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Single-dose compared to multi-dose metronidazole for the treatment of trichomoniasis in women: A meta-analysis

Katharine Howe, MPH

Tulane University School of Public Health and Tropical Medicine Department of Epidemiology khowe2@tulane.edu (802)-376-9113

Patricia Kissinger, PhD

Abstract

Background—*Trichomonas Vaginalis* is the most common curable sexually transmitted infection worldwide. While the Centers for Disease Control and Prevention and the World Health Organization recommend a single 2-gram dose of metronidazole for the first line of treatment for *T. vaginalis* among HIV negative women, high rates of repeat infections are found. The purpose of this meta-analysis was to compare treatment failure between single versus multi-dose metronidazole for the treatment of *T. vaginalis*.

Methods—A systematic literature search was performed using search terms including metronidazole AND trichomoniasis AND women. Embase, MEDLINE, and Clinicaltrials.gov were used to search for relevant studies as well as hand searching relevant articles. These databases were last searched on January 25, 2016. To be included in this meta-analysis the study had to be a clinical trial, evaluate *T. vaginalis*, use oral metronidazole, and compare single dose metronidazole to multi-dose metronidazole.

Results—There were 487 articles that were assessed for relevance and quality. Of these articles, 6 met the eligibility criteria and were included in the final results. The pooled risk ratio indicated higher treatment failure for single dose compared to multi-dose 1.87 (95% confidence interval of 1.23-2.82, p<0.01). When the one study that included HIV+ women was excluded from analysis, the findings were similar with a pooled risk ratio of 1.80 (95% confidence interval 1.07–3.02, p < 0.03).

Conclusions—CDC recently changed treatment recommendations for HIV+ women to multi- rather than single-dose. These data suggest that those recommendations should be considered for all women.

Summary—In this meta-analysis of two different dose of metronidazole (MTZ) for treatment of trichomoniasis, treatment failure was 1.87 times (95% C.I. 1.23 - 2.82) more likely for 2 g single-dose versus multi-dose. More recent and rigorous trials are needed.

Corresponding author: Patricia Kissinger, PhD, Tulane University School of Public Health and Tropical Medicine, Department of Epidemiology, 1440 Canal Street Suite 2004, kissing@tulane.edu, (504)-988-7320.

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Keywords

trichomoniasis; *Trichomonas vaginalis*; metronidazole; treatment; single-dose; multi-dose

Introduction

Trichomoniasis is the most common curable sexually transmitted infection worldwide and is caused by the *Trichomonas vaginalis* (*T. vaginalis*) protozoan parasite. According to the World Health Organization in 2008 it was estimated that there were 276.4 million new cases of *T. vaginalis* among both men and women, with 187 million living with it at a given point in time.[1] In the United States, the Centers for Disease Control and Prevention (CDC) report that there are currently an estimated 3.7 million people who have the infection, with only 30% of them demonstrating symptoms.[2] The true prevalence is unknown since *T. vaginalis* is not a reportable disease.[3]

If left untreated or sub-optimally treated, *T. vaginalis* has been associated with vaginitis, cervicitis, urethritis, pelvic inflammatory disease, as well as other adverse birth outcomes including preterm delivery, premature rupture of membranes, and low-birth-weight infants.[4, 5] *T. vaginalis* can amplify both acquisition and transmission of HIV.[6]

Given the potential for serious sequelae of *T. vaginalis* infections, proper treatment is paramount.[7] Rates of repeat infections with *T. vaginalis* range from 5%–31% [8–12] and are particularly common among HIV infected women with rates as high as 37%.[13] While some providers may believe that persons who retested positive post-treatment were re-infected from an untreated partner, one observational study found that most of the early repeat positives were likely treatment failure rather than re-infection.[8] Moreover, most studies, to date, have found low rates (i.e. < 5%) of metronidazole (MTZ) resistant *T. vaginalis*,[9, 14] suggesting that host factors may be involved. Indeed, one randomized trial among HIV infected women found the multi-dose treatment to be superior to the 2 g single-dose.[15] While is it unknown why the multi-dose was superior to single dose among HIV+ women, a secondary analysis of this trial found this difference only among women who had concomitant asymptomatic bacterial vaginosis.[16] Since there is a high prevalence of concomitant BV among HIV+ women with *T. vaginalis*,[17] there is further reason to use multi-dose MTZ, which would treat both issues.

Metronidazole, a drug from the nitroimidazole class developed in 1959, is the most common medication used for treating trichomoniasis. Prior to the introduction of MTZ, most of the treatments available were topical treatments which provided relief of symptoms, but did not cure the infection. And while a metronidazole gel exists, it has been demonstrated to be ineffective for treating trichomoniasis, and is therefore not recommended.[18, 19] Both the Centers for Disease Control and Prevention(CDC) [19] and the World Health Organization (WHO)[20] currently recommends that individuals be treated a single 2 gram dose orally. If treatment failure occurs, CDC recommends 500 mg twice a day for 7 days and WHO recommends 400–500 mg twice daily for 7 days. Tinidazole, another nitroimidazole, has demonstrated higher clearance rates and fewer side effects for both men and women

compared to MTZ,[21] but is 3 – 5 times more expensive in generic form compared to MTZ and may be cost prohibitive in resource challenged times.[22]

There have been several studies conducted since 1971 which have compared the efficacy of single gram doses compared to multi gram doses of metronidazole.[23, 24] While many of these studies found trends for superiority of the multi-dose, they did not find statistically significant differences, and thus, concluded that the single and multi-dose regimens were equivalent. This is problematic, since most of the studies were not powered for equivalence and were susceptible to beta error. The purpose of this meta-analysis is to re-evaluate these studies and calculate an overall effect measure of single dose of metronidazole compared to multi-dose treatment with metronidazole for the treatment of *T. vaginalis*.

Methods

Eligibility Criteria

A comprehensive literature search was completed by the investigators using Embase and MEDLINE. Additionally, ClinicalTrials.gov was used to collect data on the gray literature, for studies evaluating data on trichomoniasis and metronidazole. Further articles were to be identified by hand searching relevant related articles. These databases were last searched on January 25, 2016. The search terms that were used for this research included (*trichomonas* OR *trichomon** OR *trichomonas vaginalis* OR *trichomoniasis*) AND (*metronidazol** OR *metronidazole* OR *flagyl* OR *protostat*) AND (*Women*). Once the search was completed all of the retrieved articles were put into EndNote X7 to be organized.

To be included in this meta-analysis, the articles had to be written in English and the study had to be a clinical trial, evaluating trichomoniasis, use oral metronidazole, and it had to compare single dose oral metronidazole to multiple dose oral metronidazole. The search was not limited by dates.

Study Selection

The initial screening process was completed independently and in duplicate. Each of the investigators screened the articles to assess their eligibility based on the criteria stated above. Once this process was complete, the investigators compared their results for which articles needed to be looked at for further review or which articles were to be excluded, and any discrepancies were resolved by a consensus.

Following the initial title and abstract review the full text articles were identified and found. Any articles that were not immediately accessible were retrieved through interlibrary loan through Tulane University's Matas Library. Each investigator reviewed the articles for eligibility and to identify the articles for data abstraction. This second phase was also done independently and in duplicate. The investigators compared their results and any discrepancies were resolved by a consensus. If there were multiple analyses done on the same dataset it was decided that the most recent study which presented the most complete data would be selected.

Data Collection Process

Data for the meta-analysis was abstracted using a standardized form in duplicate by two independent investigators. After the investigators completed the data abstraction, the duplicates were compared. Discrepancies were discussed among the investigators, and resolved by a consensus. The variables that were collected included information on blinding, randomization, number of study participants, HIV status of the participants, number loss to follow-up, number of participants in each arm, types of treatments for the respective arms, as well as the number of treatment failures in the respective arms.

Quality Assessment

Study quality was assessed on the basis of randomization, blinding, and loss to follow-up. Studies were rated to be low risk of bias, medium risk of bias, or high risk of bias studies. A study was classified as low risk of bias if it was blinded, randomized and had a relatively small amount of loss to follow up (i.e. < 25%). It was considered low risk of bias if it all three criteria were met, medium risk if it fulfilled one to two of these criteria, and high risk if it did not fulfill any of the criteria.

Statistical Analysis

The relative risks were calculated from the information extracted. The pooled effect size was initially calculated using a fixed effects model, and included the Dersimonian and Laird Q test and I^2 statistic to assess for heterogeneity. If significant heterogeneity was found, further analysis was completed using a random effects model. All statistical analyses were completed using STATA 12.0 statistical software [25]. The pre-specified sub-group analysis was to include only those studies that were done among HIV- individuals, as the earliest studies that were conducted were conducted in a time before HIV was recognized. Additionally, a sensitivity analysis of studies by study quality was performed.

Results

Literature Search

The initial search was done using EMBASE, MEDLINE and clinicaltrials.gov, which returned a total of 484 unduplicated articles. Of these, 471 papers were excluded because: they were not written in English (n=30), not done among humans (n=5), not a clinical trial (n=282), did not examine *T. vaginalis* (n=31), did not examine MTZ (n=57) or did not compare single-dose to multi-dose (N=66). Of these articles, 13 were pulled for full text review, and additional 7 were excluded because they did not meet the inclusion criteria after that review, leaving a total of 6 that were included in the final analysis. The results of the literature search using the search strategy above, are detailed in Figure 1.

Study characteristics

There were a total of 6 studies included in this meta-analysis. The study by Kissinger et al. was the only study which included information about HIV status and was conducted exclusively on HIV positive women.[15] The remaining studies were conducted prior to the availability of HIV testing thus HIV status is unknown. There were 4 studies which were

randomized controlled trials, and two of those studies were also blinded where individuals received a placebo for the alternate treatment regimen. It was therefore concluded that there was 1 study which met the criteria for low risk of bias, 3 studies that met the criteria for medium risk of bias, and 2 studies that met the criteria for high risk of bias. For a summary of the individual study characteristics please see Table 1.[15, 23, 26–29]

Synthesis of results

The pooled effects were calculated using a fixed effects model due to the lack of heterogeneity (i.e. I^2 0%, p=0.88) and the small sample size. Figure 2 was conducted using the inverse variance weighting method. Women who received 2 g single-dose MTZ were 1.87 times more likely to have treatment failure than women who received multi-dose MTZ 95% C.I. 1.23 to 2.82, P < 0.003). In the subgroup analysis, which excluded the one study with all HIV infected women, the results were similar with a relative risk of 1.80 (95% C.I. 1.07 to 3.02, P < 0.03). The subgroup analysis finding are similar to those of Kissinger et al. [15] whose cohort was all HIV infected, suggesting that superiority of multi-dose over single-dose MTZ, likely holds true for HIV negative women.

Risk of bias within studies

The risk of bias within studies was evaluated using blinding, randomization, and loss to follow-up. Due to the small sample size it was difficult to make any conclusions about the difference in the estimates of the various qualities of the studies. However, it appeared that the studies with a low and medium risk of bias are closest to the overall pooled estimate which would indicate that the quality of the study did not dramatically change the overall effect estimate.

Risk of bias across studies

According to the Cochrane Handbook for Systematic Reviews a funnel plot should not be included to detect publication bias if there are less than 10 studies included [30]. Because this analysis only included 6 studies, assessment for publication bias was not done and no funnel plot was generated.

An influence analysis was conducted to determine if a particular study were excluded if the overall effect estimate would change (data not shown). This influence analysis provided results that were very similar to the overall results, which indicated that there was no particular study with substantial influence.

Discussion

Summary of Evidence

The overall results of this meta-analysis which includes 6 studies comparing single and multi-dose metronidazole treatments for trichomoniasis significantly favor the multi-dose over the single-dose regimen. Women who receive single-dose metronidazole are 1.87 times more likely to experience treatment failure compared to those who were prescribed multi-dose metronidazole treatment and this result did not appear to be influenced by any one study.

It is possible, but not probable that some studies were omitted because of our methods and exclusion criteria. Although efforts were made to search gray literature, no studies in the gray literature were found. While we did not restrict our search by language, if a paper was unavailable in English it was excluded from our meta-analysis. From the titles of these studies, the only item that was provided in English, it appeared that most of these studies did not fit eligibility criteria. Moreover, assessment of publication bias, commonly performed in meta-analyses, was not possible for this study due to the small number of studies published on this topic that met the inclusion criteria. The more important limitation, however, is the scarcity and quality of studies that evaluate this topic.

It was surprising to find so few studies published that compared the recommended doses of MTZ, 2 of which were classified as having the potential for high bias, and all but one of the studies were conducted before 1982. Clinical trial methods have improved substantially since that time. Future evaluations of MTZ should be conducted using present state of the art clinical trial methods (http://clinicalcenter.nih.gov/ccc/clinicalresearch) and presented using Consolidated Standards of Reporting Trials (http://www.consort-statement.org). One such study is underway (Federal Drug Administration Investigational New Drug # 118276). This study is multi-centered, powered for equivalency, utilizes more advanced diagnostics such as nucleic acid amplification techniques (NAAT) and InPouch culture, detailed sexual exposure questions are elicited via computer assisted, self-administered interview, and multi-locus sequencing technique (MLST) genotyping techniques and MTZ susceptibility testing are used to more precisely evaluate if retest positives are treatment failure or re-infection.

With any medication, side effects are a concern. An evaluation of side effects was not possible because the studies did not systematically assess them. However, five of the six studies reported more side effects in the 2 g dose compared to the multi-dose. Woodcock only reported side effects in the 2-gram arm. Side effects mentioned were: nausea, vomiting and difficulty swallowing multiple pills.

While parasitic cure is important, alleviation of clinical symptoms is also important. No evaluation of failure rates by symptoms was done because the studies either did not evaluate symptom by arm. In the three studies that did collect information on symptoms, it was only collected at baseline and ranged from 30% – 100%. Future studies should examine clinical symptom as well as parasite control.

Another important limitation is that not all positive tests at follow-up were treatment failures. Some could have been re-infection by an untreated and infected sex partner. Since not all studies measured sexual re-exposure, it was not possible to determine the origin of a positive test of cure. This is of particular concern given the wide range of time to test of cure (i.e. 24 hours to 3 months) and the longer the follow-up, the greater chance there would be that a retest positive would be re-infection rather than treatment failure. Despite this potential for error, most studies retested by 21 days and at least one study found that the majority of early repeat *T. vaginalis* infections (i.e. before 21 days) are actually treatment failure. [31]

A final limitation of these studies are the diagnostic tests that were used to evaluate treatment failure. All but one used microscopy, which can have sensitivity as low as 48% but can be higher depending on the expertise of the microscopist.[32] Using microscopy as a diagnostic, therefore, could have underestimated the actual rate. It would, however, been unlikely to affect the relative risk if the same microscopist evaluated specimens for both arms of the study, or microscopists were well trained and monitored. Culture was used in the Kissinger et al. study.[15] Culture has higher sensitivities, but can miss some parasites after treatment.[33, 34] NAAT testing would have the highest with sensitivities approaching 100%,[35] but should not be used before 3 weeks as it could pick up remnant DNA causing false positives.[36, 37]

While the studies that served as inputs for this meta-analysis are few and most were conducted over 30 years ago, all but one indicate superiority for the multi-dose of medication, suggesting that the recommendation for the 2 g MTZ dose treatment of *T. vaginalis* needs to be re-examined.

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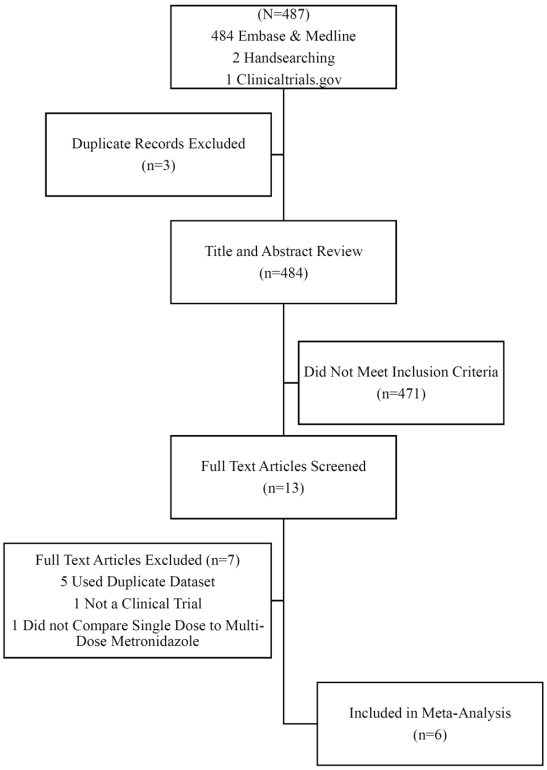

Figure 1.
Inclusion/Exclusion of studies

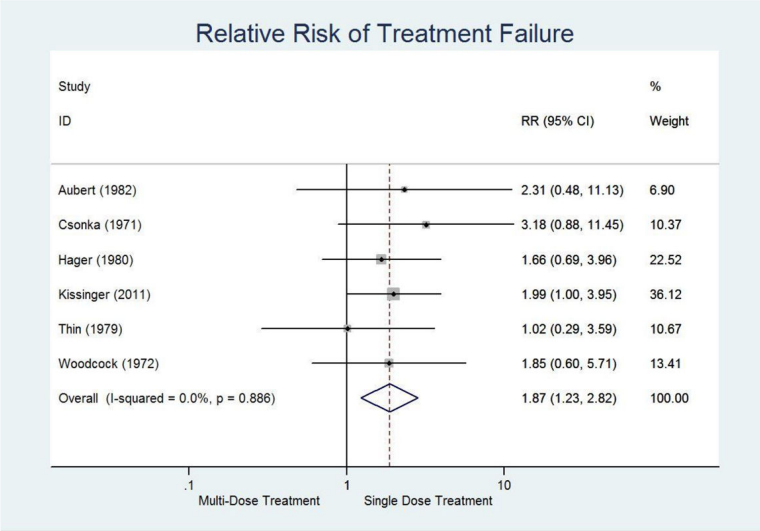

Figure 2.
Overall Results, Fixed Effects Method

Table 1

Summary of individual study characteristics

Author, Year	Randomization	Blinding	Participants	Intervention Treatment	Control Treatment	Outcomes	Mode of Diagnosis	Follow-up visits	Lost to Follow-up (%)	Risk of Bias
Aubert, 1982 [26]	No – participants chose treatment plan	No mention	263 women attending the family planning clinic at the University of Medicine and Dentistry in New Jersey	One2-g dose (eight 250-mg metronidazole tablets ingested at dinner)	One 250-mg metronidazole tablet, 3 times a day, for 7 days	Parasitological cure, vaginal symptoms, medication side effects, compliance with the recommendations	Microscope identification	7 to 21 days after treatment	93 (35.6)	High
Csonka, 1971 [23]	Yes	No mention	112 women attending clinics for sexually transmitted diseases at the Central Middlesex Hospital and Watford General Hospital (UK)	One2-g dose (five 400-mg tablets ingested under supervision at the clinic)	One 200-mg tablet, 3 times a day for 7 days	Parasitological cure	Dark-ground examination of vaginal secretions and by culture in a modified Bushby medium	24 hours later, 7 days later, and monthly for 3 months	15 (13.4)	Medium
Hager, 1980 [28]	Yes	Double-blind	468 women attending the venereal disease clinics of DeKalb County and Fulton County, Georgia	One, 2-g dose (eight 250-mg tablets given in one dose) and placebo tablets 3 times a day for 7 days	Eight placebo tables given in one dose, then one 250-mg tablet, 3 times a day, for 7 days	Parasitological cure, medication side effects	Motile trichomonads in material obtained from the posterior vaginal fornix	Follow up visits were 7 to 21 days after treatment	292 (62.4)	Medium
Kissinger, 2010 [15]	Yes	No mention	270 HIV+ women undergoing a routine gynecological exam performed by a health care provider between May 1, 2006 and July 17, 2009 at HIV outpatient clinics in New	One, 2-g dose (4 pills under direct observation of the study coordinator)	One 500-mg tablet, twice a day, for seven days	Parasitological cure, medication side effects, treatment adherence	InPouch culture technique with the vaginal swab obtained by the physician	6–12 days after completion of dose	15(5.6)	Medium

Author, Year	Randomization	Blinding	Participants	Intervention Treatment	Control Treatment	Outcomes	Mode of Diagnosis	Follow-up visits	Lost to Follow-up (%)	Risk of Bias
			Orleans, LA; Houston, TX; and Jackson, MS							
Thin, 1979 [29]	Yes	Double-blind	192 women from St Bartholomew's and Eastern Hospitals (UK)	One, 2-g dose (five 400-mg tablets) followed by one placebo tablet twice a day for 5 days	Five placebo tablets immediately followed by one 400-mg tablet, twice a day, for 5 days	Parasitological cure	Wet preparation made by mixing vaginal secretion with saline on a slide and examining it under a microscope	7 to 14 days after the start of therapy	47 (24.5)	Low
Woodcock, 1972 [27]	No	No mention	203 participants attending the St. Mary's Hospital Special Clinic (UK)	One, 2-g dose (five 400-mg tablets) take under supervision	One 200-mg tablet, 3 times a day for 7 days	Parasitological cure	Routine darkfield microscopy of vaginal secretions	1–12 weeks	70 (34.5)	High

Table 2

Data extracted from studies

Author, Year	Single-Dose Treatment Failures	Single-Dose, Total Followed	Single-Dose Cure Rate, %	Multi-Dose Treatment Failures	Multi-Dose, Total Followed	Multi-Dose Cure Rate, %	P-value of Cure Rate Difference
Aubert, 1982 [26]	6	96	93.8	2	74	97.3	0.47
Csonka, 1971 [23]	7	36	82	3	49	94	NS[1]
Hager, 1980 [28]	13	93	86	7	83	91.6	>0.1
Kissinger, 2010 [15]	21	125	83.2	11	130	91.5	0.045
Thin, 1979 [29]	4	52	92.3	5	66	92.4	NS[1]
Woodcock, 1972 [27]	9	73	87.7	4	60	93.3	NS[1]

[1]Not Significant