Cellulose sulfate

Brand Name: Ushercell
Drug Class: Microbicides

Drug Description

Cellulose sulfate, also known as CS, is a high molecular weight carboxymethylcellulose-based polymer. [1] It is a noncytotoxic, antifertility agent that exhibits in vitro antimicrobial activity against sexually transmitted pathogens, including HIV. [2]

HIV/AIDS-Related Uses

Two Phase III clinical trials to study cellulose sulfate's effectiveness in preventing the sexual transmission of HIV have been halted as of January 2007. One trial in HIV uninfected women being conducted in South Africa, Benin, Uganda, and India was halted because preliminary results at some trial sites indicated using the microbicide could lead to potential increased risk of HIV infection in these women. Simultaneously, a Nigerian study of cellulose sulfate was halted. Although the second study did not detect an increased risk of HIV infection associated with the microbicide, the trial was halted as a precautionary measure in light of the preliminary results from the first study.[3] At interim analysis of the first trial, 24 women using cellulose sulfate and 11 women using placebo developed HIV. Possible causes for the increased infection rate include inflammatory reactions, local immune dysfunction, or vaginal flora disruption.[4] [5] After the final study visit, conducted in May 2007, analysis showed no statistically significant difference in onset of HIV infection (25 women using cellulose sulfate and 16 using placebo) and no potential to prevent HIV transmission.[6]

Non-HIV/AIDS-Related Uses

Cellulose sulfate is being tested for effectiveness in prevention of sexually transmitted diseases and for contraceptive use. Preclinical and clinical studies have demonstrated a high level of safety. Laboratory tests reveal the potential of cellulose sulfate to be an effective safeguard against pregnancy and infections from gonorrhea, chlamydia, and herpes simplex virus (HSV)-1 and -2. Placebo-controlled Phase III trials are evaluating its use in the prevention of male-to-female transmission of Neisseria gonorrhoeae and Chlamydia trachomatis.[7]

Cellulose sulfate displays direct microbicidal activity against human papillomavirus in vitro.[8] In January 2006, Polydex Pharmaceuticals received a European patent regarding the use of cellulose sulfate and other sulfated polysaccharides to prevent and treat papilloma virus infections in humans and other mammals. The patent acknowledges that microbicidal agents that may otherwise have a broad spectrum of prevention capabilities have thus far been ineffective against papilloma viruses.[9]

Two CONRAD-sponsored studies tested contraceptive activity of cellulose sulfate, and both efficacy trials ended in 2006.[10] One of these studies tested the contraceptive effectiveness of cellulose sulfate in preventing pregnancy when used by a woman in a sexually active, HIV uninfected couple for 6 months.[11]

In vitro, cellulose sulfate inhibits Gardnerella vaginalis and anaerobes that cause bacterial vaginosis (BV).[12] BV may act as a cofactor in the heterosexual transmission of HIV, so the impact of cellulose sulfate and other vaginal microbicides on BV warrants evaluation.[13] Because cellulose sulfate inhibits BV pathogens, cellulose sulfate may provide contraceptive and antimicrobial activity without increasing a patient's risk of BV.[14]

Studies have also been conducted to test the safety of cellulose sulfate in conjunction with use of a diaphragm or magnetic resonance imaging (MRI).[15]

Pharmacology

In vitro, cellulose sulfate blocks cell surface receptors, inhibits HIV binding and penetration of epithelial layers and dendritic cells, blocks the gp120-CD4 coreceptor interaction, and acts against coreceptors CCR5 and CXCR4 in primary isolates and laboratory strains.[16] Cellulose sulfate gel 6% has been shown to stimulate acrosomal loss, inhibit hyaluronidase, and impede sperm penetration into cervical mucus in vitro.[17] Cellulose sulfate inhibits HIV entry and sperm-egg interaction in

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Pharmacology (cont.)

vitro, reaching 95% or greater inhibition of sperm binding capacity at a concentration of 1 mg/mL. Cellulose sulfate does not affect sperm motility and is not cytotoxic.[18] [19] Cellulose sulfate inhibits HIV-1 strains with a 50% inhibitory concentration (IC50) of 50 ug/ml. It is especially effective against HSV-1 and -2 at an IC50 of 0.12 to 0.25 ug/ml.[20]

Linear gel spread, as evaluated in a study of 2.5 ml and 3.5 ml gel volumes inserted vaginally, takes place primarily in the first 5 minutes after gel insertion. Lateral spreading (surface contact) appears to continue after linear spreading slows or stops. Upright patient movement has a greater effect on gel distribution than gel volume does. Using a larger gel volume increases linear spreading but provides less consistent lateral spreading. The greatest linear and lateral spreading have been noted 50 minutes after insertion in women using 3.5 ml of gel who have walked around after insertion. Even under these conditions, women had bare spots in coverage, particularly in the proximal vagina. Thus, the spreading of cellulose sulfate without intercourse did not result in complete vaginal coverage, even at 50 minutes after product insertion.[21]

Vaginal cellulose sulfate tablet inhibition of sperm enzyme and of HIV, HSV, and Chlamydia appears comparable to that of the gel formulation. Cellulose sulfate tablets do not inhibit Lactobacillus in vitro.[22]

In rabbit models, cellulose sulfate 6% gel was active as a contraceptive for at least 18 hours after application and was partially active for at least 24 hours. A gel concentration as low as 0.1% was an effective contraceptive when applied within 30 minutes of insemination.[23]

Adverse Events/Toxicity

Results of all 11 cellulose sulfate studies sponsored by CONRAD have indicated the microbicide is safe, acceptable, and effective as currently marketed spermicides and sexual lubricants. These 11 studies include 5 safety studies in women,2 safety studies in men, 2 contraceptive effectiveness studies, and studies testing the safety of the microbicide when used with a diaphragm or MRI.[24]

Cellulose sulfate 6% gel administered vaginally four times daily for 14 days did not differ with respect to epithelial disruption, candidiasis, BV, and acceptability from K-Y jelly placebo.[25] A blinded crossover study of 6% gel was conducted with 2.5 and 3.5 ml volumes. Each woman used each gel volume twice; after one application, women had restricted upright movement, and after the other, they were allowed to walk around. Excessive leakage was not noted with either volume.[26]

In a safety and acceptability study conducted in the United States and the Dominican Republic, HIV uninfected women used cellulose sulfate 6% gel or K-Y jelly placebo twice daily for 14 days. Some level of product leakage was reported by all study participants. There was no noticeable difference in the proportion of overall vaginal leakage of moderate or severe intensity between the cellulose sulfate and K-Y jelly placebo groups.[27]

In a Phase I, two-part cohort study of 180 women in India, Nigeria, and Uganda using cellulose sulfate 6% gel or K-Y jelly placebo, the majority of women had no problem with either gel, and most found the gels easy to use. Fewer women using cellulose sulfate than using K-Y jelly placebo reported genital symptoms in Cohort 1; new colposcopic findings were detected in only 9% of women using cellulose sulfate, compared to 21% of women using K-Y jelly. In Cohort 2, fewer women using cellulose sulfate than using K-Y jelly placebo reported genital symptoms; 11% in each group had new colposcopy findings. Differences between the groups were not considered to be statistically significant.[28]

In a survey study of HIV infected women using 6% gel once or twice daily for 14 days, women liked the gel's color, smell, and consistency somewhat to a lot. Overall, 31% of women reported that the gel soiled clothing or bed linens. In women using the gel once daily, 4 out of 7 reported leakage during sex; 4 out of 7 also reported leakage after sex. Many women reported that they would prefer a microbicide that could go unnoticed by a sex partner. Primary issues with the gel were soiling of

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Adverse Events/Toxicity (cont.)

clothes and leakage of gel during sex.[29]

In a Phase I trial in which men directly applied either cellulose sulfate gel or an active control containing nonoxynol-9 for 7 consecutive days, the cellulose sulfate gel was not more irritating than the active control. Symptoms reported by one patient after using cellulose sulfate included slight stinging and mild tingling.[30]

One South African clinical trial tested the safety of the Ortho All flex diaphragm when used with cellulose sulfate gel or with K-Y jelly, compared with cellulose gel use alone, over 6 months in HIV uninfected women. Very few of the participants in this study had ever used diaphragms before. This combination was found to be safe with no serious adverse events or adverse events related to diaphragm use reported. Colposcopic findings were observed in 60% to 80% of study participants. Seven severe findings were observed in those using the microbicide in combination with the diaphragm; however, these differences were not statistically significant. The location of these findings on the external genitalia suggest that they may have been due to trauma following diaphragm insertion.[31]

Cellulose sulfate vaginal tablets are not cytotoxic. The gel formulation has shown an acceptable safety profile in macaques.[32] [33]

Clinical Trials

For information on clinical trials that involve Cellulose sulfate, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Cellulose sulfate AND HIV Infections.

Dosing Information

Mode of Delivery: Intravaginal.[34]

Dosage Form: Cellulose sulfate 6% vaginal gel in a 3.5 ml prefilled applicator for insertion prior to sexual intercourse.[35] [36]

Cellulose sulfate 200-mg vaginal tablets containing excipients generally regarded as safe (GRAS). Tablets disintegrate in less than 30 seconds in 10 ml of fluid to form a smooth, homogenous, viscous, and bioadhesive dispersion.[37]

Cellulose sulfate 6% vaginal gel has been tested in women up to four times daily for up to 14 consecutive days.[38] [39] [40]

Cellulose sulfate 0.1% vaginal gel has been tested for contraceptive use.[41]

Because the optimal applied volume of gel is not known, volumes ranging from 2.5 to 5 ml have been tested.[42]

Chemistry

CAS Name: Cellulose, hydrogen sulfate[43]

CAS Number: 9032-43-3[44]

Physical Description: Cellulose sulfate is a thick and odorless gel with a slightly hazy, light brown tint.[45]

Stability: Vaginal tablets stored in accelerated stability conditions recommended by the International Council on Harmonization (ICH) for Zone IV countries were stable for a period of 3 months.[46]

Other Names

Sodium cellulose sulphate[47]

Sodium cellulose sulfate[48]

CS[49]

Cellulose sulphate[50]

Further Reading

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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