Difficult-to-Treat Trichomoniasis: Results with Paromomycin Cream

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Vaginal trichomoniasis poses a difficult therapeutic challenge when metronidazole is ineffective or contraindicated. We conducted a retrospective study of 6.25% paromomycin cream in the treatment of nine women referred with cases of vaginal trichomoniasis where metronidazole resistance or allergy was present. Results obtained immediately and 1 month after treatment were reviewed. The median age of the patients was 46 years; four women were nulliparous. The median symptom duration was 1 year. Five women were allergic to metronidazole. In four cases, resistance to high doses of metronidazole was demonstrated. Smears or cultures were positive immediately after treatment for three patients; a fourth relapsed 2 weeks later. Of these patients for whom treatment failed, one was cured with a 3-week course of paromomycin cream, and another was successfully treated with paromomycin cream and oral tinidazole. Three patients developed vaginal ulcerations that resolved spontaneously. Adverse effects may be a result of local formulation. Paromomycin cream was useful for treatment of cases of trichomonas infection where metronidazole resistance or allergy was encountered.

Vaginal infections caused by *Trichomonas vaginalis* are among the most common sexually transmitted diseases in the United States; it is estimated that 3 million infections occur annually [1]. Metronidazole, given as either a single dose or a 7-day regimen, is the only approved treatment in the United States. Cure rates of ~95% can be expected [2]. For patients who do not respond to treatment and in whom reinfection has been excluded, increasing doses of metronidazole are recommended. For patients who are allergic to metronidazole, the guidelines of the Centers for Disease Control and Prevention do not offer any alternative therapy, although desensitization to metronidazole has been used successfully for two patients [3].

Paromomycin, an aminocyclitol antibiotic derived from *Streptomyces fradiae*, has a spectrum of activity that includes many protozoa. In 1995, we reported the case of a woman with infection due to metronidazole-resistant *Trichomonas* who was cured with a 2-week course of 6.25% paromomycin cream [4]. We describe herein our experience with paromomycin cream in a larger series of patients referred with cases of trichomonas infections where metronidazole was either ineffective or contraindicated.

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Methods

The Vaginitis Centers at Temple University (Philadelphia) and Wayne State University (Detroit) were established to evaluate and treat women referred because of chronic vaginal symptoms; in the aggregate, the centers evaluate ~700 new patients per year. A retrospective chart review of patients receiving paromomycin cream from August 1995 to November 1997 was performed. Patients with trichomonias infections proven at our centers by either a saline preparation positive for motile trichomonads or a culture positive for *Trichomonas* were offered paromomycin cream if there was documented clinical resistance to metronidazole or a history of serious manifestations allergy to metronidazole. Demographic data were obtained. Patients had been followed up with visits immediately and 4–6 weeks after the 2-week course of paromomycin cream. Patients either avoided sexual intercourse or used latex condoms during sexual intercourse during the follow-up period to exclude the possibility of reinfection. Cultures for *T. vaginalis* were performed if clinically indicated (i.e., persistent symptoms or findings of saline microscopy such as increased polymorphonuclear leukocytes suggestive of infection but where the organism could not be visualized).

Paromomycin is an amorphous, white to light yellow powder that is very soluble in water, moderately soluble in alcohol, and sparingly soluble in absolute ethanol. Our vaginal preparation utilized commercially available capsules of paromomycin sulfate. The capsules were opened, and the powder contents were levigated into a hydrophilic cream base; the dose was 250 mg of paromomycin per 4-g applicator. Patients were instructed to use one applicator nightly for 2 weeks.
Results

During the study period, a total of nine patients received a 2-week course of paromomycin cream. The median age of the patients was 46 years (range, 29–50 years); four women (44%) were nulliparous. The median duration of symptoms was 1 year (range, 0.3–14 years), and all the patients noted that they had been given a diagnosis of vaginal trichomoniasis at the onset of their symptoms. Five women received paromomycin because of a history of allergic reactions to metronidazole, consisting of urticarial skin reactions in 3, generalized edema in 1, and anaphylactic shock in 1. In the other four cases, resistance to high doses of metronidazole had been demonstrated. The highest doses of metronidazole that were used were a 2-week course of 1 g of oral metronidazole given twice daily in two cases and a 2-week course of 1 g of oral metronidazole together with 500 mg of intravaginal metronidazole given three times daily in two cases.

Immediately after completion of paromomycin treatment, saline smears from all patients except for one were negative for Trichomonas. However, cultures for two patients were positive and a fourth patient’s infection relapsed 2 weeks after treatment. Of these four patients for whom treatment failed, two were retreated with a 3-week course of paromomycin cream; one of these patients was cured. Overall, six of nine women were cured with paromomycin cream alone; all of the cured patients had complete resolution of their vaginal symptoms.

One patient for whom treatment failed subsequently did not respond to a combination of 500 mg of oral tinidazole four times daily and 500 mg of intravaginal tinidazole twice a day; she was given a combination of paromomycin cream for 5 days and 500 mg of oral tinidazole four times daily for 14 days. Treatment failed for two other patients who were allergic to metronidazole. One of them was successfully desensitized to and treated with metronidazole. The second one had a fixed drug reaction to metronidazole and could not be desensitized; she remained infected at the time of this writing.

Three patients developed mild irritation following administration of paromomycin cream. Three patients had vaginal ulcerations during the treatment that later resolved spontaneously. All three were treated at the same clinic, and we believe that this adverse effect may have been a result of the formulation at that site. However, there were no obvious differences in formulation between the two pharmacies.

Discussion

Although trichomoniasis is a relatively common sexually transmitted infection, it is fortunate that T. vaginalis remains for the most part highly susceptible to metronidazole; cure rates associated with standard oral regimens exceed 95% [2]. Even in clinical settings that specialize in seeing women with chronic vaginitis, most cases that are refractory to treatment with metronidazole eventually respond to higher doses of metronidazole [5]. Trichomoniasis in the presence of a metronidazole allergy also seems to be rare, with no cases described in a series of 45 patients seen at a chronic vaginitis center [5]. Clinical experience with desensitization to metronidazole in the setting of trichomoniasis is limited to two patients [3]. Our experience with one patient suggests that certain allergic reactions to metronidazole are not amenable to desensitization.

Although true cases of trichonomiasis where there is metronidazole resistance or a metronidazole allergy are rare, the options for their treatment are very limited, and these patients pose a difficult challenge. In vitro studies have shown that mebendazole, furazolidone, and rifabutin are the drugs most active against metronidazole-resistant trichomonads [6]. Clinical experience with these medications is either lacking or, in the case of mebendazole, disappointing [7]. Alternative treatments that have been used with variable success include systemic tinidazole [8], povidone-iodine douches [9], and nonoxynol 9 [10]. For women for whom these treatments fail, including prolonged courses of high doses of metronidazole, their chronic infections can cause profound morbidity, ranging from local symptoms and discomfort to extensive psychosocial ramifications of having a chronic incurable sexually transmitted disease.

Paromomycin was studied in the early 1960s as a possible treatment for trichomoniasis. Because it is not absorbed from the gastrointestinal tract, it has been studied only in topical formulations. An initial study by Dumont and colleagues [11] suggested that it might be effective. Subsequently, Spitzbart [12] studied 57 women who received 30-mg vaginal suppositories three times a day and found a 63% failure rate; he recommended abandoning this treatment in favor of metronidazole. In our study, patients received 250 mg of paromomycin per applicator; the higher dose may explain our efficacy rate.

After our initial success with 6.25% paromomycin cream [4], we decided to offer it as treatment to patients for whom metronidazole was not an acceptable therapy because of resistance or allergy. In this report, the largest published series of refractory trichomonal infections, our results indicate that paromomycin is an effective alternative treatment for vaginal trichomoniasis in patients unresponsive or allergic to nitroimidazole agents. Our ninth patient, for whom treatment initially failed, serves to emphasize how difficult these cases with metronidazole resistance or allergy can be. After her initial treatment with paromomycin, she received a high dose of another alternative agent, tinidazole, but she did not respond. With no other known treatments and somewhat out of desperation, she was given a combination of oral tinidazole and paromomycin cream, which resulted in a clinical and microbiological cure.

Of some concern, however, are local adverse events. Although these effects were self-limited and observed only at one clinic, further experience with this medication is necessary to obtain more accurate information with regard to efficacy and
safety. Because of the limited number of cases where this therapy might be indicated, even at specialized centers such as ours, such experience could perhaps best be obtained through the development of a centralized registry of refractory trichomonal infections.

References