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EVALUATION OF THE EFFICACY AND TOLERABILITY OF TWO DIFFERENT DOSAGES OF FENTICONAZOLE VAGINAL OVULES (600 MG AND 1000 MG) IN PATIENTS WITH VAGINAL TRICHOMONIASIS: A CONTROLLED, DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL VERSUS PLACEBO

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ABSTRACT

A double-blind clinical trial was performed in two clinical centers to evaluate the efficacy and the safety of two dose schedules of fenticonazole (one 600-mg or one 1000-mg ovule applied for 2 consecutive days) versus placebo in the treatment of vaginal trichomoniasis. Sixty-one patients were included in the study in the following three treatment groups: 600-mg ovules, 21 patients; 1000-mg ovules, 20 patients; and placebo, 20 patients. A vaginal swab was obtained before treatment and on day 7 for phase-contrast direct microscopic identification of *Trichomonas* species and a cultural examination was performed to exclude a possible mycotic or bacterial etiology. The severity of vaginal signs and symptoms (erythema, itching, discharge, edema, and burning) were evaluated with a semiquantitative scale (0 to 3). At baseline, all patients were positive for *Trichomonas vaginalis* on microscopic examination; on final evaluation the test was negative in 13 (65.0%) patients in the 600-mg group (one patient did not have a final examination performed), in 10 (58.8%) of the 1000-mg group, and in 3 (15.0%) of the placebo group. The difference between patients receiving active drug and placebo was highly significant (chi-square test, $P \leq 0.005$), while no significant difference existed between the two groups of drug-treated patients. A highly significant reduction of the symptomatic scores was observed in both active-treatment groups as compared with placebo, but, as in the case of the microbiologic findings, no difference was found between the two groups of fenticonazole-treated patients. Side effects of mild or moderate intensity were present in three patients in the 1000-mg dose group. Two patients had a burning sensation and one had a burning sensation and discharge. One of the patients with a burning sensation interrupted the treatment. Such symptoms could also be part of the underlying disease.

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INTRODUCTION

Trichomonas vaginitis is a common infection, normally transmitted by sexual intercourse, sustained by the protozoan *Trichomonas vaginalis*. It is estimated that more than 180 million women worldwide are infected by the parasite, even if not all of them develop clinically overt disease, since the infection is asymptomatic in about 50% of cases. About 30% to 70% of their sexual partners are also infected, at least transiently, and may develop urethritis or prostatitis.[1] In clinically overt vaginitis the parasite is often present in association with other pathogens, particularly yeasts. The treatment of vaginal trichomoniasis is therefore of outstanding social interest.

Fenticonazole, an imidazole derivative, synthesized and developed by Recordati S.p.A., Milan,[2,3] is one of the most effective and well-tolerated antimycotic compounds against dermatophytes and against various strains of *Candida* species. It also possesses a considerable in vitro antitrichomonas activity, even greater than that of other imidazole derivatives (tioconazole, clotrimazole, miconazole).[4] Its clinical efficacy and tolerability in the topical treatment of vaginal candidiasis is well documented.[5–8] Previous studies in vaginal trichomoniasis[9,10] and in mixed infections (*Trichomonas* species + *Candida* species)[11] have shown the good clinical and microbiologic efficacy of a single administration of the compound at a dose of 600 mg or 1000 mg. The higher (1000 mg) dose appeared more effective in one study (microbiologic sterilization in 64% versus 28%)[10] but both doses were equally effective (100%) in another study.[9] In two studies[10,11] in which a second dose of 600 mg was applied to the non-cured patients on days 4 and 7 a further 40% and 80% of the patients, respectively, were microbiologically cured at a follow-up examination. The above-mentioned data suggested that the most effective dose schedule of the drug in vaginal *Trichomonas* species infections still needs to be determined. The aim of this study was therefore to evaluate, using a double-blind, placebo-controlled design, whether two consecutive daily administrations of 600-mg or 1000-mg vaginal ovules were able to achieve a satisfactory cure rate of the disease.

PATIENTS AND METHODS

The study was done in a selected population of women with *Trichomonas* species as the single infectious agent; mycotic, bacterial, and mixed infections were considered exclusion criteria.

The trial was performed according to a controlled, randomized, double-blind, parallel-group design in two clinical centers: the Institute of Gynecology and Obstetrics, Genoa University, and the Second Obstetrics and Gynecology Clinic, Milan University.

Sixty-one patients, aged 18 to 70 years with *T vaginalis* infection as a single agent, confirmed by phase-contrast direct microscopic examination of vaginal swabs, were included in the study. The patients were in good general health: diabetic patients or those with liver, renal, cardiac disorders, or immunodeficiency were excluded. Patients who received topical administration of vaginal medications or systemic administration of antimicrobial and antiseptic agents during the 2 weeks prior to the trial; alcoholics or drug addicts; pregnant (confirmed or suspected) or lactating women; and patients simultaneously enrolled in other clinical trials were also excluded.

Patients were randomized into three groups (A, B, and C) to receive the following differential treatment: Group A: 600-mg fenticonazole, 1 ovule daily on days 1 and 2, followed by 600-mg placebo, 1 ovule daily on days 3 and 4; Group B: 1000-mg fenticonazole, 1 ovule daily on days 1 and 2, followed by 1000-mg placebo, 1 ovule daily on days 3 and 4; and Group C: 1000-mg placebo, 1 ovule daily on days 1, 2, 3, and 4. Placebo ovules were administered on days 3 and 4 to each trial group to discourage patients from taking self-prescribed treatments, particularly in the presence of persistent symptoms. The patients were not treated on days 5 and 6 to avoid interference with clinical and microscopic examinations performed on day 7. At the trial entry (day 0) and at the end of the trial (day 7), the patients were asked to assess the severity of their vaginal symptoms (itching, burning, and discharge) according to the following semiquantitative scale, where 0 = no discomfort, 1 = slight, 2 = moderate, and 3 = severe. Physicians evaluated the signs of infection (erythema and edema) using the same scale.

At day 0, a vaginal swab was obtained from each patient for phase-contrast direct microscopic identification of *Trichomonas* species and for cultural tests to exclude mycotic (mainly *Candida* species) and bacterial infections. At day 7, another phase-contrast direct microscopic examination was performed. The microbiologic test is considered the primary efficacy parameter; symptoms and signs, secondary parameters.

At the end of the trial, the investigator expressed his or her opinion on efficacy, based on symptoms and the result of the direct microscopic examination of swabs, graded according to the following scale: *Very good:* negative microscopic examination; the score for all, or at least 50% of symptoms and signs present on day 0, dropped by at least 2 points or fell to zero; *Good:* negative microscopic examination; the score for at least 50% of symptoms and signs present on day 0 was reduced; *Moderate:* positive microscopic examination; the score for at least 50% of symptoms and signs present on day 0 sensibly improved (dropped by 1 or more points); and *Absent:* positive microscopic examination; either the improvement in the score is reported for less than half of the symptoms and signs present on day 0 or the scores failed to drop by more than 1 point.

The occurrence of any possible adverse effect was monitored throughout the trial. Any adverse effect was evaluated according to its duration, severity, relation with the medication under evaluation, and action taken. The severity was defined as follows: *Mild:* the event is generally transient, does not require specific therapy, and does not interfere with the patient's daily activities; *Moderate:* the event produces a low level of inconvenience and might interfere with patient's daily activities. Such an inconvenience is normally ameliorated by simple therapeutic measures; *Severe:* the adverse event interrupts the usual daily activities of the patient and generally requires systemic drug administration or other treatment.

As required by the Helsinki Declaration, each patient provided her fully informed consent before participating. The study was approved by the relevant ethical committee.

The data obtained in the trial, expressed as mean values ± standard error (SE), were analyzed using parametric and nonparametric statistical procedures. More specifically, averages of the parametric variables were analyzed between treatment groups by one-way analysis of variance (ANOVA), including treatment as a factor. Nonparametric variables, expressed as scores, were analyzed with nonparametric tests: Wilcoxon test for paired data (baseline versus final evaluations), (Kruskal-Wallis nonparametric ANOVA) for observations between groups at baseline and final conditions, and Mann-Whitney U test for multiple comparisons. Contingency tables (Pearson's chi-square test) were used for nominal semiquantitative variables. The limit for rejection of the null hypothesis of no difference between groups was set for each procedure at the value of $P < 0.05$. All the calculations were performed on a Macintosh Quadra 700 computer, using the program Systat V.5.2 (Systat Inc., Evanston, Illinois).

RESULTS

Sixty-one patients were included in the study, randomized into the following three treatment groups: Group A: 600-mg ovules, 21 patients; Group B: 1000-mg ovules, 20 patients; and Group C: placebo, 20 patients. The demographic and admission variables in the three groups are shown in Tables I and II, respectively. After the randomization, three comparable groups were formed, using the demographic variables and the admission characteristics considered. No significant difference among these groups was shown after analyzing the data by the one-way ANOVA or by the contingency tables (chi square).

Efficacy was evaluated in 58 patients (two patients withdrew for personal reasons and one interrupted the treatment because of side effects). The three groups, 600-mg, 1000-mg, and placebo, were composed of 21, 17, and 20 patients, respectively.

Table I. Demographic variables in the three study groups. Values are expressed as mean ± SE.

	600-mg Ovules (n = 21)	1000-mg Ovules (n = 20)	Placebo (n = 20)
Age (y)	38.1 ± 2.3	41.4 ± 2.7	36.0 ± 2.0
Body weight (kg)	60.4 ± 2.0	59.9 ± 1.8	58.1 ± 1.3
Height (cm)	162.3 ± 1.2	163.2 ± 1.3	163.0 ± 1.1

At baseline, all patients had positive microscopic *T vaginalis* findings evaluated by phase-contrast direct microscopic examination. At the final evaluation, the examination was negative in 13 (65.0%) patients in the 600-mg group (one patient did not have a final examination performed), in 10 (58.8%) in the 1000-mg group, and in 3 (15.0%) in the placebo group.

The difference between treated patients and placebo patients was highly significant (chi-square test, $P \leq 0.005$), while no significant difference was observed between the two groups of active-treatment patients.

The mean values of the symptomatic scores recorded before and at the end of the study are shown in Table III. In the figure, the sums of the symptomatic scores recorded at baseline and final evaluation are presented.

At baseline, the mean intensity scores of all the evaluated symptoms were not significantly different among the three groups (Kruskal-Wallis

Table II. Admission characteristics in the three study groups.

	600-mg Ovules (n)	1000-mg Ovules (n)	Placebo (n)
No. of pregnancies	1.70 ± 0.32† (17)	1.64 ± 0.39† (17)	1.07 ± 0.21† (15)
Parity	1.2 ± 0.2† (20)	1.27 ± 0.24† (18)	1.26 ± 0.22† (13)
No. of abortions	0.75 ± 0.25† (12)	0.88 ± 0.30† (9)	0.50 ± 0.22† (10)
Method of contraception			
None†	13	15	12
Estro-progestogens	4	2	5
Intrauterine device	4	2	3
Condom	0	1	0
Menopause (no/yes)	19/2 (21)	17/3 (20)	17/3 (20)
Duration of actual vulvovaginal episode (d)	154.3 ± 75.1† (21)	50.8 ± 19.36† (20)	77.9 ± 38.68† (20)
Previous treatments for the actual episode (no/yes)	12/9 (21)	12/8 (20)	11/9 (20)
Previous vaginitis (no/yes)	9/12 (21)	8/11 (19)	10/10 (20)
Previous therapy for vaginitis (no/yes)	16/1 (17)	14/4 (18)	12/2 (14)

* Information was missing for some patients.
† Values are expressed as mean ± SE.

Table III. Mean scores of signs and symptoms recorded in the three groups of patients at baseline and at final evaluation. Values are expressed as mean ± SE.

	600-mg Ovules (n = 21)	1000-mg Ovules (n = 17)	Placebo (n = 20)
Erythema			
Baseline	1.42 ± 0.235	1.29 ± 0.20	1.20 ± 0.18
Final	0.71 ± 0.15†	0.47 ± 0.17*	0.85 ± 0.20
Itching			
Baseline	1.28 ± 0.19	1.29 ± 0.18	1.55 ± 0.15
Final	0.42 ± 0.13†	0.76 ± 0.13	1.25 ± 0.23
Discharge			
Baseline	2.28 ± 0.17	2.00 ± 0.17	2.25 ± 0.16
Final	1.33 ± 0.17†	0.88 ± 0.11†	1.35 ± 0.15*
Edema			
Baseline	1.14 ± 0.19	1.35 ± 0.20	0.95 ± 0.19
Final	0.42 ± 0.13†	0.29 ± 0.11†	0.75 ± 0.21
Burning			
Baseline	1.71 ± 0.26	1.76 ± 0.27	1.50 ± 0.18
Final	0.57 ± 0.23*	0.58 ± 0.22*	0.90 ± 0.19
Total scores			
Baseline	7.85 ± 0.74	7.70 ± 0.75	7.45 ± 0.51
Final	3.47 ± 0.63†	3.00 ± 0.60†	5.10 ± 0.87

* $P < 0.05$ versus baseline.
† $P < 0.01$ versus baseline.

nonparametric ANOVA). At the end of the trial, using the same statistical test, only itching appeared significantly different among the three groups analyzed, but if the baseline and final scores in the three treatment groups (Wilcoxon test) are compared, it appeared that symptomatic scores were nearly always significantly reduced by the drug treatment but never (except for discharge) by placebo. If the two active-treatment groups are compared, no statistically significant difference was observed for any symptom (Mann-Whitney U test).

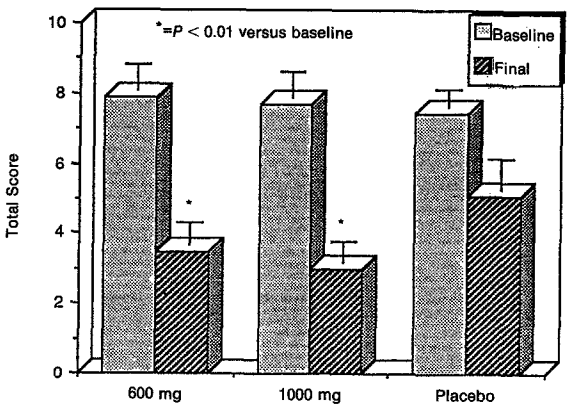

Figure 1. Total symptomatic scores (mean ± SE) in the three groups of patients.

The final evaluation of efficacy was "very good" or "good" in 13 (65%) of 20 patients in the 600-mg group (in one patient the evaluation was missing), in 10 (58.8%) of 17 patients in the 1000-mg group, and in 3 (15%) of 20 patients in the placebo group. When the active-treatment groups are compared with the placebo group, a statistically significant difference was observed (chi-square test, $P < 0.005$), while no statistically significant difference was observed between the two active-treatment groups.

Side effects of mild or moderate intensity were present in three patients in the 1000-mg dose group. Two patients had a burning sensation, and one patient had a burning sensation and discharge. One of the patients with burning sensation interrupted the treatment.

DISCUSSION AND CONCLUSION

This double-blind study has shown that fenticonazole is effective in eradicating *T vaginalis* infections in 60% to 65% of treated patients. About 60% of treated patients had a negativization of the swabs (evaluated by direct microscopic examination) and a substantial reduction of the vaginal symptoms at the final evaluation (7 days after initiating treatment).

There was no substantial difference between the two dose schedules used, both of which were significantly more effective than placebo. The 1000-mg ovules produced a slightly better response on local vaginal symptoms as indicated by the fact that the final symptomatic scores were lower than those of the 600-mg group. However, the difference between the two groups was not statistically significant, probably because of the relatively low number of patients included in this study. A bias might have been introduced by the fact that a smaller number of patients than originally planned were actually recruited.

The comparison of the results obtained in this clinical trial with those of previous studies in which fenticonazole was used in vaginal trichomoniasis is not straightforward. Few studies[9–11] are available, and none of them used the dose schedule of 2 consecutive days. Also, methodological differences may affect comparison. For example, in the pilot study by Manth et al,[9] the final evaluation was done 1 or 2 days after the single-dose therapy in a small number of patients. Although unlikely, this short-interval evaluation after treatment might have underestimated possible recurrences. The methodological difference and the relatively short median duration of the infectious episodes of the patients included in that study (14 days) might explain the high sterilization rate (almost 100%) achieved by these authors with a single 600-mg or 1000-mg vaginal ovule.

In another study by Gorlero et al,[10] the higher single 1000-mg dose appears to be more effective than the single lower 600-mg dose in producing the microbiologic sterilization of the swabs obtained a week later (64%

versus 28%). The 64% value is very similar to the microbiologic result obtained in the study described here with two 600-mg ovules (a total dose of 1200 mg). Since two consecutive 1000-mg ovules did not prove more effective in the present trial, at least considering the microbiologic results, it is likely that the best therapeutic regimen could be considered a single 1000-mg ovule administration or two consecutive 600-mg ovules per day. A direct comparison of these two treatment schedules is obviously necessary for a proper validation of this working hypothesis.

Fenticonazole is also very effective against *Candida* species and therefore could be useful in treating the relatively frequent mixed vaginal infections, as recently shown by Bukovsky et al[11] in an open clinical trial involving 87 patients. It is better to treat vaginal infections topically rather than orally (usually with metronidazole), because oral treatments are often associated with poor patient compliance due to their long duration (6 to 7 days) and associated side effects. Moreover, even if metronidazole appears to be safe in humans, there is some experimental evidence that metronidazole is carcinogenic in rodents and mutagenic in bacteria.[1]

Finally, we want to underline that fenticonazole ovules in this, as in previous studies of vaginal infections,[5–11] were very well tolerated. Only slight local side effects were reported in very few patients, and no systemic reactions were reported. Systemic reactions are unlikely since fenticonazole is systemically poorly absorbed.[12] Moreover, the side effects usually reported, burning sensation and discharge, are also symptoms of the underlying disease, and therefore may not be related to drug treatment.

References:

1. Plorde JJ. Trichomoniasis and other protozoan infections. In: *Harrison's Principle of Internal Medicine.* 12th ed. New York: McGraw-Hill, Inc: 1991:805–807.
2. Nardi D, Cappelletti R, Catto A, et al: New alpha-aryl-beta,N-imidazolylethyl benzyl and naphthylmethyl ethers with antimycotic and antibacterial activity. *Arzneim-Forsch/Drug Res.* 1981;31:2123–2126.
3. Tajana A, Cappelletti R, Leonardi A, et al. Synthesis and antimycotic activity of alpha-aryl-beta,N-imidazolylalkyl benzyl ethers. *Arzneim-Forsch/Drug Res.* 1981;31:2121–2123.
4. Fontana C, Cammarata E, Greco M, Oliveri S. In vitro activity of fenticonazole on *Trichomonas vaginalis* and *Gardnerella vaginalis. Curr Ther Res.* 1990;48:44–51.
5. Gastaldi A. Treatment of vaginal candidiasis with fenticonazole and miconazole. *Curr Ther Res.* 1985;38:489–493.
6. Brewster E, Monici Preti P, Ruffmann R, Studd J. Effect of fenticonazole in vaginal candidiasis: A double-blind clinical trial versus clotrimazole. *J Int Med Res.* 1986;14: 306–310.
7. Wiest W, Ruffmann R. Short-term treatment of vaginal candidiasis with fenticonazole ovules: A three dose schedule comparative trial. *J Int Med Res.* 1987;15:319–325.

8. Studd J, Dooley MM, Welch CC, et al. Comparative clinical trial of fenticonazole ovule (600 mg) versus clotrimazole vaginal tablet (500 mg) in the treatment of symptomatic vaginal candidiasis. *Curr Ther Res.* 1989;11:477–483.

9. Manth SM, Rindt W, Schnitker W, et al. Fenticonazole in the treatment of vaginal Trichomonas infections. *Curr Ther Res.* 1989;45:1060–1066.

10. Gorlero F, Bosco P, Barbieri M, et al. Fenticonazole in the treatment of vaginal Trichomonas infections: A double-blind randomized pilot clinical trial. *Curr Ther Res.* 1992; 51:367–376.

11. Bukovsky I, Schneider D, Arieli S, Caspi E. Fenticonazole in the treatment of vaginal trichomoniasis and vaginal mixed infections. *Adv Ther.* 1991;8:166–171.

12. Novelli A, Periti E, Massi GB et al. Systemic absorption of 3H-fenticonazole after vaginal administration of 1 gram in patients. *J Chemother.* 1991;3:23–27.