Intravaginally applied metronidazole is as effective as orally applied in the treatment of bacterial vaginosis, but exhibits significantly less side effects

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ABSTRACT

Objective: Metronidazole is the drug of choice for the treatment of bacterial vaginosis (BV). However, so far the oral administration has not been clinically compared to the intravaginal application regarding efficacy, side effects and patient satisfaction in a scientific sound fashion.

Study design: Therefore, this randomized, double-blind, placebo-controlled clinical trial was designed to demonstrate non-inferiority of short-term intravaginal (i.vag.) application of metronidazole (2×1000 mg pessaries 24 h apart) vs. a single oral dose (p.o.) of metronidazole (1×2000 mg tablets) in 263 patients with BV (double-dummy design). The follow-up period was 12 weeks. In addition, the number and the type of adverse events induced by the two regimens were compared, assuming better tolerability of the intravaginal application.

Results: Following the diagnosis of BV a total of 129 women (mean age 36.2 years) was orally treated with a single dose of 2 g metronidazole whereas a total of 134 patients (mean age 35.5 years) was treated intravaginally with 1 g metronidazole each day on two consecutive days and included in the per-protocol analysis. Non-inferiority of i.vag. application compared to p.o. administration was statistically significant regarding efficacy: Following intravaginal application the cure rate, assessed on day 8 after starting of the treatment, was 92.5% as compared to 89.9% after oral administration. Nausea was the most common adverse event reported in 10.2% i.vag. vs. 30.4% p.o. of all cases (p<0.001), abdominal pain in 16.8% i.vag. vs. 31.9% p.o. (p<0.01), a “metallic taste” in 8.8% i.vag. vs. 17.9% p.o. (p<0.05). Women treated i.vag. were highly satisfied with the treatment and more content as compared to the women treated p.o. with metronidazole (p<0.05, intent-to-treat analysis).

Conclusion: In this clinical trial the intravaginal application was as effective as the oral administration of metronidazole in treating BV. However, significantly less adverse events were reported after short-term intravaginal as compared to oral application (p=0.023) and probably led to a better patient compliance.

1. Introduction

Bacterial vaginosis (BV) is by far the most common cause of vaginal discharge in women of reproductive age [1]. This commonness is supported by prescription data: there are 1.52 m. prescriptions with the diagnosis BV written by physicians in Germany alone from January until June 2007. Moreover, BV is associated with a number of severe gynecologic and obstetric disorders, e.g. pelvic inflammatory diseases (PID), an increased risk for HIV-infection or preterm labor and preterm birth (for details see: [2–4]).

Currently, the standard treatment options are the antimicrobial substances metronidazole and clindamycin which are able to cure BV in up to 94% [5], but with reported recurrence rates of 40–80% within the first 6 months after treatment [6]. Interestingly, metronidazole as well as clindamycin may be administered either orally or intravaginally. However, new data point to the development of persistent resistance of anaerobic gram(−) bacteria and gram(+) cocci after intravaginal application of clindamycin for the treatment of BV [7].
Germany by the guideline [9].

of a single dose of 2 g metronidazole is still recommended to the current recommendations of the CDC; the oral administration 500 mg once or twice daily for 7 days is recommended. In contrast, however, the intravaginal application of metronidazole 0.75% (5 g) once daily for 5 days [8]. In Germany, this gel is not approved, but instead metronidazole may be applied intravaginally as gel (Arilin Rapid, vaginal pessaries containing 1000 mg metronidazole, Dr. August Wolff GmbH & Co. KG Arzneimittel, D-33611 Bielefeld, Germany) and placebo pessaries or vaginal metronidazole 1000 mg once daily over a time course of 2 days [Arilin Rapid, vaginal pessaries containing 500 mg metronidazole, Dr. August Wolff GmbH & Co. KG Arzneimittel, D-33611 Bielefeld, Germany] and placebo tablets (double-dummy design). After clinical evaluation of the patient and obtaining written consent, the patient was included in the study and therapy was initiated on day 1. On day 8, the patient was again evaluated.

277 patients were randomized to receive metronidazole either orally (n = 137) or intravaginally (n = 140) according to the study protocol. Two patients of the intravaginal treatment group were excluded because of violations of the study criteria. Two patients of the oral and 3 patients of the intravaginal treatment group were excluded because they did not complete the study. Additionally, 6 patients of the oral and 1 patient of the intravaginal treatment group were excluded because of violations of the study protocol. Thus, a total of 129 patients were treated orally and a total of 134 patients treated intravaginally were included in the per-protocol analysis (Fig. 1).

Patients allocated to i.vag. or p.o. metronidazole did not differ significantly with regard to age, weight, race, smoking habits, menstruation status, hysterectomy status, contraceptive history, and history of BV.

Comparisons between the two treatment groups were made by means of the exact Fisher-test for nominal data and the Mann–Whitney-test for ordinal data. Analysis was performed using statistical software (SPSS version 12.0). All tests of significance were two-sided. Statistical significance was assumed for \( p < 0.05 \). This clinical trial aimed to compare metronidazole-containing pessaries with metronidazole-containing oral tablets (non-inferiority trial according to the “Guidelines on the choice of the non-inferiority margin” (EMEA/CPMP/2158/99)) and according to “Points to consider on switching between superiority and non-inferiority” (EMEA/CPMP/482/99).

The primary objective (primary endpoint) of the study was to show that the efficacy of the pessaries was clinically non-inferior as compared to the oral application of metronidazole at day 8.
Efficacy was defined as cure of BV. Healing of BV was defined as the absence of clue cells, and the absence of at least two of the following three criteria: typical vaginal discharge, amine odor, and a pH > 4.5. Non-inferiority was assessed using a two-sided 95% confidence interval for the difference of cure rates (p.o.–i.vag.). Non-inferiority margin for difference of cure rates was 20%. Non-inferiority was accepted when the upper limit of this confidence interval was below the specified non-inferiority margin of 20%. The follow-up period for the patients considered cured was 12 weeks (n = 176).

The efficacy analysis was performed as per-protocol analysis. However, the results of the intent-to-treat analysis were also reported because there is an ongoing debate which analysis is more appropriate for non-inferiority trials [10,11].

The secondary objective of the study was to compare overall medication tolerability and the occurrence of adverse drug reactions following topical or oral administration of metronidazole. The clinical assessment of the respective physician and the patients’ diaries were both used as outcome measures of overall patients’ medication tolerability. All patients who took the study medication and for whom any adverse effects were documented or patients’ diaries were available (n = 275) were included in the evaluation of adverse events. The analysis of patients’ overall satisfaction with therapy and physicians’ rating of tolerability (test of superiority) was performed as intent-to-treat analysis.

3. Results

3.1. Study population

A total of 263 patients with acute symptomatic BV was treated, 129 patients received metronidazole orally and 134 intravaginally. The average age was 36.2 ± 14.1 years and 35.5 ± 12.7 years with a body weight of 64.5 ± 12.6 kg and 64.0 ± 11.7 kg, respectively. Interestingly, in the groups 24 and 27.6% of the patients were smoking. 64.3 and 64.2%, respectively, experienced the first episode of BV. 9.3% vs. 9.7% suffered from 1 recurrence/year, 12.4% vs. 15.7% from 2 recurrences/year and 7.8 and 9.7% from 3 or more recurrences/year. There were no significant differences regarding the mode of contraception.

3.2. Clinical efficacy

The primary endpoint of the study was to show that the efficacy of the pessaries was clinically non-inferior as compared to the oral application of metronidazole. The cure rate in patients treated with intravaginally applied metronidazole was slightly higher compared to patients treated with oral metronidazole (92.5% vs. 89.9%) (Fig. 2). The upper limit of two-sided 95% confidence interval (−9.87 and 4.64%) for the difference in cure rates (−2.6%) was clearly below the specified margin of inferiority (20%). This was also the case for the intent-to-treat analysis (difference = 2.3%; two-sided 95% confidence interval (−9.91 and 5.39%). Thus, non-inferiority of intravaginally applied metronidazole was accepted. Overall, the recurrence rates within the follow-up period of 12 weeks was lower as expected. Recurrences occurred in 10.0% (p.o.) vs. 13.9% (i.vag.). There was no statistical significant difference.

3.3. Tolerability and adverse events

The secondary objective of the study was to compare overall medication tolerability and the occurrence of adverse drug reactions following intravaginal or oral administration of metronidazole. According to the ratings of the physicians the overall tolerability of the intravaginal administration of metronidazole was better as compared to the oral administration (p = 0.048). The physicians rated the tolerability of the i.vag. metronidazole in 53.7% as very good, but only in 42.6% when the metronidazole was taken orally. Moreover, the patients’ overall satisfaction with the intravaginal administration of metronidazole was higher as compared to the oral administration (p = 0.046). This is explained by the number of the reported adverse events. Significantly more AEs were reported after oral administration of metronidazole as compared with the intravaginal administration (71.1% vs. 57.7%, p = 0.023) (Table 1). The most common side effects were nausea (30.4% p.o. vs. 10.2% i.vag., p < 0.001), abdominal pain (31.9 vs. 16.8% i.vag., p = 0.005) and headache (24.1% p.o. vs. 31.1% i.vag., p = 0.047). Nausea, abdominal pain and metallic taste as adverse events occurred significantly less often in patients treated with intravaginal metronidazole as compared to the orally treated patients. The number and type of the reported AEs are shown in Fig. 3.

4. Discussion

The presented double-dummy designed clinical study showed clearly that the intravaginal application of metronidazole is as effective as the oral administration in the treatment of BV, but exhibits significantly fewer adverse events. Moreover, the overall patient satisfaction with the intravaginal treatment is higher as compared with the oral treatment.

Oral metronidazole is still the most frequent form of administration when treating BV with a reported average cure rate of 82% [2,12]. The intravaginal application of metronidazole (0.75% gel formulation, twice daily for 5 days) was first reported to be effective for the treatment of BV by Hillier et al. in 1993 with a reported cure rate of only 73% [13]. However, the small number of patients investigated (n = 30) made it difficult to obtain statistically valid results. Subsequent studies using the 0.75% metronidazole gel either once or twice daily for 5 days reported similar cure rates of 61–71% with 41–178 patients investigated [14–17]. A cure rate of 64% was obtained with a single 100 mg dose of metronidazole formulated in a biodhesive vaginal tablet compared to a cure rate of 29% in the placebo group [18]. The cure rate after oral administration of metronidazole in this study is

![Fig. 2. Cure rates of patients treated with metronidazole intravaginally (92.5%) or orally (89.9%).](image-url)
This is in accordance with previously published studies [15,17,20,25]. The significantly fewer AEs reported after intravaginal application explain the higher overall patient satisfaction as compared with the oral administration of metronidazole.

Treatment of BV with intravaginally applied clindamycin has been reported to be effective [22,26]. However, a study to compare intravaginally applied clindamycin with the metronidazole pessaries used in this study seems not indicated, because there is growing evidence of antimicrobial resistance of anaerobic bacteria to clindamycin, which may increase the vaginal reservoir of macrolide-resistant bacteria [7].

In conclusion, the present clinical study showed clearly non-inferiority of the short-term intravaginal application of metronidazole as compared with the oral administration regarding the cure rate. Thus, both forms of application are equally effective. However, the tolerability of the medication due to significantly lower adverse events following the short-term intravaginal application was significantly better, leading to a higher overall patient satisfaction as compared to the oral administration of metronidazole. Thus, failure of patients to comply with the prescribed treatment is assumed to be less likely, when taking metronidazole pessaries. Moreover, costs resulting from adverse drug reactions after intravaginal application will be less as compared to the oral administration. Therefore, intravaginal pessaries of metronidazole applied for only 1 or 2 days should be considered as a very effective, well-tolerated alternative treatment for BV.

References