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Case Report

Experience of successful treatment of patients with metronidazole-resistant *Trichomonas vaginalis* with zinc sulfate: A case series

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ABSTRACT

Objective: There are no universally successful guidelines for the treatment of metronidazole-resistant vaginal trichomoniasis. This is distressing for patients and frustrating for physicians. We therefore decided to evaluate whether zinc sulfate douche is effective in treating vaginal trichomoniasis, because the compound is a natural antimicrobial chemical defense in humans.
Case reports: In our retrospective case review, eight cases of metronidazole-resistant trichomoniasis were treated with 1% zinc sulfate douche with or without tinidazole between 2005 and 2012. Except for one patient who was pregnant, seven patients were successfully treated and were negative for microscopic findings with no clinical symptoms at follow up.
Conclusion: Although the exact role of zinc sulfate in metronidazole-resistant trichomoniasis is not clear, our patients experienced a therapeutic effect with zinc sulfate douche treatment. We therefore recommend zinc sulfate douche as an option for the treatment of metronidazole-resistant vaginal trichomoniasis.

Introduction

Trichomoniasis is caused by the protozoan parasite *Trichomonas vaginalis* [1], which was first discovered in 1836 by the European physician Alfred Donné [2]. The annual incidence of trichomoniasis worldwide is estimated to be approximately 248 million cases, which makes it the most common nonviral sexually transmitted disease [3]. Among women of reproductive age in the United States, the prevalence of *T. vaginalis* infection is 3.1–8.7% [4,5]. Risk factors for *T. vaginalis* infection in adult women include poverty, lower educational level, douching, concurrent chlamydial infection, non-Hispanic black race/ethnicity, a greater number of lifetime sex partners, and older age [4,6,7]. Approximately 50–60% of *T. vaginalis* infections in women are asymptomatic [8]. The most common symptom is malodorous vaginal discharge [9]. Other symptoms include dyspareunia, dysuria, lower abdominal pain, or vulvovaginal irritation [10,11]. Common signs include vulvovaginal erythema, edema, frothy yellowish-gray or green vaginal discharge, elevated pH (>6), and rarely a *strawberry* cervix [12]. Associated complications of vaginitis caused by *T. vaginalis* include pelvic inflammatory disease; cervical dysplasia; and perinatal complications such as preterm birth, premature rupture of membranes, and low-birth-weight infants [11].

Metronidazole was introduced for the treatment of trichomoniasis in 1959 [13]. The cure rate for a single 2-g dose of oral metronidazole is 90–95% [14]. Another recommended regimen for trichomoniasis is a single 2-g dose of tinidazole, which has resulted in cure rates of approximately 86–100% [14]. Low-level metronidazole resistance has been reported in 2–5% of vaginal trichomoniasis cases [15,16]. Metronidazole resistance is clinically defined as a failure to cure infection after two consecutive courses of treatment [17]. Once other causes of treatment failure, including reinfection and medication noncompliance have been ruled out, the possibility of a resistant vaginal trichomoniasis must be considered [18]. Although various therapeutic regimens have been attempted and reported, there is no consensus on therapy for metronidazole-resistant vaginal trichomoniasis [19].

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Table 1
Case histories of seven patients.

	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (y)	39	28	41	45	28	25	20
Duration of infection (mo)	3	3	18	12	24	5	3
Contraception (before treatment)	None	None	None	None	OC	OC	None
Treatment before referral	High-dose oral metronidazole	500-mg oral metronidazole b.i.d. for 7 d, three courses	IV metronidazole, oral ornidazole, metronidazole vaginal pessary	High-dose oral metronidazole	High-dose oral metronidazole and high-dose tinidazole	High-dose oral metronidazole and vaginal gel	High-dose oral metronidazole
Sexual history	No sexual relationship with husband since onset of symptoms	No sexual relationship with husband since onset of symptoms	No sexual relationship with husband since failure of treatment	No sexual relationship since failure of treatment	No sexual relationship with partner since onset of symptoms	No sexual relationship with partner for 5 mo	No sexual relationship with partner since onset of symptoms
Diagnostic methods	Microscopy test	Microscopy test	Microscopy test	Microscopy test	Microscopy test	Microscopy test	Microscopy test
Treatment before zinc sulfate douching	500-mg oral tinidazole b.i.d. for 19 d + gyno Betadine vaginal tab for 19 d	2-g oral metronidazole for 4 d	500-mg oral tinidazole b.i.d. for 21 d + gyno Betadine vaginal tab for 14 d	1000-mg oral tinidazole b.i.d. + gyno Betadine vaginal tab for 28 d	No treatment	2-g oral tinidazole for 7 d	2-g oral tinidazole and amoxicillin + gyno Betadine vaginal tab for 7 d
Duration of 1% zinc sulfate douching (d)	28	14	14	14	27	25	21
Combined therapy	No	No	2-g oral tinidazole	2-g oral tinidazole	2-g oral tinidazole	2-g oral tinidazole	2-g oral tinidazole
Interval of first case review after 1% zinc sulfate douching and findings	1 mo, clinical improvement and negative microscopy	1 wk, clinical improvement and negative microscopy	3 wk, positive microscopy →second course of treatment included 1% zinc sulfate douching with tinidazole	1 wk, clinical improvement and negative microscopy	2 wk, clinical improvement and negative microscopy	2 wk, clinical improvement and negative microscopy	2 wk clinical improvement and negative microscopy
Last follow up	5 y	2 mo	4 mo	3 mo	6 mo	6 mo	3 mo
Recurrence	No	No	Yes	No	No	No	No

b.i.d. = 2 times/d; IV = intravenous; OC = oral contraceptive.

Herein we report our experience with zinc sulfate douche, which has a therapeutic effect on metronidazole-resistant vaginal trichomoniasis.

Case Reports

Case 1

A 29-year-old woman, gravida 0, para 0, was referred for treatment of 1-year persistent *T. vaginalis* infection, which caused persistent malodorous vaginal discharge with irritation and dysuria. She denied any sexual contact since these symptoms began. Before referral, she previously received several courses of metronidazole and tinidazole, both at standard and high dosages by intravenous and oral routes. On the day of her initial visit to our hospital, a yellowish-green vaginal discharge was present and trichomonads were visualized under saline wet mount examination. She did not have co-infections such as *Mycoplasma*, *Ureaplasma*, and *Chlamydia*. She was treated with 1% zinc sulfate douching 2 times/d for 14 days with concomitant oral tinidazole 500 mg 2 times/d for 12 days. She then used only the zinc sulfate douche without the tinidazole for 7 days. Apart from mild irritation, she tolerated the treatment well. Follow up was performed monthly for 3 months after treatment, and then once every 3 months, with wet mount and physical examination. There was no evidence of infection. The patient remained asymptomatic for the following 3 months, at the end of which her case was reviewed. Subsequently, she returned to her hometown.

Cases 2–8

Table 1 presents the data on seven patients who had a history of 3 months to 2 years of symptomatic vaginal trichomoniasis and received a variety of therapies before referral. Six of them received high-dose oral metronidazole or tinidazole therapy for 4–28 days after referral. They did not respond to this therapy.

Subsequently, two of them were treated with single 1% zinc sulfate douches, and the others were treated with a combination of 1% zinc sulfate douching and oral tinidazole for 14–28 days. All of our patients experienced clinical improvement, lasting for days or weeks, with a negative vaginal wet smear. The interval of follow up was weekly for 1–2 months and then monthly for 3–6 months. At the case review from 2 months to 5 years after therapy, six of the seven patients remained asymptomatic and the results of clinical and laboratory examinations were normal. Only one patient presented with a recurrence, which occurred 4 months after treatment. She was not eligible to receive additional 1% zinc douche treatment because of pregnancy.

Discussion

Metronidazole-resistant vaginal trichomoniasis is considered rare but remains a major therapeutic challenge to physicians. It is associated with significant patient suffering and reduction of the quality of life. The mechanisms that lead to such a refractory response are unclear. Inactivation of metronidazole by vaginal bacteria, ineffective delivery of the drug to the vaginal area, lack of absorption of the medication [20], and low zinc concentrations in serum [21] have been proposed as possible explanations for treatment failure.

T. vaginalis seems to respond to sudden environmental changes (e.g., temperature, microflora, pH, iron, polyamines, zinc, host immune responses, and other unknown factors) [22]. Trichomoniasis mostly affects women; in the case of men, most are cured rapidly of the infection, suggesting that these sex variations may be related to differences in the urogenital microenvironments affecting the pathobiology of trichomonads. The zinc-rich environment in the prostatic glands creates hostile conditions for *T. vaginalis* to survive. Zinc is a known antimicrobial chemical defense in humans; men with zinc concentrations >1.6mM in their prostatic secretions can suffer chronic prostatitis due to *T. vaginalis* infection [23]. The normal concentration of zinc (4.5–7mM) in the prostatic fluid of the majority of men has a trichomonacidal effect that helps to limit or resolve this infection [23]. However, zinc concentrations similar to those found in men with chronic prostatitis (<1.6mM) are not trichomonacidal, and allow the parasite to survive in the prostatic gland, causing a nonspecific acute inflammation [23]. Vazquez Carrillo et al [24] reported that Zn^{+} alters trichomonal virulence by affecting its morphology, proteome, and expression of several of its virulence factors when the DU145 prostatic cell line is used as a host cell.

In the presented report, a retrospective case review identified eight cases of metronidazole-resistant trichomonas between 2005 and 2012. In the absence of resistance testing, resistance was defined clinically. Patients received 1% zinc douche with or without oral tinidazole for 14–28 days. All of our patients experienced clinical improvement, lasting for days or weeks, with a negative vaginal wet smear. At their last review, seven patients remained symptom free with normal clinical examination results and negative wet mount, and only one patient presented with a recurrent infection. We did not re-administer zinc sulfate douche to the patient with the recurring infection because she was pregnant at the time. In rare cases, zinc sulfate douche was described to cause mild cervical ulcer; thus, we avoided its use during pregnancy. Although the exact role of zinc sulfate douche is uncertain, the therapeutic effect of zinc was clearly achieved in our patients.

This study has several limitations. Our investigation was a retrospective medical record review rather than a prospective evaluation. In addition, *in vitro* susceptibility tests to metronidazole or tinidazole in patients were not carried out. However, we believe that zinc sulfate therapy merits further independent evaluation.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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