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Case report

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Successful treatment of trichomoniasis with tinidazole following desensitization in a patient allergic to metronidazole

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Abstract

Metronidazole desensitization is recommended in patients with trichomoniasis and history of an allergic reaction to metronidazole due to presumed cross reactivity with tinidazole and lack of reliably safe and effective alternative therapies. We report our experiences in a patient with persistent trichomoniasis who failed to complete metronidazole desensitization due to a burning sensation over her whole body and pruritus but was later successfully desensitized to tinidazole without experiencing any adverse effects.

Keywords

Desensitization, metronidazole, tinidazole, *Trichomonas vaginalis*, trichomoniasis

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Introduction

Trichomonas vaginalis, the causative agent of trichomoniasis, is responsible for approximately 3.7 million infections annually in the United States and has limited treatment options.[1,2] Among the various antimicrobial classes, only the 5-nitroimidazoles, metronidazole and tinidazole, are recommended for the treatment of trichomoniasis.[1] Alternative therapies to these agents are plagued by unacceptably high failure rates and/or adverse effects. Due to the presumed cross-reactivity of metronidazole and tinidazole and the lack of alternative treatment options, it is recommended that patients with trichomoniasis who are allergic to either of these agents undergo desensitization to metronidazole.[1] Here, we present a case of a patient with persistent trichomoniasis who was unable to successfully complete intravenous metronidazole desensitization, despite multiple attempts, who subsequently completed oral tinidazole desensitization successfully.

Case summary

A 43-year old female seen by her gynecologist for complaints of vaginal discharge and odour was diagnosed with trichomoniasis following confirmation by nucleic acid amplification testing (NAAT) (NuSwab Vaginitis Plus®, LabCorp). She was prescribed metronidazole 500 mg orally twice daily for 7 days, but shortly after taking her first dose she developed hives, pruritus, shortness of breath, and vomiting. She was subsequently admitted to our hospital to undergo metronidazole desensitization (Table 1) with a plan to be prescribed metronidazole 500 mg orally twice daily for 7 days if successfully desensitized. Following administration of the third intravenous metronidazole dose (0.5 mg), the patient reported warmth in her calves, increased salivation, and pruritus for which she received single intravenous doses of diphenhydramine 50 mg and methylprednisolone 125 mg. Approximately 90 minutes after the last metronidazole dose, the desensitization

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Table 1. Metronidazole and tinidazole desensitization protocols.

	Metronidazole[a,b]			Tinidazole[c]	
Step	Dose (mg)	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Volume (mL)
1	0.005	0.005	1	3.3	0.1
2	0.015	0.005	3	6.7	0.2
3	0.05	0.05	1	10	0.3
4	0.15	0.05	3	33	1
5	0.5	0.5	1	67	2
6	1.5	0.5	3	100	3
7	5	5	1	250	1/2 tablet
8	15	5	3	500	1 tablet
9	30	5	6	1000	2 tablets
10	60	5	12	—	—
11	125	5	25	—	—
12	250	500 mg	1/2 tablet	—	—

Note: Metronidazole doses were administered every 15 minutes and tinidazole doses were administered every 30 minutes. Underlined values represent metronidazole doses associated with reactions leading to discontinuation of the desensitization protocol.

[a]The first metronidazole desensitization attempt was initiated at Step 3.

[b]Metronidazole doses for Steps 1–11 were prepared from an intravenous solution with an initial concentration of 5 mg/mL and was serially diluted 10-fold in sodium chloride as necessary.

[c]Tinidazole doses for Steps 1–6 were prepared from an oral suspension (33.3 mg/mL) created by crushing a single 500 mg tinidazole tablet and mixing with 15 mL of cherry syrup.

protocol was restarted at a lower starting dose and at a reduced infusion rate. However, after the ninth intravenous metronidazole dose (30 mg), the patient developed whole body pruritus accompanied by a burning sensation under her skin. Desensitization was subsequently discontinued and the patient was discharged the following day with instructions to use intravaginal boric acid 600 mg suppositories nightly for 14 days. Her partner was treated with metronidazole 2 g orally for one dose.

Following boric acid therapy, the patient noted an improvement in odour but persistent vaginal discharge. She then self-initiated a second course of boric acid suppositories without provider consent but stopped on her own due to development of vaginal bleeding. Due to symptom recurrence, she was prescribed nitazoxanide 1 g orally twice daily for 7 days but was unable to obtain the medication due to the cost. Approximately 6 weeks later, her symptoms persisted and a repeat NAAT was positive for *T. vaginalis*. Reinfection was considered unlikely since her partner had received appropriate therapy with metronidazole and according to the patient, they only had sexual contact on one occasion since then and reported using a condom. Following careful discussion, she was agreeable to attempt oral tinidazole desensitization (Table 1) despite her previous reaction to metronidazole. The patient successfully completed the tinidazole desensitization protocol without experiencing any adverse effects, although she did preemptively receive a single dose of intravenous diphenhydramine prior to the final tinidazole dose. Repeat NAAT testing was not performed but the patient reported resolution of her symptoms and has remained asymptomatic for six months following tinidazole therapy.

Discussion

Cross-reactivity between metronidazole and tinidazole may be expected given their structural similarities as 5-nitroimidazoles. This expected cross-reactivity is particularly problematic in patients with trichomoniasis due to the unavailability of reliably safe and effective alternative therapies. In our case, the failure to complete metronidazole desensitization followed by treatment failure with boric acid suppositories and then the inability to obtain nitazoxanide ultimately led to the decision to attempt tinidazole desensitization. To the best of our knowledge, this is the first published case of tinidazole desensitization in any setting.

Previous data on the cross-reactivity between metronidazole and other members of the 5-nitroimidazole class have yielded conflicting results. Cross-reactivity between metronidazole and tinidazole has been previously demonstrated by oral provocation tests in at least three cases,[3–5] although in one of these cases no cross-reactivity was noted with secnidazole.[5] Singbal et al. previously described the case of a patient who developed anaphylaxis and Stevens-Johnson syndrome following repeated exposure to tinidazole but

interestingly noted that the patient had previously received metronidazole on multiple occasions without experiencing any adverse effects.[6] Additionally, Sehgal et al. reported their experiences in a patient who developed a bullous fixed drug eruption following exposure to metronidazole, which was confirmed by oral provocation testing.[7] Cross-reactivity with tinidazole was also assessed by oral provocation testing but results were inconclusive.

Despite our positive experiences reported here, a few limitations should be noted. First, the reaction to metronidazole experienced by our patient was considered non-life threatening, which should be taken into consideration by clinicians when deciding whether to pursue tinidazole desensitization. Second, the pre-emptive administration of diphenhydramine prior to the final dose of tinidazole may have potentially masked symptoms of a hypersensitivity reaction. However, as our intention was to treat the patient with what was the approximate equivalent of a single 2 g dose of tinidazole, it was felt that avoiding any unnecessary risk of a hypersensitivity reaction was warranted. Finally, while we cannot definitively rule out that the reaction to metronidazole experienced by our patient was caused by an excipient, the similar reaction produced by both the oral and intravenous formulations of metronidazole suggests the lack of cross-reactivity between metronidazole and tinidazole observed in our case is unlikely attributed to differences in the excipients.

The lack of alternative agents for trichomoniasis outside the 5-nitroimidazole class is a significant issue for patients unable to tolerate metronidazole. Based on our experiences, oral desensitization with tinidazole in a closely monitored environment may be a potential option in this scenario. Further studies are needed to better describe the potential of cross-reactivity between metronidazole and tinidazole.

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