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Pharmacokinetic and Pharmacodynamic Effects of Metronidazole May Account for the Superior Efficacy of Multidose Therapy Among Women With Trichomoniasis

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Presently, the Centers for Disease Control and Prevention[1] and the World Health Organization[2,3] recommend 2 g of metronidazole (MTZ) in a single dose for the treatment of trichomoniasis in women. For over three decades, 2-g single dose MTZ has been recommended as the first line treatment. These recommendations come largely from studies conducted in non-pregnant, symptomatic women. A randomized clinical trial among human immunodeficiency virus–infected women,[4] another randomized clinical trial among human immunodeficiency virus–uninfected women published in the *Lancet Infectious Diseases*,[5] and a meta-analysis of published studies[6] consistently found that single-dose MTZ is less effective compared with multidose (500 mg orally twice daily for 7 days) therapy. Even with multidose therapy, early *Trichomonas vaginalis* repeat infection rates are high, and there are indications that these are mostly due to treatment failure rather than reinfection from untreated sexual partners.[7] Interestingly, national *T. vaginalis* susceptibility testing has found a low prevalence (~4%) of MTZ resistance.[8] Thus, other reasons for treatment failure, particularly regarding to the 2-g single dose, should be considered.

Early pharmacokinetic studies of MTZ in healthy female volunteers have demonstrated that a single 2-g dose should maintain trichomonacidal concentrations for up to 48 hours.[9] However, some patients receiving this dose experience treatment failure despite *T. vaginalis* being fully susceptible to MTZ in vitro.[10] This suggests that in vivo pharmacokinetic and pharmacodynamics effects of MTZ may be playing a role in treatment failure. Here, we suggest two potential effects which may account for the superior efficacy of multidose MTZ versus single dose among women with trichomoniasis: competition for MTZ and inadequate accumulation of the metabolites of MTZ.

Although serum MTZ concentrations are quite high after the single 2-g MTZ dose, the delivery of adequate drug concentration at the site of *T. vaginalis* infection may be insufficient. Microorganisms reduce MTZ inside cells and, under anaerobic conditions,

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promote DNA strand breakage and cell death.[10] There are several microorganisms commonly present in the vaginal microbiota (i.e., *Escherichia coli, Enterococcus faecalis, Proteus* spp., and *Klebsiella* spp.) known to absorb MTZ while being unable to reduce it, thus making them non-susceptible to the medication.[10] This process, known as MTZ inactivation, may result in lower drug concentration at the site of infection below that required to be trichomonacidal. Therefore, treatment success may depend upon saturating these "sponge" organisms through either a higher single dose of therapy, which may be intolerable, or through scheduled, successive doses (i.e., multidose therapy).

Second, accumulation of a MTZ metabolite may contribute to treatment success, particularly in the setting of multidose therapy. *Trichomonas vaginalis* susceptibility to MTZ is largely determined in vitro using a method developed by Meingassner and Thurne that tests metronidazole in serial dilutions.[8] After a single 2-g oral dose, MTZ achieves serum concentrations of approximately 40 mg/L within 2 hours with a half-life of approximately 8 hours. In vitro susceptibility results do not reflect the true state of MTZ metabolism. Metronidazole is metabolized by the liver to multiple products, including an active metabolite, hydroxylmetronidazole, with activity against *T. vaginalis* approximately 30% to 65% that of MTZ. This metabolite has a peak serum concentration 7.6 mg/L and a half-life of up to 19 hours, longer than that of MTZ.[11] The longer half-life of this metabolite suggests that significant accumulation may occur with repeat dosing, potentially increasing its therapeutic contribution and leading to treatment success. Hydroxy-metronidazole is not currently evaluated in *T. vaginalis* susceptibility testing.

It is unknown if an extended course of tinidazole is also superior to a single dose for trichomoniasis. Although tinidazole works similarly to MTZ and also has an active metabolite, the half-life of tinidazole (12–14 hours) is nearly double that of MTZ. In a small pharmacokinetics study, 2 g of tinidazole and 2 g of MTZ maintained similar serum concentrations for the first 6 hours when given orally. However, MTZ concentrations decreased more rapidly, and by 72 hours, no MTZ was detectable in any subjects while tinidazole was detectable in 8 of 11 subjects.[9] Clinical outcomes with tinidazole dosing are worthy of additional exploration.

The two traditional dosing methods of MTZ have competing goals of efficacy (multidose regimen) and patient compliance (single 2-g dose). Novel MTZ dosing regimens may need to be explored in future clinical trials to maximize efficacy, compliance, and safety, and such regimens should ideally address the above pharmacokinetic and pharmacodynamic considerations. While a larger single dose, such as 3 or 4 g, of MTZ is appealing, patient tolerability would likely be unacceptable. An example regimen may employ a loading dose, such as 2-g load followed by 500 mg every 8 hours for 6 days. The loading dose would be largely curative and rapidly saturate the site of infection while the additional doses would circumvent MTZ inactivation and take advantage of drug accumulation. A 2-g daily pulse dose for 2 or 3 days would possibly reach the same therapeutic conclusions. Although none of these proposed regimens has been studied and therefore cannot be recommended, novel dosing regimens should be investigated in future studies.

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