Sexually Transmitted Diseases, July 2007, Vol. 34, No. 7, p.519–522
DOI: 10.1097/01.olq.0000253340.76118.89

Safety Trial of the Vaginal Microbicide Cellulose Sulfate Gel in HIV-Positive Men

VICKY JESPERS, MD,* ANNE BUVE, PHD,† AND LUT VAN DAMME, PHD†

Objective: **Cellulose sulfate (CS) is a promising vaginal microbicide. Because men will be exposed to the microbicide when engaging in vaginal intercourse, safety and acceptability need to be assessed in men.**

Design: **This randomized double-blind phase I study assessed the safety and acceptability of seven consecutive daily doses of CS versus KY Jelly in 36 HIV-positive men.**

Results: **No new or worsening of existing genital findings were observed during the follow-up examination. Mild genital symptoms were reported in 42% of CS users (itching, burning, tingling, testicular pain, dysuria, and warm or cold feeling) and 8% of KY Jelly users.**

Conclusion: **CS gel applied to the penis was well tolerated in this HIV-positive male population. The itching and burning symptoms were not severe and can be explained by the preservative benzyl alcohol present in the CS gel.**

EFFICACIOUS FEMALE-CONTROLLED PREVENTION METHODS are urgently needed to help women protect themselves against HIV and other sexually transmitted infections.[1,2] Microbicides are topical formulations designed to block HIV infection when applied vaginally before intercourse.[3] An ideal microbicide should be safe and acceptable to both women and their male partners, and thus safety and acceptability trials need to be done in men as well as in women.[4] In addition, safety needs to be established in HIV negative and HIV-positive individuals.[5]

Cellulose sulfate (CS) gel is in clinical development as a microbicide and a contraceptive.[6,7] It is a noncytotoxic, anionic polymer that possesses in vitro antimicrobial activity against sexually transmitted pathogens. Complete inhibition of infection of HIV-1, HIV-2, HSV-2, and HPV has been shown in vitro at concentrations less than 200 μg/mL.[8,9] Fifty percent inhibition of *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, *G. vaginalis, T. vaginalis, C. albicans, S. aureus*, and *P. aeruginosa* was seen at concentrations ≤12 mg/mL. Importantly, no effect on lactobacilli was observed.[10] CS has a nonspecific action on HIV and possibly a direct inhibitory activity on HIV receptors.[3,9]

CS has been tested as a vaginal microbicide in five safety trials in women and in one safety trial of penile applications in HIV negative men.[11–15] More recently CS was tested in two contraceptive studies enrolling a total of 233 couples.[16] The results of these studies suggest that CS is as safe and acceptable as marketed spermicides and sexual lubricants as well as the "universal placebo." Two HIV prevention trials are currently ongoing.[6]

The authors thank all the participants, without whom the study would not have been possible, and Tessa James, our dedicated study nurse.

This work was supported by CONRAD with funds provided by USAID.

Correspondence: Vicky Jespers, MD, STD/HIV Research and Intervention Unit, Institute of Tropical Medicine, 2000 Antwerp, Belgium. E-mail: vjespers@itg.be.

Received for publication April 12, 2006, and accepted October 28, 2006.

*From the *Institute of Tropical Medicine, Antwerp, Belgium; and †CONRAD, Arlington, Virginia*

To ensure the safety of male sexual partners of the female participants in the HIV prevention trials and to meet the requirements of drug-regulating authorities, we performed a phase I study of CS in HIV-positive men.

Methods

Study Design

This randomized phase I double-blind, placebo-controlled trial was conducted in 2003–2004 at the Institute of Tropical Medicine (ITM), Antwerp, Belgium; and was approved by its ethical committee, as well as the Institutional Review Board of the Eastern Virginia Medical School (Norfolk, VA). Study volunteers were recruited through existing databases and advertisements approved by the ethical committee. The trial was designed to determine the safety of seven consecutive daily doses of CS (2 mL) compared to KY Jelly (2 mL) when applied to the penis in HIV-positive men. End points were defined by signs and symptoms of genital irritation, other adverse experiences, changes in laboratory parameters, and product acceptability. Evidence of genital irritation included itching, tingling, burning, unusual discharge, and genital pain, as well as signs of irritation identified on examination of the genitalia with a handheld magnifying glass. Product acceptability was assessed through a questionnaire.

Thirty-six men, 18 circumcised and 18 uncircumcised, were enrolled and randomly assigned to 6% CS gel or KY Jelly in a 2:1 ratio, stratified by circumcision status. Twelve circumcised and 12 uncircumcised men were assigned to CS gel and 6 circumcised and 6 uncircumcised men to KY Jelly. Since this was a phase I study, the sample size was based on the usual number enrolled in phase I microbicide safety trials and on the number that was thought feasible to enroll rather than on statistical considerations. No statistical tests on end points were planned for and data are presented by descriptive statistics. The 2 mL study product was packaged in prefilled single-use applicators. The 2 mL CS gel contained 120 mg sodium cellulose sulfate, 5% sorbitol and 5% glycerine as humectants, 0.25% carbomer as thickener, 1% benzyl alcohol as preservative and water. The inactive control was KY Jelly personal lubricant (Personal Products Company, Skillman, NJ).

Enrollment of Study Participants

Participants were at least 18 years of age, HIV-positive but in good general health with a CD-4 count of ≥200 cells/mm^3, no

TABLE 1. Baseline Characteristics of Study Participants

	Uncircumcised		Circumcised		
	CS (n = 12)	KY (n = 6)	CS (n = 12)	KY (n = 6)	All Participants (n = 36)
Mean age in years (range)	39.9 (26–47)	39.3 (24–55)	41.8 (19–61)	40.2 (27–64)	40.5 (19–64)
Ethnic group (%)					
Caucasian	10 (83.3)	5 (83.3)	8 (66.7)	4 (66.7)	27 (75)
African/Caribbean	0 (0)	1 (16.7)	4 (33.3)	2 (33.3)	7 (19.4)
Hispanic	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (2.8)
Other	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (2.8)
Partner status (%)					
Living with partner	7 (58.3)	4 (66.7)	6 (50)	1 (16.7)	18 (50)
Not living with partner	5 (41.7)	2 (33.3)	6 (50)	5 (83.3)	18 (50)
No partner	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mean CD4 count (range)	594 (252–1144)	543 (460–595)	500 (338–748)	641 (290–1524)	562 (252–1524)

change in HIV treatment in the last 30 days, or no expected change before study completion. Participants agreed to abstain from all activities that could cause irritation or injury to the penis during the 7 days of product use. Participants were excluded if they had genital pain at enrollment, a recent sexually transmitted infection (STI), an allergy to constituents of the study products, a genital piercing, a dermatological, medical or social condition likely to affect the interpretation of study results or patient safety; or if they had participated in another investigational study in the past month. Withdrawal was to be instituted for medical or personal reasons, failure to follow protocol requirements, and a current STI.

Volunteers were screened at the ITM HIV clinic or by telephone for eligibility, and if eligible, they were given an appointment for the screening visit. The study was explained in detail at this visit and all participants provided written informed consent before starting the study procedures. The next two visits (enrollment and follow-up) were planned within 1 month. Study participants were randomized at the enrollment visit by entering their names on the next line of the trial register. The trial number in the register determined the prelabeled boxes to which they had been allocated. Only in case of an emergency could individual details of treatment, available in sealed envelopes, be accessed by the investigator.

Assessment of Study Participants

Participants were assessed on three occasions: at screening, at enrollment and at follow-up (the day after finishing the study product). At screening a medical history was taken and blood samples were taken for serum chemistries, blood counts and CD4 count. At each visit a symptom-directed physical examination and genital examination with the naked eye and hand-held magnifying lens were done. The baseline appearance of the penile shaft, foreskin, glans, scrotum, and urethral meatus was recorded. Digital photographs were taken of all abnormalities and as a standard procedure at enrollment and follow-up for comparison. At enrollment, the participants' laboratory results were reviewed to confirm eligibility. Eligible candidates were provided with the seven disposable applicators (as assigned by randomization), detailed oral and written product use instructions, and instructions on how to complete the study diary. The gel was to be applied to the dorsal aspect of the penis and spread out evenly each night before retiring for seven consecutive nights. In the morning, 6 to 10 hours after the application, the gel had to be washed off with water and/or soap. Application and removal times as well as any adverse events were noted on the diary card. At the follow-up visit, planned within 24 hours of the last application, the diary card was reviewed and a short acceptability questionnaire was completed by the participants. Blood samples were collected for serum chemistries and blood counts to assess systemic toxicity.

Results

Baseline Data

Of the 40 men screened, 36 men were enrolled in the study (24 in the CS gel group and 12 in the KY Jelly group) and all 36 completed the study. Participants' baseline characteristics are summarized in Table 1.

There were very few findings on the physical examination at baseline. One person (CS) had a seborrheic keratosis on the penile shaft, two men (CS and KY) had erythema on the glans, and one person (KY) had a sebaceous cyst on the scrotum. Most men were taking antiretrovirals at baseline. Blood values were out of normal range (±20%) at screening for 10 (41.7%) and 6 (50%) men in the CS and KY Jelly group, respectively. All but one (a low bilirubin) were related to blood count results and in 25% of men the mean cellular haemoglobin was raised more than 20%. These abnormal blood count results were longstanding and related to the use of antiretroviral medication.

Compliance and Sexual Activity

Compliance with use of the study gel was very good (99.2%). Thirty-five men used the gel seven times and one person used the gel five times. Each single application stayed on the penis for an average of 9.3 hours (range 8–13, SD 1.1) and 9.5 hours (range 8–11, SD 0.75) for the CS and KY jelly groups, respectively. Fifty percent of participants in the CS group as well as the KY group left the gel on for more than 10 hours, on at least one occasion. Two participants violated the protocol by masturbating on one occasion.

Adverse Events

There were no new or worsening findings on clinical examination during the study. The erythema in the participant in the CS group had disappeared at the final visit and the other findings remained the same. Ten men (42%) in the CS group, 7 circumcised and 3 uncircumcised, and one circumcised person (8%) in the KY Jelly group experienced symptoms of genital irritation. Thus more circumcised men (44%) reported symptoms than uncircumcised men (17%). Reported symptoms are summarized in Table 2. Tingling and burning were the most frequent symptoms, reported by 29% of men in the CS group and by 0% of men in the KY jelly

TABLE 2. Summary of Symptoms of Genital Irritation

	CS (n = 24)		KY (n = 12)		All Participants (n = 36)	
Symptom	No. Men (%)	No. Reports (%)	No. Men (%)	No. Reports (%)	No. Men (%)	No. Reports (%)
Tingling	4 (16.7)	7 (31.8)	0 (0)	0 (0)	4 (11.1)	7 (29.2)
Itching	1 (4.2)	1 (4.5)	0 (0)	0 (0)	1 (2.8)	1 (4.2)
Burning	3 (12.5)	9 (40.9)	0 (0)	0 (0)	3 (8.33)	9 (37.5)
Testicular pain	1 (4.2)	1 (4.5)	0 (0)	0 (0)	1 (2.8)	1 (4.2)
Dysuria	1 (4.2)	1 (4.5)	1 (8.3)	2 (16.7)	2 (5.5)	3 (12.5)
Cold feeling	2 (8.3)	2 (9.1)	0 (0)	0 (0)	2 (5.5)	2 (8.3)
Warm feeling	1 (4.2)	1 (4.5)	0 (0)	0 (0)	1 (2.8)	1 (4.2)
*Total**	*10 (41.7)*	*22 (100)*	*1 (8.3)*	*2 (16.7)*	*11 (30.5)*	*24 (100)*

*Total may be less than the sum of the individual symptoms since each participant may have reported more than one symptom.

group (two-sided Fisher exact test; $P = 0.07$). All but one of the symptoms, a case of tingling in the CS uncircumcised group which was classified as not product related, had resolved by the time of discontinuation. All symptoms were reported as mild.

Fifty percent of men in both groups had out of range laboratory values at the final visit (Table 3). These out of range values were already present at baseline for 14 out of the 18 (77.8%) men. The new abnormal values for the CS group consisted of an increase in LDH on two occasions, a decrease in bilirubin, an increase in ALT and an increase in leucocytes. In the KY Jelly group, the new abnormal values were an increase in leucocytes and an increase in neutrophils. All changes were classified as mild, not clinically significant and not product related.

Acceptability

Ease of use was the aspect most liked by 37% of CS gel, users and 17% of KY gel users. The aspects of the gel least liked were stickiness and slowness of drying which were reported by 33% and 12% of men in the CS group and 42% and 33% in the KY Jelly group, respectively. Men with symptoms were slightly less likely to complain of stickiness than men without symptoms (40% vs. 50%). The overall acceptability was the same for men with symptoms compared to men without.

Discussion

This was the second male tolerance study with cellulose sulfate and the first in HIV-positive men.[13] In our study, KY Jelly was used as the control product. In the ongoing phase III trials for HIV prevention, a hydroxyethylcellulose-based gel, the "universal" placebo is being used.[17]

There were no new findings during the clinical examination, and one of the preexisting findings of erythema (CS) of the glans disappeared. All symptoms were mild and those that were classified as related to product use had resolved by the final visit. More men in the CS group (42%) than in the KY Jelly group (8%) had symptoms. Seven out of the 24 CS users (29%) complained of a mild tingling and/or burning feeling compared to none in the KY Jelly group. No relationship was seen between reporting of symptoms and leaving the product on for more than 10 hours, masturbation, race or past dermatological problems. It was expected that trapping of product under the foreskin would lead to symptoms, but circumcised men (44%) reported more symptoms than uncircumcised men (17%). In the CS study among HIV negative men, only one person (4%) in the CS group had symptoms (mild tingling and burning) versus 3 (25%) in the nonoxynol-9 control group.[13] In this study, methylparaben was the main preservative in the CS gel. The CS study gel composition had been changed before our study to include benzyl alcohol in the vehicle. We think that the benzyl alcohol could be responsible for the "tingling" symptom (32% of reported symptoms), as this symptom is a common side effect of topical products with benzyl alcohol as the preservative. It is thought that the tingling and burning experienced by men will be less after vaginal exposure because of dilution of the product by vaginal fluids and the shorter length of exposure. Acceptability in a recent 6 month contraceptive trial exposing men to CS with the same formulation was high, with three quarters of men and women liking the product.[16] The final results of this study may provide more data on symptoms men experience after vaginal exposure.

The high number of out-of-range laboratory values at baseline was unanticipated but was clinically acceptable in the context of HIV illness. All shifts in blood parameters were mild and none was thought to be product related.

In conclusion, CS was well tolerated with all reports of irritation being mild. It should be noted that CS in actual use will not be applied directly to the penis but rather to the vagina, resulting in

TABLE 3. Summary of Out of Range Laboratory Values*

	CS (n = 24)		KY (n = 12)		All Participants (n = 36)	
Out of Range Values at	No. Men (%)	No. Reports	No. Men (%)	No. Reports	No. Men (%)	No. Reports
Screening visit, Total	10 (41.7)	15	6 (50)	9	16 (44.4)	24
Final visit, Total	12 (50)	16	6 (50)	10	18 (50)	26
New	3 (12.5)	5	1 (8.3)	2	4 (11.1)	7
Existing and worsened	5 (20.8)	7	3 (25)	5	8 (22.2)	12
Existing but not worsened	4 (16.7)	4	2 (16.7)	3	6 (16.7)	7

*out of range is defined as outside normal ±20%.

less intense and briefer contact than in this study. The tingling symptom could have been caused by the benzyl alcohol.

References

1. Ramjee G. Microbicides and other prevention strategies. XVI International AIDS Conference Toronto Canada 2006. Available at http://www.aids2006.org/PAG/PSession.aspx?s=653.
2. Stein Z. HIV prevention: The need for methods women can use. Am J Public Health 1990; 80:460–462.
3. Stone A. Microbicides: A new approach to preventing HIV and other sexually transmitted infections. Nat Rev Drug Discov 2002; 1:977–85.
4. Finley B, Plescia C, Harrison P, et al. An analytical overview of the microbicide preclinical and clinical pipeline http://www.microbicide.org/microbicideinfo/reference/AMD.AIDS2006.PosterPresentation.7Aug06.pdf. XVI International AIDS Conference Toronto Canada 2006.
5. Finley B, Plescia C, Harrison P, et al. An analytical overview of the microbicide preclinical and clinical pipeline. XVI International AIDS Conference Toronto Canada 2006. Available at http://www.microbicide.org/microbicideinfo/reference/AMD.AIDS2006.PosterPresentation.7Aug06.pdf.
6. Phase III trial updates. Lut Van Damme. Microbicides Conference Cape Town 2006. Available at http://www.microbicides2006.org/Feedback.htm.
7. Anderson R, Feathergill K, Diao X, et al. Preclinical evaluation of sodium cellulose sulfate (Ushercell) as a contraceptive antimicrobial agent. J Androl 2002; 23:426–38.
8. Christensen N, Reed C, Culp T, et al. Papillomavirus microbicidal activities of high-molecular-weight cellulose sulfate, dextran sulfate, and polystyrene sulfonate. Antimicrob Agents Chemother 2001; 45:3427–32.
9. Scordi-Bello I, Mosoian A, He C, et al. Candidate sulfonated and sulfated topical microbicides: Comparison of anti-human immunodeficiency virus activities and mechanisms of action. Antimicrob Agents Chemother 2005; 49:3607–15.
10. Simoes J, Citron D, Aroutcheva A, et al. Two novel vaginal microbicides (polystyrene sulfonate and cellulose sulfate) inhibit Gardnerella vaginalis and anaerobes commonly associated with bacterial vaginosis. Antimicrob Agents Chemother 2002; 46:2692–95.
11. El Sadr W, Mayer K, Maslankowski L, et al. Safety and acceptability of cellulose sulfate as a vaginal microbicide in HIV-infected women. AIDS 2006; 20:1109–16.
12. Malonza I, Mirembe F, Nakabiito C, et al. Expanded Phase I safety and acceptability study of 6% cellulose sulfate vaginal gel. AIDS 2005; 19:2157–63.
13. Mauck C, Frezieres R, Walsh T, et al. Cellulose sulfate: Tolerance and acceptability of penile application. Contraception 2001; 64:377–81.
14. Mauck C, Weiner DH, Ballagh S, Creinin M, Archer DF, Schwartz J, Pymar H, Lai JJ, Callahan M. Single and multiple exposure tolerance study of cellulose sulfate gel: A Phase I safety and colposcopy study. Contraception 2001; 64:383–91.
15. Schwartz J, Mauck C, Lai J, et al. Fourteen-day safety and acceptability study of 6% cellulose sulfate gel: A randomized double-blind Phase I safety study. Contraception 2006; 74:133–40.
16. Mauck C, Frezieres R, Walsh T, et al. Noncomparative contraceptive effectiveness trial of cellulose sulfate gel. Obstet Gyneccol 2006; 107(Suppl 4):14S.
17. Tien D, Schnaare R, Kang F, et al. In vitro and in vivo characterization of a potential universal placebo designed for use in vaginal microbicide clinical trials. AIDS Res Hum Retroviruses 2005; 21:845–53.