Tinidazole Therapy for Metronidazole-Resistant Vaginal Trichomoniasis

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Treatment of patients with metronidazole-refractory vaginal trichomoniasis constitutes a major therapeutic challenge, and treatment options are extremely limited. Although the majority of patients infected with trichomonads, who demonstrate reduced in vitro susceptibility to metronidazole, respond to high-dose but poorly tolerated regimens of metronidazole, clinical failure is by no means uncommon. We report a cure rate of 22 (92%) of 24 patients with refractory trichomoniasis treated with high doses of oral and vaginal tinidazole. This series included 15 cases with increased in vitro minimal lethal concentration values of metronidazole. Tinidazole, despite the high doses used, was extremely well tolerated, with few side effects. Topical paromomycin was effective in 7 (58%) of 12 patients treated, but frequent local vulvovaginal adverse reactions precluded extensive use. Widespread reports of metronidazole resistance and limited treatment options emphasize the need for additional trichomonacidal agents.

An estimated 170 million cases of vaginal trichomoniasis occur annually on a worldwide basis [1], with 3 million cases reported in the United States. The prevalence depends on the patient population selected, with low rates (5%) in family planning clinics to extremely high rates (50%–75%) among female sex workers, in STD clinics, and in nonindustrialized countries [1, 2]. Historically, in contrast to Neisseria gonorrhoeae and Chlamydia trachomatis infections, which have been linked to endometritis, pelvic inflammatory diseases, ectopic pregnancy, and infertility, vaginal trichomoniasis has been relatively trivialized and has received only scant attention. More recently, trichomoniasis has been associated with premature birth [3, 4] and HIV transmission [5, 6]; hence, eradication of this widespread infection has become a greater priority, particularly in underdeveloped countries with high rates of both vaginal trichomoniasis and heterosexual HIV transmission [5–7].

Worldwide, the nitroimidazole drug family has remained the only effective and available group of agents for systemic therapy of vaginal trichomoniasis. The only approved medication available in the United States for the treatment of trichomoniasis is metronidazole, prescribed as a single 2-g oral dose or as a 7-day course of 500 mg b.i.d., with an expected cure rate of 90% [8]. Metronidazole-resistant trichomoniasis is by no means a new phenomenon; it has been observed for almost as long as metronidazole has been used for this indication. Although metronidazole resistance has been considered rare, treatment of these rare patients who do not respond to treatment is extremely problematic for physicians and is associated with enormous patient suffering. We report our experience with 33 adult female patients with metronidazole-resistant vaginal trichomoniasis, 24 of whom were treated with tinidazole, another member of the nitroimidazole group.

PATIENTS AND METHODS

We performed a retrospective review of charts of patients seen at the Vaginitis Clinics in the Detroit Medical Center.
Center and Temple University Medical Center (Philadelphia) from January 1996 through December 2000. Patients who met the case definition of metronidazole-resistant vaginal trichomoniasis were selected for further study. "Metronidazole-resistant trichomoniasis" was defined clinically as failure to respond to conventional therapy with oral metronidazole, 500 mg b.i.d. for 7 days (total dose, 7 g). Patients in whom treatment failed and for whom reinfection from a sexual partner was a possibility were excluded from the case definition. "Failure to respond" was defined as persistence or recurrence (within 28 days) of symptoms and signs of vaginitis together with the following confirmatory laboratory features of vaginal trichomoniasis: high vaginal pH, increased numbers of polymorphonuclear leukocytes, and a visualization of motile trichomonads using microscopy. In vitro Trichomonas cultures of individual specimens were performed using Diamond’s Medium Modified (Remel) or the InPouch TV culture system (Biomed Diagnostics). Trichomonal minimal lethal concentrations (MLCs) of metronidazole were measured aerobically in Diamond’s medium that contained 0.75 g/mL, 1.5 g/mL, 3.1 g/mL, 6.2 g/mL, 12.5 g/mL, 25 g/mL, 50 g/mL, 100 g/mL, and 200 g/mL of metronidazole, and they were examined at 24 h and 48 h for the presence of motile trichomonads [9, 10]. A control strain of Trichomonas vaginalis American Type Culture Collection (ATCC) 30001 (MLC, 0.5 μg/mL) was used in all studies.

In 12 patients, intravaginal administration of 5 g paromomycin (250 mg/g) therapy, as described elsewhere [11], was prescribed once per day for 14 days. Tinidazole was used in 2 different regimens. In Detroit, oral tinidazole was prescribed at a dosage of 500 mg q.i.d. together with intravaginal tinidazole (same oral tablets), 500 mg b.i.d. for 14 days (total dose, 42 g). In Philadelphia, a slightly higher dose consisted of oral tinidazole, 1 g t.i.d., and vaginal tinidazole, 500 mg t.i.d., also for 14 days (total dose, 63 g). Because tinidazole is not currently commercially available, the tablets were made by a private formulation company. All patients were seen immediately after treatment completion and again 4 to 6 weeks later. Patients were considered cured if all symptoms and signs of vaginal trichomoniasis resolved with therapy and the patients had negative results of microscopy at least 4 weeks after completion of therapy. In the majority of patients, a follow-up culture was performed. Patients were also instructed to notify investigators if symptoms returned after the final follow-up visit.

RESULTS

Review of medical records revealed 33 cases (24 in Detroit, 9 in Philadelphia) of metronidazole-resistant trichomoniasis seen during a 5-year period (1996–2000). The mean age of the female patients was 37.2 years (range, 25–58 years). Racial demographic analysis revealed 15 African American, 1 Hispanic, and 15 white women (race was unknown for 2 women). The median duration of vulvovaginal symptoms was 15.9 months (range, 4 months to 15 years) Practitioners referred 76% of the women who had previously had resistant trichomoniasis diagnosed, and 24% of the women were referred because of refractory vaginitis of unknown etiology. Before referral, all patients had received and did not respond to multiple courses of oral metronidazole, including single-dose regimens of 2 g and conventional regimens of 500 mg b.i.d. for 7 days (total dose, 7 g). More than half of the patients had received additional courses of high-divided-dose metronidazole therapy in excess of 20 g, and 6 patients received courses of total-dose metronidazole in excess of 40 g.

Two patients with resistant trichomoniasis were cured with metronidazole only. One patient in Detroit responded to oral metronidazole, 500 mg q.i.d. for 14 days (total dose, 28 g), and 1 patient in Philadelphia was cured with oral metronidazole, 1 g orally t.i.d. for 14 days, together with 500 mg t.i.d. vaginally, also for 14 days (total dose of metronidazole, 63 g).

Twelve patients received 13 courses of paromomycin; 5 patients did not respond to treatment and 7 (58%) were cured. Twenty-four patients (including 5 patients who did not respond to paromomycin) were treated with the divided-dose regimens of oral and vaginal tinidazole. Cures were obtained in 22 patients (92%). Of the 2 patients who did not respond to treatment, 1 was cured with a second course that combined oral tinidazole and vaginal paromomycin for 14 days. She had also previously not responded to treatment with paromomycin alone. Only 1 patient repeatedly did not respond to multiple courses of tinidazole (MLC, 30 μg/mL).

Paromomycin was associated with a high frequency of local side effects in Detroit (4 of 6 women); these included vulvo-vestibular excoriation and ulceration. In 1 patient, local vestibular ulceration was so severe that it was accompanied by urinary retention, and the patient required hospitalization. In Philadelphia, an identical formulation of paromomycin that had been prepared in a different pharmacy was used, and fewer side effects were encountered. High-dose oral tinidazole was extremely well tolerated, and no patient discontinued therapy because of gastrointestinal intolerance.

In vitro susceptibility of isolates of T. vaginalis to metronidazole was determined in 15 patients. Results are shown in figure 1. The median MLC was 32.5 μg/mL, with a range of 6.25–200 μg/mL, as measured under aerobic conditions. The MLC for the control strain of T. vaginalis ATCC 30001 was 0.5 μg/mL.

DISCUSSION

Trichomonal resistance to metronidazole was reported within 2 years of its introduction and has been reported in many areas
Figure 1. Results of in vitro susceptibility of isolates of Trichomonas vaginalis to metronidazole in 15 patients. ● Isolates; ■ control strain (American Type Culture Collection 30001; minimum lethal concentration, 0.5 μg/mL).

of the world. Because there are no ongoing surveillance data of vaginal trichomoniasis and clinical and microbiologic response to treatment, accurate data regarding the incidence of metronidazole resistance are sparse.

Furthermore, there are no consistent definitions of T. vaginalis in vitro or in vivo resistance to metronidazole. In 1991, Lossick and Kent [2] estimated that high-level resistance to metronidazole (MLC, >400 μg/mL) occurs in 1 in 2000–3000 cases of vaginal trichomoniasis [12]. Saurina et al. [13] recently studied the prevalence of in vitro metronidazole resistance among urban clinic attendees in Brooklyn and determined that 3 (2.5%) of 118 isolates recovered from 107 patients exhibited aerobic low-level resistance (50–100 μg/mL); none of the 3 patients was cured by the usual 2-g single dose of metronidazole. Two patients with low-level in vitro resistance were cured by treatment with divided-dose oral metronidazole, 500 mg b.i.d. for 7 days. No isolate had moderate or high resistance to metronidazole. These results indicate that high-level resistance to metronidazole is extremely rare. Low-level in vitro resistance is similarly uncommon, but patients with low-level in vitro resistance may be cured with conventional divided-dose metronidazole therapy given for 7 days (total dose, 7 g).

Several other studies have shown a high predictability for clinical treatment success or failure with oral metronidazole on the basis of low and high MLC extremes [2, 10, 12, 14]. However, these same studies report considerable overlap between MLCs and treatment outcome with intermediate MLCs and even with low-level in vitro resistance [2, 10, 12]. Thus, many consider metronidazole resistance to be a clinical diagnosis made on the basis of a compliant patient’s lack of response to appropriate therapy, after reinfection has been excluded. Moreover, the literature is replete with anecdotal reports and larger patient series in which metronidazole resistance seems relative and may be overcome with increasing doses of the drug [2, 15–19]. Accordingly, current Centers for Disease Control and Prevention (CDC) guidelines for patients who do not respond to metronidazole treatment recommend retreatment with metronidazole at a dosage of 500 mg b.i.d. for 7 days (total dose, 7 g), then 2 g metronidazole per day for 3–5 days, if necessary [8]. In patients who do not respond to this regimen, increasing doses of metronidazole may still successfully effect a cure. In a series of 31 refractory cases of vaginal trichomoniasis previously treated with a variety of metronidazole regimens, Lossick and Kent [2] and Lossick et al. [12] cured most patients with either metronidazole, 2 g per day for 3 to 7 days (total dose, 14 g), or eventually with 1 g t.i.d. combined with intra-vaginal, 500 mg per day for 14 days (total dose, 49 g). The limiting factor in most patients was gastrointestinal tolerance of oral metronidazole, particularly dose-limiting nausea. In rare cases, investigators resorted to high-dose iv metronidazole, although nausea and vomiting may still supersede and treatment may be associated with seizures and encephalopathy [20]. At least 1 well-documented failure with intravenous metronidazole has been reported [16]. High-dose therapy with metronidazole, especially when prolonged, is also associated with other important complications, including pancreatitis, neutropenia, and peripheral neuropathy [13, 16].

Gillette et al. [21] recently reported results similar to those described by Lossick and Kent [2], Muller et al. [10], and Lossick et al. [12], in the largest case series ever performed, which used patient data and isolates from 195 cases of metronidazole-resistant trichomoniasis collected by the CDC during a 14-year period from 38 states and 2 foreign countries. Of the 195 isolates, 17 (8.7%) were susceptible in vitro to metronidazole, 13 (6.7%) were marginally resistant (MLC, 50–100 μg/mL), 46 (23.6%) were moderately resistant (MLC, 100–200 μg/mL),
mL), and 119 (61%) had high-level metronidazole resistance (MLC, >400 μg/mL). Initial treatment consisted of metronidazole 2 g per day for 3–5 days. Patients who did not respond to treatment were retreated and, of the 82 patients with known treatment outcomes, most were cured (79%) with the Lossick regimen of oral metronidazole, 3 g per day, and vaginally over 14 days (total dose, 49 g). Resistance to metronidazole was geographically widely distributed, and no clustering or temporal trends in patients were observed. Because peak serum levels of metronidazole are higher after single-dose therapy than they are after divided-dose therapy, the fact that women with low- and high-level resistance can be cured with prolonged daily dose therapy (i.e., 1–2 g per day) for 14 days suggests that the duration of therapy is critical.

In patients who do not respond to high-dose metronidazole therapy, a variety of regimens have been evaluated for possible effectiveness, with rare or only occasional success. These include zinc sulfate, povidone-iodine douche, arsenicals, nonoxynol-9 cream, mebendazole, albendazole, furazolidone, and rifabutin [22–27]. These agents, although they demonstrate considerable in vitro activity, have been clinically disappointing.

Tinidazole, like metronidazole, is a 5-nitroimidazole with activity against anaerobic bacteria and protozoa [28, 29]. The tinidazole plasma elimination half-life is approximately twice that of metronidazole (12–14 h vs. 6–7 h) [7, 28]. Clinically, tinidazole has been shown at equivalent dosing to have overall efficacy against trichomoniasis that is equal to that of metronidazole. In vitro studies indicate that tinidazole MLC levels are routinely lower than are those of metronidazole [28]. Moreover, analysis of trichomonads recovered from patients refractory to metronidazole shows that some Trichomonas strains are more susceptible to tinidazole than are others. Side effects and complications are of comparable nature to those of metronidazole, but several reports indicate a lower incidence and reduced severity [30]. Anecdotally, several investigators have eradicated clinically refractory vaginal trichomoniais with high-dose tinidazole after failing repeatedly with high doses of metronidazole [2, 21, 31–33]. Although some investigators have shown significantly lower aerobic MLCs for tinidazole as compared with those of metronidazole, major in vitro differences were not always evident, even in patients cured with tinidazole [33]. In the present study, 23 (92%) of the 25 women were successfully treated with a single course of tinidazole, and 1 of the 2 who did not respond to treatment responded to a second course in combination with topical paromomycin (24 [96%] of 25 women). Hence, only 1 patient who did not respond to treatment was encountered, and tinidazole was remarkably well tolerated. Although Lossick and Kent [2] concluded that the majority of clinically resistant cases of trichomoniasis would respond to increasing doses of metronidazole, they nevertheless also demonstrated that, when dealing with highly resistant strains (MLC, >400 μg/mL), patients often do not respond to metronidazole treatment despite having received high oral doses exceeding a total course of 40 g. In their report, 5 of 6 women who responded to tinidazole did not respond to a 40-g course of metronidazole.

Paromomycin was previously reported to be useful in the management of resistant trichomoniasis [11, 34]. It was used fairly effectively (cure rate, 58%) in 12 patients and remains an important option; however, local side effects were considerable and can be quite severe.

This study has several limitations. Our investigation was a retrospective medical record review rather than a prospective, randomized study of tinidazole compared with equivalent doses of metronidazole administered orally and vaginally. In vitro metronidazole MLC levels in this study, although significantly higher than were those measured with the control strain, did not demonstrate the MLC levels of >400 μg/mL previously reported and most likely reflect the technique used and the lack of a control resistant reference strain. We cannot unequivocally state that oral and vaginal administration of metronidazole in a regimen that exceeded a 40-g total dose might not have similarly cured at least some of the patients who did not respond to a 7-g total dose course of oral metronidazole. Nevertheless, many of the patients in our study had received considerably more than 7 g of metronidazole in conventional courses, and none had responded to repeated courses of metronidazole. Given the paucity of such cases (~6 per year in 2 centers), the feasibility of a prospective randomized, double-blind study is small. Similarly, the optimal or minimal dose of tinidazole for cases that are clinically resistant to metronidazole is by no means established. Patients in Detroit received a total dose of 42 g of tinidazole, in contrast to 63 g in Philadelphia. Because cure rates were identical, one may assume that the higher-dose regimen is unnecessary. However, it is conceivable that similarly high cure rates might be obtained with lower doses of tinidazole. Moreover, the contribution of vaginal tinidazole in addition to high-dose oral therapy is unknown. The regimen used was selected empirically and on the basis of desperation in the face of repeated failure with even heroic doses of systemic metronidazole.

Another limitation of this study was that, although a positive culture result was obtained in almost all patients, in vitro susceptibility tests to metronidazole were obtained in only 15 patients, and only 3 patients were tested for susceptibility to tinidazole. Thus, we are unable to show that patients who did not respond to metronidazole and who had high MLC values to metronidazole, who subsequently were cured with tinidazole, actually had lower in vitro MLC values with tinidazole. Thus, this study fails to provide in vitro evidence of selective metronidazole and metronidazole resistance and retained tinidazole susceptibility among the clinically resistant trichomonal isolates.
What is needed is a national monitoring system of patients who meet an acceptable case definition of metronidazole resistance that is based on clinical and laboratory criteria, including in vitro testing of the isolates to both metronidazole and tinidazole. Thereafter, patients would be randomized to receive a blinded regimen of tinidazole in various dosages by means of one or both administration routes.

Because this retrospective study was not intended to be an epidemiologic investigation, we have not uncovered any new information on the pathogenesis of metronidazole-resistant trichomoniasis. Neither are we able to estimate the incidence of drug-resistant trichomoniasis. Our own experience establishes that we are encountering resistance more frequently, but this may be the result of an accrual or referral bias [35]. Current hypotheses that have incriminated (1) generic metronidazole as less bioavailable or (2) widespread, inappropriate use of topical metronidazole remain entirely speculative. Nothing has been said of the role of partner treatment of women with resistant trichomoniasis. Almost all the patients in this study had been celibate for many months before receiving curative therapy. Erratic partner treatment with tinidazole was given in this study.

In summary, vaginal trichomoniasis, when chronic and refractory, is associated with considerable suffering and morbidity and is by no means rare. High-dose systemic and vaginal tinidazole alone was successful in eradicating severe clinically metronidazole-resistant vaginal trichomoniasis in 92% of the patients treated. Despite the high doses used, tinidazole was extremely well tolerated and seemed safe. This study emphasizes the need for a national registry to monitor resistance trends and afford collection of patients for enrollment in prospective, randomized studies of nitroimidazoles and other new trichomonacidal agents.

The CDC offers antimicrobial susceptibility testing and therapeutic guidance for cases that are likely to be resistant to antimicrobial agents. Physicians with patients who have not responded to standard therapy regimens can access this service by calling the Division of Sexually Transmitted Diseases Prevention at the CDC, at telephone number 404-639-8363. This service not only assists clinicians in therapeutic decisions, but acts as an informal surveillance system.

References
26. Livengood CH III, Lossick JG. Resolution of resistant vaginal tricho-


