Treatment of Vaginal Infections with Intravaginal Pentamycin in Clinical Practice

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Citation

J Balmer. *Treatment of Vaginal Infections with Intravaginal Pentamycin in Clinical Practice*. The Internet Journal of Gynecology and Obstetrics. 2008 Volume 11 Number 1.

Abstract

Objectives: To evaluate the effectiveness of intravaginal pentamycin, a polyene antibiotic with a broad spectrum of antimicrobial activity, for the treatment of vaginal infections in clinical practice. Methods: This study was conducted on 159 women (aged 17-65 years) with vaginal infections caused by Candida albicans (N = 82), Trichomonas vaginalis (N = 8), or mixed microorganisms (N = 69). Patients were treated with intravaginal pentamycin (6 mg daily for 5 days, N = 104; 3 mg daily for up to 10 days, N = 55), alone (65.4% of cases) or in combination with other therapies. Results: Eradication of the causative agents was demonstrated in 100% of patients with trichomoniasis, 87.8% of patients with candidiasis, and 84.0% of patients with mixed infections. Irrespective of the dose of pentamycin administered, treatment was well-accepted by most patients and well-tolerated in all cases. Conclusion: Intravaginal pentamycin, either alone or in combination with other therapies, is effective in more than one form of vaginal infections.

INTRODUCTION

Vaginitis is one of the most frequent conditions for which women seek medical care [1] and the most common gynecologic diagnosis in the primary care setting [2]. Vaginal discharge and symptoms are usually related to one of the following conditions: vaginal candidiasis, trichomoniasis and bacterial vaginosis [1]. In these conditions, the vaginal flora has been altered by introduction of a pathogen or by changes in the local environment that allow pathogens or normal saprophytes to proliferate [2]. Candidal infection is most frequently provoked by Candida albicans, a fungal organism that is part of the normal flora of the vagina of reproductive-age women, but causes over 90% of cases of symptomatic vaginal candidiasis [3]. When candidal infection is sustained by other Candida species, such as Candida glabrata and Candida tropicalis, it is often resistant to treatment [14]. Mixed infections are observed frequently [5]. Trichomoniasis is caused by the protozoan Trichomonas vaginalis and represents the most common non-viral sexually-transmitted infection [124]. Bacterial vaginosis has become a major cause of vaginal disorders in recent years [167], but its prevalence is difficult to estimate because a substantial number of women are asymptomatic [67]. In many cases it develops as a consequence of the loss of lactobacilli, which normally occurs in post-menopausal women or results from the use of antibiotics for other infections [8]. The predominant organisms that cause bacterial vaginosis are Gardenerella vaginalis, Mycoplasma hominus and Ureaplasma urealyticum [1678]. Other bacteria identified in the vaginal secretions of patients affected by this disease include anaerobes like Prevotella, Mobiluncus, Bacteroides, and Peptostreptococcus species [1678].

Most forms of vaginal infections usually respond to pathogen-specific treatments [13] but, in absence of a single drug that can treat the most frequent infections, treatment efficacy largely depends on the ability of health care providers to make the correct diagnosis with appropriate laboratory tests [149]. Moreover, many women with vaginal complaints self-treat incorrectly with over-the-counter drugs without consulting health care providers for a confirmatory diagnosis [10]. The inappropriate or indiscriminate use of antimicrobials for these disorders weaken the natural defenses against infections and favor the emergence of strains of microorganisms resistant to treatment or the development of mixed infections [110]. As a result, forms of difficult-to-treat vaginal infections and recurrences of vaginal candidiasis or trichomoniasis are frequently observed [14511]. The availability of a drug effective in more than one form of infectious vaginitis would reduce the need for a confirmatory diagnosis and the risk of treatment failure.

Pentamycin is a polyene macrolide antibiotic [1213], naturally produced by Streptomyces penticus, which exerts its antimicrobial effects by altering the barrier function of the cell membranes of microorganisms [13]. Pentamycin exhibits a broad spectrum of antimicrobial activity [121415]. In particular, its in-vitro activity against trichomonads is similar to that of metronidazole and its activity against various Candida species is similar to that of the azole antifungal agent miconazole. Pentamycin has also shown in-vitro activity against several pathogenic bacterial strains, but it is inactive against the lactobacilli that colonize the normal vagina [15]. Because of the high molecular weight (670.85) and bi-polar molecular structure [16], topically applied pentamycin does not penetrate into the circulation. Vaginal pentamycin (Pruri-ex®, 3mg vaginal tablet) is registered in Switzerland for the treatment of vaginal candidiasis, trichomoniasis and mixed infections. In the near future, it will be commercialized in many other countries, including Latin America, Asia, Russia, Middle East and North Africa, but there are limited data on the use of this product in literature [1517]. This article describes the results of a study that evaluated the effectiveness and tolerability of intravaginal pentamycin for the treatment vaginal candidiasis, trichomoniasis and mixed infections in clinical practice in Switzerland.

MATERIALS AND METHODS

This study was conducted on 159 women, aged 17 to 65 years, who attended the gynaecology clinic for symptoms of vaginitis (including itching, burning, dyspareunia, leucorrhoea and xanthorrhea) and had a diagnosis of candidiasis, trichomoniasis or mixed infectious vaginitis on the basis of the history, complete gynecological examination, wet mount microscopy and microbiology testing (Gram staining and cultures). The causative agents were Candida albicans in 82 cases, Trichomonas vaginalis in 8 cases, and mixed microorganisms in 69 cases (Table 1).

Figure 1

Table 1: Patient characteristics and response to previous treatments

Type of infection and causative agent(s)	Number of patients	Age [mean years (range)]	No response to previous treatments [N (% of total)]
Candidiasis - *Candida albicans*	82	30.5 (18-51)	23 (28.0)
Trichomoniasis - *Trichomonas vaginalis*	8	33.6 (17-65)	2 (25.0)
Mixed infections	69	32.5 (19-51)	22 (31.9)

In patients with mixed infections, various combinations of Candida albicans, Trichomonas vaginalis, Gardnerella vaginalis, other Candida species or various bacteria were isolated from the vaginal secretion by microbiology testing (Table 2). Depending on the type of vaginal infection, 25.0% to 31.9% of the patients had previously received various antimicrobial therapies, not including pentamycin, without benefits (Table 1).

Patients were treated with intravaginal pentamycin at the recommended doses of either 6 mg daily (one tablet in the morning and in the evening) for 5 days (N = 104) or 3 mg daily (one tablet in the morning) for up to 10 days (N = 55) (Table 2). As per common practice, pentamycin was used alone in 65.4% of the cases and in combination with other therapies (mainly metronidazole or topical azole antifungal agents, or clindamycin) in the other cases, depending on the results of microbiology testing (Table 2).

Figure 2

Table 2: Treatment modalities and duration by type of infection and causative agent(s).

Type of infection and causative agent(s)	Pentamycin treatment (number of patients)				
	6 mg for 5 days	3 mg for up to 10 days	Alone	In combination with other therapies	
				Oral	Local
Candidiasis - *Candida albicans*	62	20	52	2	29
Trichomoniasis - *Trichomonas vaginalis*	7	1	4	4	0
Mixed infections	35	34	48	13	9
- *Candida albicans*			6	1	3
- *Trichomonas vaginalis*			5	9	0
- *Gardnerella vaginalis*			3	2	1
- Other			34	1	5

The treatment success rate was evaluated by determining the proportion of patients who experienced resolution of symptoms at the end of the treatment period and the

proportion of women in whom post-treatment microbiology testing showed eradication of the causative agents. Treatment tolerability was assessed by monitoring adverse events. Treatment acceptance was examined by asking the patients to rate their level of satisfaction as “good”, “insufficient” or “null”. The data were analyzed separately in each subgroup of patients, according to the type of infection and to the treatment dose and duration, with the use of descriptive statistics.

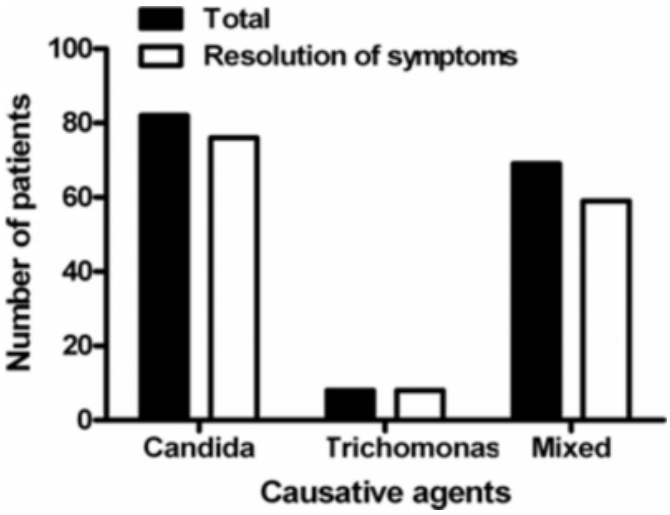
RESULTS

TREATMENT SUCCESS RATE BY INFECTION TYPE

Resolution of symptoms was experienced by 100% (8/8) of patients with vaginal trichomoniasis, 92.7% (76/82) of patients with vaginal candidiasis and 85.5% (59/69) of patients with mixed infections (Figure 1).

Figure 3

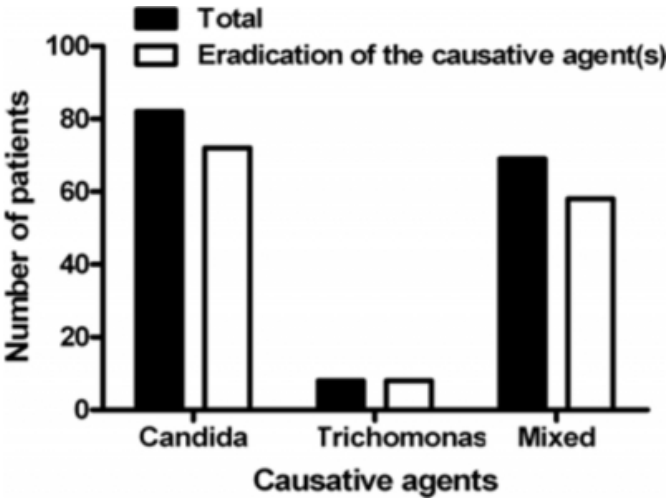
Figure 1: Treatment success in terms of resolution of symptoms.



Treatment success was confirmed by eradication of the causative agents in 100% (8/8) of patients with vaginal trichomoniasis, 87.8% (72/82) of patients with vaginal candidiasis and 84.0% (58/69) of patients with mixed infections (Figure 2).

Figure 4

Figure 2: Treatment success in terms of eradication of the causative agent(s).

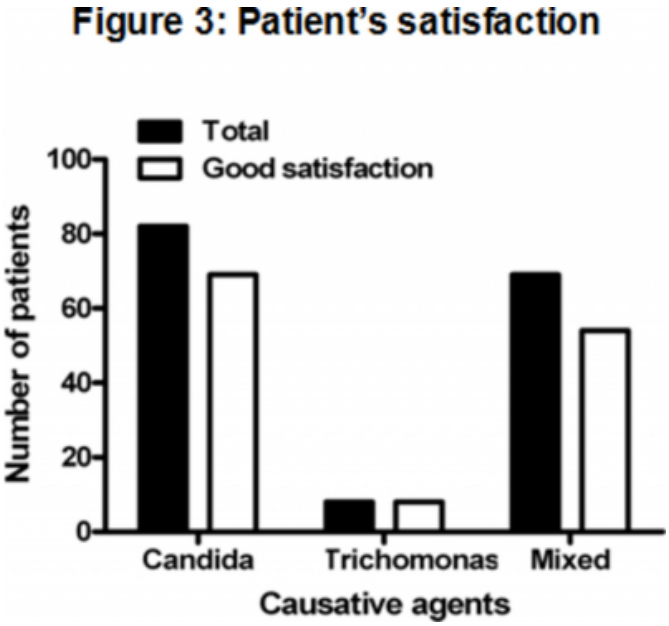


TREATMENT ACCEPTANCE RATE BY INFECTION TYPE

Treatment acceptance was rated as “good” by 100% (8/8) of patients with vaginal trichomoniasis, 84.1% (69/82) of patients with vaginal candidiasis and 78.3% (54/69) of patients with mixed infections (Figure 3).

Figure 5

Figure 3: Patient’s satisfaction



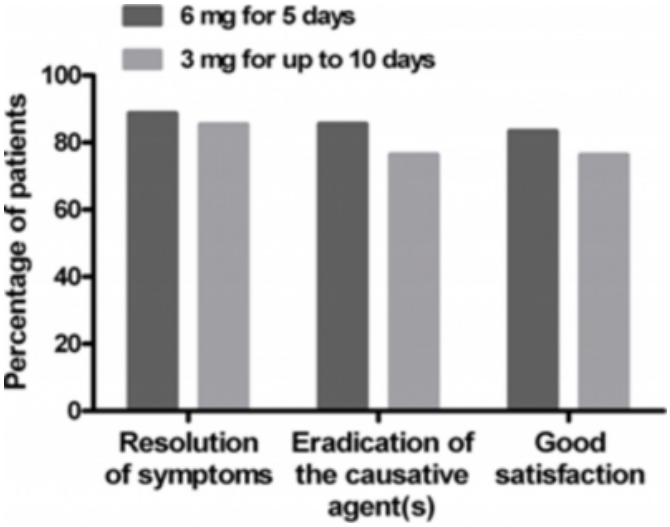
TREATMENT SUCCESS RATE AND ACCEPTANCE RATE BY DOSE AND TREATMENT DURATION

When the effectiveness of treatment was evaluated on the basis of the dose of intravaginal pentamycin administered

and duration of treatment, the overall treatment success rate was slightly higher with the dose of 6 mg daily for 5 days than with the dose of 3 mg daily for up to 10 days (Figure 4). Resolution of symptoms was experienced by 88.7% of patients who received the 6-mg dose regimen and by 85.4% of patients who received the lower dose for up to 10 days (Figure 4). Treatment success was confirmed on microbiology testing in 85.5% of cases treated with 6 mg daily of pentamycin for 5 days and 76.4% of cases treated with 3 mg daily for up to 10 days (Figure 4). Acceptance of treatment was rated as "good" by 83.4% of patients who used the higher dose of pentamycin for 5 days and by 76.3% of patients who received the 3-mg dose for up to 10 days (Figure 4).

Figure 6

Figure 4: Treatment success rates and acceptance rates in the groups of patients who received 6 mg daily of pentamycin for 5 days or 3 mg daily for up to 10 days, singly or in combination.



Treatment with intravaginal pentamycin, singly or in combination with other therapies, was tolerated well, irrespective of the dose and treatment duration. There was no report of local adverse events, such as irritation or burning, attributable to the use of this drug.

DISCUSSION

Most forms of vulvovaginal infections can be successfully treated by using one or more pathogen-specific antimicrobials, according to international guidelines and recommendation [149]. Oral metronidazole and the nitroimidazole derivative tinidazole are the primary drugs used for bacterial vaginosis and trichomoniasis, while topical azole antifungal agents are the first-line treatment for candidal vaginitis [124]. Mixed infections need treatment with a combination of drugs, which usually includes metronidazole and a topical azole antifungal medication [45]. However, many physicians find it difficult to diagnose accurately and manage effectively these disorders in clinical practice [18]. Before vaginitis is treated, the cause must be ascertained by using appropriate laboratory tests [1259]. This is often not done, and treatment failure results [518]. Moreover, some strains of Candida albicans resistant to topical azole antifungals [410] and strains of Trichomonas vaginalis resistant to treatment with metronidazole and tinidazole [192021] have been recently isolated, making it necessary to carry out susceptibility testing of microorganisms to the recommended antimicrobials in certain cases [4]. The results of this study suggest that vaginal pentamycin may be effective in more than one form of infectious vaginitis. Therefore its use in clinical practice would reduce the need for a confirmatory diagnosis and the risk of treatment failure.

This study included data from a relatively large number of patients, who had a complete evaluation of their disease and microbiology testing before and after treatment. Fifty percent of patients with trichomoniasis and over 60% of patients with candidiasis (63.4%) and mixed infections (69.6%) were treated with vaginal pentamycin alone. The vast majority of patients experienced resolution of symptoms by the end of the treatment period, irrespective of the infection type. Treatment success was confirmed by eradication of the causative agents in 100% of patients with vaginal trichomoniasis and in 87.8% of patients with vaginal candidiasis. These results support and extend, on a larger population of affected women, previous observations on the effectiveness of vaginal pentamycin for the treatment of vulvovaginal infections caused by Trichomonas vaginalis and Candida albicans [1517]. The treatment success rate for vaginal infections sustained by Candida albicans is similar to that reported in literature with topical azoles (80%-90%) [3].

This study also included patients suffering from vaginal infections caused by mixed microorganisms, which are considered difficult-to-treat forms of vaginal infections [1411]. Indeed, about one-third of these patients had not experienced any benefit from previous treatments with other antimicrobials. Treatment with vaginal pentamycin alone or in combination with other pathogen-specific drugs induced complete resolution of symptoms and eradication of the causative agents in 84% of patients. Most of the observed treatment success was due to intravaginal pentamycin

because this product was used alone by about two-third of patients.

Treatment with intravaginal pentamycin, singly or in combination with other therapies, was well-tolerated by patients, irrespective of the dose and treatment duration. The favorable tolerability profile of this drug is confirmed by the absence of reports of adverse events in the population of over 40,000 patients who have been treated with pentamycin in clinical practice since the first registration in Switzerland.

In addition to efficacy and tolerability, this study also examined patients' satisfaction with the use of intravaginal pentamycin. Treatment acceptance was rated as "good" by 100% of patients with vaginal trichomoniasis, 84.1% of patients with vaginal candidiasis and 78.3% of patients with mixed infections. These findings correlated with the treatment success rate reported for each type of vaginal infection and also confirmed the good tolerability of the drug.

When the effectiveness of treatment and its acceptance were evaluated on the basis of the dose of intravaginal pentamycin administered and duration of treatment, the overall treatment success rate was slightly higher with the dose of 6 mg daily for 5 days than with the dose of 3 mg daily for up to 10 days. Acceptance of treatment was rated as "good" by 83.4% of patients who used the higher dose of pentamycin for 5 days and by 76.3% of patients who received the 3-mg dose for up to 10 days. These results may reflect a better compliance with treatment when the drug was administered for a short period of time. However, the use of a high dose of pentamycin from the beginning of the treatment period may also increase the chance of complete eradication of the causative germs. In this context, it is worth noting that a 10-mg dosage strength of vaginal pentamycin (FemiFect®, Lumavita AG, Basel, Switzerland) is being developed for registration in the European Union and in the United states of America. This product may be effectively used once daily for shorter periods of time than the 3-mg dosage strength, thereby increasing patients' acceptance and compliance with treatment.

In conclusion, the results of this study suggest that intravaginal pentamycin, either alone or in combination with other therapies, may be effective for the treatment of vaginal candidiasis, trichomoniasis and mixed infections. The drug seems to exhibit a favorable tolerability profile and is well-accepted by patients. Controlled clinical trials and comparative studies in various forms of vaginal infections are warranted to substantiate the promising findings of this study.

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