Frequent Use of Menfegol Spermicidal Vaginal Foaming Tablets Associated with a High Incidence of Genital Lesions

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Menfegol is a spermicide with in vitro activity against human immunodeficiency virus (HIV). A randomized placebo-controlled safety study covered the use of menfegol foaming tablets for 14 days at increasing frequencies of insertion by 125 prostitutes in Dakar, Senegal. The frequencies of colposcopically diagnosed genital lesions were 5.0%, 11.8%, 27.8%, 49.7%, and 29.4% among menfegol recipients when tablets were used once every other day or 1, 2, 4, or 8 times a day, respectively ($P < .05$). Among placebo recipients, frequencies were 11.1% and 23.5% when tablets were used <8 times daily and 8 times daily, respectively. There was no association between subjective genital symptoms and the incidence of colposcopically detected lesions. The high incidence of genital lesions when menfegol foaming tablets were used more than once daily suggests that their frequent use should not be recommended to prevent HIV transmission. In use at low frequency, the tablets' toxicity might be balanced by anti-HIV properties. Safety studies on vaginal microbicides should use objective methods, such as colposcopy, to assess the incidence of lesions.

Currently, the only readily available device to decrease the transmission of human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs) is the male condom. As many women are unable to negotiate condom use, there is a need for methods they can use without the consent of their sex partners [1].

The use of spermicides with in vitro anti-HIV activity is already being promoted to decrease HIV transmission [2]. However, this is highly controversial. There is evidence that spermicides might protect against the transmission of other STD pathogens [2], and field studies suggest protection against HIV infection as well [3, 4]. However, there are no data from clinical trials to clearly show a protective effect against HIV infection. Spermicides might even increase the efficacy of HIV transmission; the use of high doses of the spermicide nonoxynol-9 has been associated with genital ulcerations [5, 6]. This is one of the possible explanations of the lack of protection against HIV infection in a randomized controlled trial of a sponge with a high dose of nonoxynol-9 among female sex workers in Nairobi [7].

Menfegol (*p*-methanylphenyl polyoxyethylene [8,8] ether) is a spermicide available in many developing countries as Neo Sampoon (Eisai, Tokyo) vaginal foaming tablets. In vitro studies have shown the susceptibility of *Neisseria gonorrhoeae*, *Haemophilus ducreyi*, *Gardnerella vaginalis*, and HIV to menfegol [8–11]. The efficacy of menfegol against STDs and HIV infection has not been assessed in vivo. From clinical trials on the contraceptive efficacy of menfegol foaming tablets, limited safety data are available: Only 5.0–9.6 complaints/100 women-years were reported in various studies [12–15]. The local toxicity of menfegol foaming tablets on the genital mucosa and systemic toxicity have not been studied previously. Both were assessed in the present safety study.

Materials and Methods

Study design. The trial was a placebo-controlled, randomized, double-blind (for tablet content) study of intravaginally administered menfegol foaming tablets used at increasing frequencies of insertion. The outcomes of interest were the incidence of genital lesions resulting in disruption of the genital mucosa and other adverse events.

Study population. Self-declared prostitutes, 18–45 years old, attending the STD clinic of the Institut d'Hygiène Social in Dakar were eligible if they had a normal pelvic condition (no clinical or colposcopic evidence of STD, vaginitis, cervicitis, or other

Received 6 June 1994; revised 5 January 1995.

Witnessed verbal informed consent was obtained from each participant. The protocol for this study was developed by Family Health International, Division of Reproductive Epidemiology and Sexually Transmitted Diseases, Research Triangle Park, NC. The study was approved by the Ethics Committee of the National AIDS and STD Programme of Senegal and by the World Health Organization (WHO) Secretariat Committee on Research Involving Human Subjects and carried out in observance of the "Proposed International Guidelines for Biomedical Research Involving Human Subjects," issued in 1982 by the Council of International Organizations of Medical Sciences and WHO.

Financial support: Global Programme on AIDS of WHO (CRD/91/0102).

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The Journal of Infectious Diseases 1995;171:1611–4

0022-1899/95/7106-0033$01.00

abnormalities) and were within 1 week of completion of their most recent menses. Exclusion criteria were pregnancy in the previous 42 days, history of an adverse reaction to a spermicidal product, and use of medication other than oral contraceptives. If, after enrollment, it was found that asymptomatic genital infection had been present at enrollment, participants were treated for it but were not excluded from the study.

Participants were asked to abstain from sexual intercourse or to use a condom during intercourse. Condoms (with a lubricant free of spermicidal products) were provided to all participants to improve compliance with the latter recommendation.

Participants were requested not to apply vaginal douches; not to insert tampons, antiseptic solutions, or other objects in the vagina; and to refrain from washing until at least 6 h after insertion of the last tablet of the day.

The recruitment target for the study was 225 participants (35 receiving menfegol plus 3 receiving placebo in each frequency-of-insertion group and 35 on placebo 8 times daily). Only 3 placebo patients were included in each frequency-of-insertion group, because placebos were used only to mask tablet content for the investigator. The number in each treatment arm was planned to be 35 to allow detection of a 5% frequency of lesions with 80% power.

Study drugs and drug administration. Menfegol tablets consisted of 60 mg of menfegol and incipients (dioctyl sodium sulfosuccinate, potassium bitartrate, sodium bicarbonate, light anhydrous silicic acid, corn starch, microcrystalline cellulose, egg-white powder, polyvinyl pyrolidon K30, and calcium stearate) to a total weight of 800 mg. Placebo tablets consisted of 800 mg of the incipient. Eisai provided all trial drugs.

Eligible subjects received a unique incremental study number corresponding to her personal supply of prerandomized study medication and to an insertion frequency (1 every other day or 1, 2, 4, or 8 times daily) of intravaginally administered tablets. Participants allocated to >1 tablet per day were asked to allow at least 1 h between insertions. Treatment was for 14 days unless an adverse event occurred or a vaginal or cervical lesion was found. If a genital lesion was found, the participant was asked to return 1 week later for reexamination.

Follow-up procedures. Evaluations were scheduled on days 0, 7, and 14, and participants were asked to come to the clinic if they encountered health problems between scheduled visits. At each visit, a medical history with focus on gynecologic problems was obtained, and colposcopy of the vagina and cervix was done. Microscopy of vaginal contents (for detection of *Trichomonas vaginalis*, yeasts, and clue cells) and culture of *N. gonorrhoeae* from an endocervical swab were done to assess the presence of genital pathogens on days 0 and 14 routinely and on day 7 in case of clinical suspicion of an STD (i.e., presence of endocervical pus or abundant vaginal secretions). Blood samples for blood chemistry (total and direct bilirubin, liver enzymes, urea, creatinine, total protein, albumin, globulins, total cholesterol, triglycerides, and high-density lipoproteins) were obtained on days 0 and 14.

Statistical analysis. The analysis was an intention-to-treat analysis, including all randomized subjects. The comparability of study groups was assessed using the χ^2 test, Fisher's exact test, the t test, the Wilcoxon two-sample test, or the Kruskal-Wallis test, as appropriate. The incidence of lesions was estimated and compared by methods for the analysis of survival data, including proportional hazards regression. Differences were considered significant at a two-sided significance level of $P \leq .05$. Vaginal and cervical lesions were considered related to study drug administration only if no concomitant disease was identified that might have explained the lesion(s).

Results

Study population. Enrollment started on 28 February 1992 and provisionally stopped because of a high incidence of genital lesions on 29 April 1992, when 125 of the planned 225 participants were enrolled. The study was permanently stopped by the Data and Safety Monitoring Board on 28 June 1992.

At baseline, participants in each treatment group were similar with respect to age (mean, 31.4 years; range, 22–44), number of sex partners per week (median, 3), prevalence of genital symptoms at enrollment, and prevalence of asymptomatic genital infection (36.8% among all participants). During the study, only 4 subjects receiving menfegol and 2 receiving placebo were lost to follow-up; 2 subjects withdrew consent to participate.

Genital lesions. Twenty-seven participants developed genital lesions considered to be caused by the tablets. Of these 27, 16 developed lesions within the first 7 days of tablet use, and 11 between 7 and 14 days. Twenty-two were menfegol recipients and 5 placebo recipients. The lesions attributed to study drug use were erosions with an erythematous or edematous wall with or without bleeding (20 lesions), breaks of the cervical epithelium with a thin layer of sloughed cells still attached (14), and a bullous semiannular lesion on the cervical mucosa (1). Several women had >1 lesion. When lesions were present, the cervix was always involved. Only 3 subjects had vaginal as well as cervical lesions.

Three subjects developed genital lesions unrelated to or of uncertain relationship to study drug use (1 subject with an endocervical polyp, 1 with concomitant candidiasis, and 1 with trichomoniasis). Two subjects developed an abnormality that rendered their evaluation impossible (both had a pronounced, thick, adherent white deposit on the cervix and vaginal wall, possibly representing the remainder of undissolved tablets).

When lesions or abnormalities occurred, use of the tablets was discontinued, but no specific treatment was given. In all 25 evaluable cases, lesions or abnormalities had healed (19 cases) or at least significantly improved (6) within 7 days.

Table 1 shows Kaplan-Meier estimates of the incidence of genital lesions over the 14-day follow-up period, with rate ratios comparing the incidence of lesions in the higher-dose groups to that in the lowest-dose groups for menfegol and placebo recipients. Incidences of lesions related to the use of menfegol tablets were 5.0%, 11.8%, 27.8%, 49.7%, and 29.4% for 1 tablet every other day and 1, 2, 4, and 8 tablets daily,

Table 1. Incidence of genital lesions attributed to the use of menfegol or placebo tablets after 14 days of follow-up.

Frequency of administration	*n*	No. developing genital lesions	Incidence of genital lesions: Kaplan-Meier incidence, %	95% CI	Rate ratio*	95% CI
Menfegol						
1/2 days	23	1	5.0	0.0–14.6	—	—
1/day	18	2	11.8	0.0–27.1	2.5	0.2–29.0
2/day	22	6	27.8	8.9–46.8	7.3	0.9–62.8
4/day	17	8	49.7	24.8–74.6	16.6	2.0–138.0
8/day	17	5	29.4	7.8–51.1	7.9	0.9–70.3
Placebo						
1/2 days to 4/day	11	1	11.1	0.0–31.6	—	—
8/day	17	4	23.5	3.4–43.7	2.4	0.3–22.7

NOTE. CI, confidence interval.
* Relative to lowest dosage groups.

respectively. The incidence of lesions among placebo-treated subjects was 11.1% when tablets were used up to 4 times daily and 23.5% when tablets were used 8 times per day. Proportional hazards regression showed that there was a significant relationship between the incidence of lesions and the frequency of tablet use ($P < .05$).

The incidence of lesions among the 85 participants (evaluable at day 14) who reported sexual intercourse during the study and the 27 who did not was similar (relative risk [RR] of lesions with a history of sexual intercourse, 0.91; 95% confidence interval [CI], 0.43–1.91). Participants with and without asymptomatic genital infection on entry to the study also had a similar incidence of genital lesions (RR of lesions in the presence of genital infection, 0.52; 95% CI, 0.21–1.27).

Relationship between symptoms and genital lesions. Table 2 shows the relationship between incident symptoms (i.e., symptoms that were not present on enrollment and appeared during the 14-day follow-up) and lesions. There was no statistically significant relationship between any of the symptoms and the occurrence of lesions. Many lesions would have escaped detection if the participants had been investigated only when symptoms occurred.

Systemic toxicity. The mean values of all blood chemistry tests remained within normal ranges. No subjects developed general symptoms that could be related to tablet use.

Discussion

The main finding of the present study was a high incidence of lesions of the genital mucosa when menfegol foaming tablets were used more than once per day. As there was also a high incidence of lesions among placebo recipients, the vehicle of the foaming tablets clearly contributed to the product's toxicity. The increasing incidence of lesions with increasing frequency of administration and the lesions' rapid healing when tablets were stopped indicate that the lesions were caused by the tablets. All lesions considered due to the study

Table 2. Relationship between the incidences of symptoms and of lesions.

Symptom	Had symptom on entry	Did not have symptom on entry: Developed symptom: developed lesion — Yes	Developed symptom: developed lesion — No	Did not develop symptom: developed lesion — Yes	Did not develop symptom: developed lesion — No	Sensitivity*	Specificity*
Vulvar itching	10	1	11	14	79	1/25 (4)	79/90 (88)
Vaginal irritation	12	3	7	22	81	3/25 (12)	81/88 (92)
Vaginal discharge	22	6	16	13	68	6/19 (32)	68/84 (81)
Lower abdominal pain	4	4	7	21	89	4/25 (16)	89/96 (92)
Genital bleeding	1	4	12	23	85	4/27 (15)	85/97 (88)
Any symptom	40	10	24	6	45	10/16 (63)	45/69 (65)

NOTE. Nos. in parentheses are %. No differences were statistically significant.
* Of appearance of new symptom for detection of a lesion.

drug constituted breaks in the genital mucosa and may facilitate HIV transmission. Thus, high-frequency use of the current formulation of menfegol tablets cannot be recommended to prevent HIV transmission. A similar dose-dependent incidence of lesions was found with nonoxynol-9 suppositories [5, 6].

We feel less confident about the interpretation of the lower incidence of lesions with 1 tablet every other day or 1 daily, because an untreated control group was not available. When the present study was designed, it was not possible to manufacture a placebo for intravaginal use, as inert carriers for intravaginal use were not available. Other controlled studies on the safety of spermicides are similarly flawed, with high incidences of genital lesions in control groups receiving "placebo" frequently (e.g., 14.7% of participants receiving 4 "placebo" suppositories/day in a study by Roddy et al. [6]). A lesson for the future is that safety studies on vaginal microbicides should include an untreated control group.

Another lesson from the present and previous studies [5, 6] is that the incidence of genital lesions should be assessed by objective methods and not by history. Genital symptoms were poor predictors of the presence of lesions, presumably because the cervix and upper vagina lack sensory nerve receptors. We suggest that colposcopy should be used for the assessment of genital lesions because of its high sensitivity and specificity and because of the ease with which lesions can be documented photographically.

The conduct of the study among prostitutes in a developing country (albeit with low HIV prevalence) needs some comment. At the time this study was planned, no studies assessing the effect of menfegol or nonoxynol-9 on the genital mucosa had been published. Menfegol tablets were considered safe because few symptoms were reported in studies on their use as a spermicide [12–15]. In retrospect, the absence of toxicity in previous studies could probably be explained by the lack of correlation between symptoms and lesions, which remained undetected because colposcopy had not been used. While a study among prostitutes was approved because it was thought that they would benefit most from its results, it is clear that the participants may have been at increased risk of acquiring HIV infection during the study. To avoid this, future initial safety studies with vaginal microbicides should be conducted among healthy volunteers at low risk of HIV infection.

Acknowledgments

We thank the staff of the Service de Maladies Sexuellement Transmissibles, Institut d'Hygiène Social, Dakar, and Jan Vielfont for their support.

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