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Tinidazole versus Metronidazole for the Treatment of Bacterial Vaginosis

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Abstract

Objective—To compare the efficacy of two different doses of tinidazole with metronidazole for treatment of bacterial vaginosis and compare side effects of the drugs.

Study design—Women were randomized to metronidazole 500 mg BID, tinidazole 500 mg BID, or tinidazole 1 gm BID all for 7 days. Follow-up visits were conducted at day 14 and day 28.

Results—593 women were enrolled. There were no significant differences between the treatment arms. Overall cure rates were 76.8% at 14 days and 64.5% at one month. Women who admitted to engaging in sexual intercourse during the study were significantly more likely to have BV at follow-up. There were no significant differences in adverse events across treatment arms.

Conclusions—There were no differences in cure rates between metronidazole and either of the tinidazole dosing regimens studied. In addition, there were no important differences in the side effect profiles of metronidazole and tinidazole.

Keywords

bacterial vaginosis; metronidazole; tinidazole

Introduction

Bacterial vaginosis (BV) is the most prevalent cause of symptomatic vaginal discharge in the U.S.¹ and has been associated with complications including preterm delivery of infants, pelvic inflammatory disease (PID), urinary tract infections (UTI) and acquisition/transmission of sexually transmitted diseases (STDs) including human immunodeficiency virus (HIV)^{2–4}. Control of BV has been advocated as a means of decreasing the prevalence of these complications. However, available treatment regimens have been disappointing in terms of initial cure and recurrence rates⁵. Tinidazole was recently licensed in the U.S. for the treatment of trichomoniasis and BV. The indication for BV was based on a tinidazole versus placebo trial⁶. There are no data on the efficacy of multi-dose tinidazole versus metronidazole for treatment of this infection. Tinidazole has the potential of being a more efficacious drug for BV based on its longer half-life and its seemingly superior side effect

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profile as compared to oral metronidazole. We compared the efficacy of two different doses of tinidazole with oral metronidazole for the initial treatment of symptomatic BV as well as short-term recurrence rates. In addition side effect profiles of the two drugs were compared.

Material and Methods

Heterosexual women attending the Jefferson County Department of Health (JCDH) STD Clinic with symptomatic BV as defined by the Amsel criteria⁷ and no evidence of STD were invited to participate in this randomized, double-blinded study. To be eligible the subject had to report symptoms of vaginal discharge and/or vaginal odor and have a vaginal pH >4.5, positive “whiff” test, and clue cells on microscopy. Women with known HIV infection were excluded from the study.

The study was approved by the Institutional Review Board at the University of Alabama at Birmingham. Subjects were administered standardized questionnaires about symptoms and a comprehensive sexual history. A pelvic examination was performed and specimens collected for vaginal pH, microscopy, Gram stain, gonorrhea and chlamydia testing, and trichomonas culture.

Women were randomized to oral metronidazole 500 mg twice a day for 7 days, tinidazole 500 mg twice a day for 7 days, or tinidazole 1 gm twice a day for 7 days. The study was initiated prior to the FDA approval of tinidazole for BV thus dosing was based on review of the literature.

Follow-up visits were conducted at days 14 and 28 of the study, and then monthly for an additional 2 visits. At each of the follow-up visits, a standardized questionnaire was administered, a pelvic examination was conducted and specimens for the diagnosis of BV were collected. Women with symptomatic BV at the follow-up visits were treated with the current standard therapy of seven days of metronidazole and discontinued from the study at that time. Any woman found to have a positive screening test for gonorrhea and/or chlamydia was treated appropriately and discontinued from the study with the exception of women with positive culture tests for *Trichomonas vaginalis* as this infection would be adequately treated with either metronidazole or tinidazole. Women with intercurrent vaginal yeast infections were treated and continued in the study.

Microbiological cure was defined as a Nugent score of less than 7. Clinical improvement was defined as normalization of two of three criteria (pH, whiff test, and clue cells) and cure was defined as normalization of all three. The persistence of two or more abnormalities constituted clinical failure.

Microbiological Methods

Vaginal pH, amine odor (“whiff” test), and microscopy were performed as previously described⁸. Vaginal smears were gram stained and interpreted according to the method of Nugent et al⁹. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were Gen-Probe Aptima Combo 2 according to manufacturer's instructions. Trichomonas cultures were performed using the In Pouch TV test (BioMed Diagnostics Inc., White City, OR)¹⁰.

Statistical Considerations

Sample size and power—Sample size estimates were computed for the efficacy analysis based on the cure rates defined as 70% for the metronidazole group, 85 % for the tinidazole 500mg bid group and 90% for the tinidazole 1gm group. Assuming a 20% loss to follow-up overall, a sample size of 192 per group or a total N of 576 was randomized to the three treatment arms with an alpha level of 0.025. No formal comparison was planned for the two

tinidazole arms. Based on 160 randomized subjects per group we would be able to detect a difference of 15% in side effects between the treatment arms. This would be an event proportion of approximately 15% in the two tinidazole arms with an alpha of 0.025.

Statistical analyses—The proportion cured of BV at the 14 day follow-up visit (7 days after completion of therapy) was compared between the metronidazole and 500mg tinidazole group using the chi-square test of proportions and exact confidence intervals were computed. The proportion cured was compared between the metronidazole and 1g-tinidazole groups in a similar fashion. Descriptive statistics of the population such as age, sexual history, STD history, etc. were compared between the treatment arms by the t test for compare continuous variables and the Fisher's exact test or the chi-square test will be used for nominal variables.

The short-term recurrence rates at 1 month, 2 months, and 3 months among subjects that were successfully cured following the initial treatment (at the 14 day visit) were compared across treatment groups by the chi-square test. Confounding variables tested in a repeated measures model to predict BV included number of partners (>1 vs. 1, new partner (yes vs. no), consistent condom usage (yes vs. no), current douching (yes vs. no) and baseline BV score (≥ 7 vs. 4–7). For all analyses a p value of <0.05 was considered statistically significant.

Adverse events were categorized as gastrointestinal, vaginal/GYN, neurologic, and other. The proportion of women experiencing an event was compared across the three treatment groups by the Fisher's exact test for each type of event and for overall events. In addition the total numbers of events (more than one event possible per person) was compared across the three treatment groups in a similar fashion.

The study statistician was responsible for preparing computer-generated randomization lists for the clinical trial, and a blocked randomization scheme was employed in generating the list. The randomization scheme was provided only to the study pharmacist who was responsible for preparing the study medication in a blinded fashion. The actual randomization assignments were kept in a secured fashion by the Biostatistics Unit.

Results

Five hundred ninety-three patients were enrolled into the study between November, 2004 and October, 2009. The allocation of subjects for the trial up to and including the one month follow-up is shown in Figure 1. The most common reason for termination was loss to follow-up (158/593, 26.7%) followed by pre-existing protocol violation (57/593, 9.6%) of which 52/57 (91.2%) were presence of STD at baseline. The demographic and behavioral characteristics of subjects by randomized treatment group are shown in Table 1. There were no significant differences with respect to race, age, or behaviors such as douching and sexual behavior. Of note, nearly 97% of subjects reported a prior history of STD. 83% reported a prior history of BV.

Cure rates defined by Nugent score are shown in Table 2. Results are limited to the 14 day and one month visit as there was no change in trends at the two and three month visits and number of remaining subjects had diminished. There were no significant differences between the three treatment arms at any of the follow-up visits. Percent treatment failure rates and 95% confidence intervals for metronidazole, tinidazole 1 gm, and tinidazole 500 mg for the 14 day visit were 17.7 (11.2, 24.1), 27.0 (19.6, 34.4) and 24.7 (17.9, 32.5) respectively. Overall the cure rate was 76.8% at the 14 day follow-up visit and 64.5% at the one month follow-up visit. Using a stricter Nugent criteria of cure defined as a score of <4 ,

there were no significant differences in cure rates between the treatment arms with the overall cure rate at the 14 day visit being 53.7%. Neither baseline Nugent score, consistent use of condoms, sex with a new partner, or multiple partners was significantly associated with cure. There was no statistical difference in clinical cure or improvement as measured by individual Amsel criteria among the three treatment arms. Cure or improvement was seen in 80.3%, 82.5%, and 73.1% of the subjects in the metronidazole, tinidazole 1 gm, and tinidazole 500 mg arms respectively at the 14 day visit. For the 1 month follow-up visit the cure or improvement rates were 55.2%, 62.3% and 58.0% respectively.

Short term recurrence rates after initial cure are shown in Table 3. There were no significant differences in short term recurrence rates between the three treatment arms. Percent recurrence rates and 95% confidence intervals for metronidazole, tinidazole 1 gm, and tinidazole 500 mg for the 1 month visit were 33.3 (24.3, 43.4), 22.5 (14.3, 32.6), and 30.2 (21.3, 40.4) respectively. Overall recurrence rates were 28.9% and 31.2% at 1 and 2 months respectively. Women who admitted to engaging in sexual intercourse during the study were significantly more likely to have BV at follow-up (RR=1.76, (95% CI 1.25, 2.49)).

Adverse events associated with each treatment arm are displayed in Table 4. There were no significant differences in adverse events across treatment arms with the exception of an increased percentage of subjects reporting bad taste in the tinidazole 1 gm arm. The overall incidence of yeast infections was 15.3%.

Discussion

Bacterial vaginosis is the most common cause of vaginitis and is associated with several important reproductive health problems including preterm birth and acquisition/transmission of HIV/STD^{1, 2, 4, 7, 11}. There is a lack of consensus on the etiologic agents or agents associated with BV; thus treatment has been based on empiricism¹², generally with metronidazole or clindamycin which were chosen for their activity against many anaerobic organisms. Unfortunately, cure rates with these antibiotics range from 50–80% and recurrence rates are high⁵. Tinidazole, a 5-nitroimidazole similar to metronidazole but with a longer half-life and more favorable side effect profile has been used for decades in Europe. Recently it was licensed in the U.S. first for treatment of trichomoniasis and giardia and later for treatment of BV. Due to its pharmacokinetics there was optimism that tinidazole would result in superior cure rates compared with metronidazole for the treatment of BV.

There have been 16 published studies encompassing over 1600 patients on the use of tinidazole for BV. The majority of the studies utilized a single 2g dose of tinidazole for BV treatment, all showing clinical efficacy. In both the reports comparing a single 2g dose of tinidazole to a single 2g dose of metronidazole, tinidazole produced higher efficacy rates. A report by Ekgren¹³ which compared a single 2g dose of tinidazole to a 2g × 2 day dose of tinidazole demonstrated higher efficacy with the 2 day dosing regimen. In that randomized, double-blind study report the 2 day dose produced an efficacy rate of 74% vs. 51% efficacy for the single 2g dose with only a small increase in the reported side effects (44% vs. 39%).

In two studies where a single 2g dose of tinidazole was compared to oral metronidazole at 500mg BID × 7 days, oral metronidazole produced slightly higher efficacy rates^{14, 15}. In the Buranawarodmkul study, efficacy rates were 86% and 92% for tinidazole vs. metronidazole, respectively. The Sanz-Sanz study produced efficacy rates of 65% and 74% for tinidazole vs. metronidazole, respectively. Although a single 2g dose of tinidazole appears more effective than a single 2g dose of metronidazole, it may be slightly less effective than seven days of metronidazole.

A more recent double-blind, double-dummy, randomized, comparative trial of a single 2g dose of tinidazole vs. a single 2g dose metronidazole vs. a single 2g dose tinidazole with a vaginal acidifier showed superior efficacy with the single 2g dose tinidazole (without the acidifier) (88%) vs. metronidazole (73%) at 4 weeks post-therapy ($p=0.06$). The cure rate in the 2g tinidazole plus acidifier arm was 87%, indicating no benefit over 2g tinidazole alone¹⁶. Additionally, tinidazole showed a statistically superior lower relapse rate at 12 weeks (tinidazole (3%), metronidazole (30%), $p=0.04$).

The study conducted for FDA approval for the treatment of BV was conducted as a placebo controlled trial and used very strict FDA recommended criteria to determine cure⁶. In this study, at 21–30 days after treatment, tinidazole 1 gm daily for five days and 2 gms once daily for 2 days resulted in significantly improved cure rates compared to placebo (36.8% and 27.4% respectively). Due to the fact that FDA criteria for cure have changed over the years it is difficult to compare cure rates of tinidazole to other licensed products for the treatment of BV. In actuality, oral generic metronidazole was never evaluated by the FDA for the treatment of BV.

Although we anticipated that tinidazole would have superior efficacy to oral metronidazole our findings did not support that hypothesis. We found no differences in cure rates between metronidazole and either of the tinidazole dosing regimens we studied. Of note, our regimens were more intensive than those approved by the FDA. In addition, there were no significant differences in the side effect profiles of metronidazole and tinidazole.

Limitations to our study include the high lost to follow up rate as well as the high risk nature of this population for STD and BV. Eighty- three percent of the women had had at least one prior episode of BV and thus may represent a more difficult to cure group of women. Nonetheless, this randomized trial showed no difference in efficacy between metronidazole and tinidazole. New approaches to therapy for this common infection are needed.

Condensation

Tinidazole was not found to be more efficacious for the treatment of bacterial vaginosis than metronidazole.

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Figure 1.

Enrollment and Analysis

At first follow-up, in the metronidazole group, 26 subjects were excluded from the analysis because 18 had a pre-existing protocol violation, 7 withdrew from the study, and 1 was withdrawn for pregnancy. In the tinidazole 1 gm twice a day group 25 subjects were excluded from the analysis because 15 had a pre-existing protocol violation, 8 withdrew from the study, 1 was withdrawn for pregnancy, and 1 discontinued the intervention due to side effects. In the tinidazole 500 mg twice a day group 21 subjects were excluded from the analysis because 19 had a pre-existing protocol violation and 2 discontinued the intervention due to side effects.

Table 1

Demographic and behavioral characteristics of subjects by randomized treatment group (n (%))

Characteristic	Metronidazole 500mg twice a day for 7 days	Tinidazole 1g twice a day for 7 days	Tinidazole 500mg twice a day for 7 days	P
Race				
African American	181 (91.9)	181 (92.4)	187 (93.5)	0.56
White	12 (6.1)	1 (0.5)	10 (5.0)	
Other	4 (2.0)	14 (7.1)	1 (0.5)	
Education				
< 12 years	42 (21.3)	45 (23.0)	40 (20.0)	0.40
12 years	70 (35.5)	84 (42.9)	84 (42.0)	
> 12 years	85 (43.2)	67 (34.2)	76 (38.0)	
Condom use last 3 months				
Always	28 (14.3)	29 (14.8)	33 (16.5)	0.70
Sometimes	97 (49.5)	86 (43.9)	91 (45.5)	
Never	68 (34.7)	80 (40.8)	72 (36.0)	
Don't know	3 (1.5)	1 (0.5)	4 (2.0)	
How long since first had BV				
< 1 year	21 (12.8)	24 (14.7)	38 (23.0)	0.04
1–5 Years	80 (48.8)	80 (49.1)	77 (46.7)	
>5 years	63 (38.4)	56 (34.4)	50 (30.3)	
Don't know	0 (0.0)	3 (1.8)	0 (0.0)	
Currently douche				
Yes	78 (39.6)	78 (39.8)	79 (39.5)	0.99
No	119 (60.4)	118 (60.2)	121 (60.5)	
History of STDs				
Yes	187 (94.9)	190 (96.9)	196 (98.0)	0.23
No	10 (5.1)	6 (3.1)	4 (2.0)	
Age	28.0± 6.2	28.5 ± 6.8	28.3±6.6	0.70
Age at first sex	15.0 ± 2.5	15.3 ± 2.0	15.5 ± 2.0	0.11
Number partners last 3 months	1.5 ± 1.0	1.4 ± 0.7	1.3 ± 0.8	0.24
Number partners last 30 days	1.2 ± 0.7	1.1 ± 0.6	1.1 ± 0.6	0.25

Table 2

Primary outcome, as defined by Nugent criteria, after completion of therapy by randomized treatment group (N (%))

Nugent Score	Metronidazole	Tinidazole 1 gm	Tinidazole 500mg	P value
14 day follow-up visit				
≥7	24/136 (17.7)	37/137 (27.0)	36/146 (24.7)	0.16
				0.19*
<7	112/136 (82.4)	100/137 (73.0)	110/146 (75.3)	0.08 ⁺
1 month follow-up visit				
≥7	42/117 (35.9)	37/114 (32.5)	45/118 (38.1)	0.66
7	75/117 (64.1)	77/114 (67.5)	73/118 (61.9)	

P values are for the comparison of all three groups unless otherwise marked

* p value for metronidazole versus tinidazole 500 mg

⁺ pvalue for metronidazole versus tinidazole 1 gm

Table 3

Short term recurrence rates, as defined by Nugent criteria, after completion of successful therapy by randomized treatment group (N (%))

Nugent Score	Metronidazole	Tinidazole 1 gm	Tinidazole 500mg	P value
	500mg BID	BID	500mg BID	
1 month follow-up				
≥7	34/102 (33.3)	20/89 (22.5)	29/96 (30.2)	0.24
<7	68/102 (66.7)	69/89 (77.5)	67/96 (69.8)	
2 month follow-up				
≥7	19/56 (33.9)	12/59 (20.3%)	22/55 (40.0)	0.07
<7	4/56 (66.1)	6/59 (79.7%)	3/55 (60.0)	

Note. Women defined as failures at 14 day visit not included in the analysis

Table 4

Frequency of initial treatment emergent events by randomized treatment group among those reporting at least one adverse event*

Event	Metronidazole 500mg n(%)	Tinidazole 1g n(%)	Tinidazole 500mg n(%)	p value
Yeast infection	32 (29.3)	27 (24.5)	33 (25.0)	0.67
Nausea/vomiting	22 (20.2)	34 (30.9)	26 (19.7)	0.08
Bad taste	12 (11.0)	46 (41.8)	20 (15.2)	<0.001
Diarrhea	4 (3.7)	6 (5.5)	1 (0.8)	0.10
Anorexia	1 (0.8)	5 (4.5)	7 (5.3)	0.17
Headache	16 (14.7)	27 (24.5)	22 (16.7)	0.13
Total Number of Subjects with at Least 1 Adverse Event	109	110	132	

* Subjects can experience more than one adverse event; the percents represent the number of subjects with that incident event out of the total number of individuals in each treatment group who experienced at least one adverse event.