses reportedly do not have this effect.

Because of the concentration of furazolidone in milk has not been determined, safe use of oral furazolidone in nursing women has not been established.

Drug interactions:

Alcohol

Rarely, patients receiving oral furazolidone have exhibited a disulfiram-like reaction to alcohol characterized by flushing, slight temperature elevation, hypotension, dyspnea, and, in some cases, a sense of constriction in the chest. All symptoms reportedly disappear within 24 hours after ingestion of alcohol. If indicated, norepinephrine may be used to combat hypotensive episodes; indirectly acting pressor agents should be avoided. The mechanism of the interaction between furazolidone and alcohol has been postulated to be either inhibition of aldehyde dehydrogenase or inhibition of monoamine oxidase. It has been recommended that ingestion of alcohol in any form be avoided during oral furazolidone treatment and for 4 days thereafter to prevent this reaction.

Laboratory Test Interferences:

Tests for Urinary Glucose

Furazolidone metabolites present in the urine following oral administration of the drug may interfere with tests performed with cupric sulfate reagent (Benedict's Qualitative Regent, Clinitest®, Fehling's Solution, yielding false-positive results for urine glucose.

REFERENCES

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- ¹ Martindale- The Complete Drug Reference
 - ² Howden A, et al. In vitro sensitivity of *Campylobacter pyloridis* to furazolidone. *Lancet* 1986; **ii**:1035
 - ³ Zheng Z-T, et al. Double -blind short-term trial of furazolidone in peptic ulcer. *Lancet* 1985; **i**:1048-9
 - ⁴ Zhao H-Y, et al. Furazolidone in Peptic Ulcer. *Lancet* 1985; **ii**:276-7
 - ⁵ Segura A.M., et al. Furazolidone, amoxicillin, bismuth triple therapy for *Helicobacter pylori* infection. *Aliment. Pharmacol. Ther.* 1997; 11: 529-32
 - ⁶ Graham D.Y., et al. Choosing the best anti-*Helicobacter pylori* therapy: effect of antimicrobial resistance. *Am. J. Gastroenterol* 1996; 91: 1072-76
 - ⁷ Graham D.Y. & Qureshi W.A. Antibiotic resistant *H.pylori* infection and it's treatment. *Curr Pharm Des* 2000;6 (15):1537-44
 - ⁸ Kwon D.H., Lee M. et al. Furazolidone and nitrofurantoin resistant *H.pylori*:prevalence and role of genes involved in metronidazole resistance. *Antimicrob. Agents Chemother.* 2001;45: 306-8
 - ⁹ Xiao S.D., Liu W.Z. et al. High cure rate of *H.pylori* infection using tripotassium dicitrato bismuthate, furazolidone and clarithromycin triple therapy for one week. *Aliment Pharmacol Ther.* 1999;13: 311-15
 - ¹⁰ Liu W.Z., Xiao S.D., et al. A new quadruple therapy for *H. pylori* using tripotassium dicitrato bismuthate, furazolidone, josamycin and famotidine. *Aliment Pharmacol Ther* 2000;14: 1519-22.
 - ¹¹ Xiao SD, Shi Y, Liu WZ. How we discovered in China in 1972 that antibiotics cure peptic ulcer. In Marshall, BJ (ed.) *Helicobacter Pioneers: Firsthand Accounts from the Scientists Who Discovered Helicobacters, 1893-1983.* Melbourne: Blackwell Science Asia, 2002; 165-202.
 - ¹² Dani R., Queiroz D.M. et al. Omeprazole, clarithromycin and furazolidone for the eradication of *H.pylori* in patients with duodenal ulcer. *Aliment Pharmacol Ther* 1999; 13: 1647-52