An Open-Label, Two-Period, Crossover Study of the Systemic Bioavailability in Healthy Women of Clindamycin Phosphate from Two Vaginal Cream Formulations

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ABSTRACT

Background: A clindamycin phosphate 2% single-dose vaginal cream (CSDVC) formulation has been designed to provide release of clindamycin equivalent to 7 daily doses of a conventional clindamycin phosphate 2% vaginal cream (CVC).

Objective: The purpose of this study was to compare the systemic bioavailability of clindamycin from 1 dose of CSDVC with that from 1 dose from a 7-day regimen of CVC in healthy women.

Methods: This was a single-center, open-label, randomized, 2-period, 2-sequence crossover study that enrolled healthy, nonpregnant, adult women. Subjects were randomly assigned to receive a single 5-g intravaginal dose of CSDVC or CVC. Blood samples were then collected for 96 hours after study medication administration. Subjects were crossed over after a 14-day washout period, and received a single dose of the other medication. Blood samples were then collected for 96 hours after administration of the second drug. The plasma clindamycin pharmacokinetic profiles were determined, using a validated assay with a lower limit of detection of 0.2 ng/mL, and compared between treatments.

Results: The median age of women was 43.5 years (range, 18–66 years), the median weight was 65.0 kg (range, 47.7–91.8 kg), and the median body mass index was 25.4 kg/m^2 (range, 19.2–34.7 kg/m^2). AUC from time 0 to the last detectable concentration (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$) and C_{max} were significantly lower with CSDVC than with CVC (geometric means of 98.61 vs 794.21 ng · h/mL for AUC_{0-t}, 100.33 vs 809.14 ng · h/mL for $AUC_{0-\infty}$, and 3.18 vs 42.27 ng/mL for C_{max}; all comparisons, $P < 0.001$ between formulations). Overall bioavailability of clindamycin from CSDVC was ~12% of that from CVC, as measured by AUC. The arithmetic mean T_{max} was significantly longer with CSDVC (26.4 vs 9.8 hours; $P < 0.007$). There were 18 adverse events reported during this study. The most common adverse event with each formulation was headache (CSDVC, 10%; CVC, 25%).

Conclusion: Systemic bioavailability of clindamycin was significantly lower and systemic absorption was significantly slower with the CSDVC formulation than with the single dose of 7-day CVC formulation in these healthy volunteers. (*Clin Ther.* 2005;27:1894–1900) Copyright © 2005 Excerpta Medica, Inc.

Key words: clindamycin, vaginal cream, vaginosis, bioadhesive, systemic exposure, pharmacokinetics.

INTRODUCTION

Bacterial vaginosis (BV) is a vaginal condition of poorly understood etiology, but it affects 8% to 23% of women in the United States during their reproductive years.[1,2] BV results from the replacement of the normal *Lactobacillus*-dominant vaginal flora with polymicrobial, primarily anaerobic, bacteria and is generally characterized by symptoms of vaginal discharge and malodor.[2] BV has been associated with adverse pregnancy outcomes, pelvic inflammatory disease, and increased risk of postoperative infections after gynecologic surgical procedures.[3–7]

Recommended antimicrobial therapy for nonpregnant women with BV may include intravaginal therapy with the antibacterial agent clindamycin. All but one of the intravaginal clindamycin therapies marketed in the United States, however, require the inconvenience of daily use for 3 to 7 days, and such inconve-

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nience has been reported to have a negative effect on treatment compliance and satisfaction.[8] Thus, an effective single-dose vaginal treatment might be beneficial to women with BV.

A patented topical drug delivery system* has been developed for use as a platform for the administration of topical active drug entities in the vaginal cavity. This water-in-oil emulsion system exhibits bioadherent properties to mucosal tissues and is composed of a drug-laden internal phase and a water-insoluble external phase.[9] The system can provide controlled delivery and release of an active drug product over a period of 2 to 7 days in a mucous membrane environment such as the vaginal cavity.[9] In vitro studies have found that using this delivery system, cream formulated with an acetate buffer of pH 4.3 (which simulates normal vaginal fluid) remains intact and releases active drug over a period of 7 days.[10] Under the same conditions, a conventional cream was found to disintegrate rapidly and release the active drug moiety into the medium.[10] A clinical study has been reported in which butoconazole nitrate 2% (a vaginally applied antifungal agent) in this formulation was found to remain in the vagina visually and analytically 63% longer than that in a conventional butoconazole nitrate 2% cream formulation.† Median retention times were 4.2 days and 2.6 days, respectively ($P < 0.003$).[11]

A clindamycin phosphate 2% single-dose vaginal cream (CSDVC)‡ that uses this system has been approved for use in the treatment of BV in nonpregnant women. CSDVC was formulated to provide release of clindamycin from the cream vehicle such that a single dose of the cream—a total of 100 mg of clindamycin phosphate—would be equivalent to 7 daily doses of a conventional clindamycin phosphate 2% cream (CVC)—a total of 700 mg of clindamycin phosphate—in the treatment of BV.[12] In this study, similar percentages of subjects with BV were found to be clinically and microbiologically cured when treated with a single dose of CSDVC or with a 7-dose regimen of CVC (overall cure rates of 42.1% and 45.6%, respectively; P = NS).

It is hypothesized that the single-dose clindamycin cream formulation achieves this efficacy by maintaining an effective local concentration of clindamycin in the vaginal cavity over a period of days rather than releasing drug from the delivery system into the vaginal cavity in a bolus, as would be expected with a 7-dose conventional cream. The clinical effectiveness of the single-dose formulation suggests that, in this formulation, clindamycin is indeed retained in the delivery system and released into the vaginal cavity over time.[12] In light of this finding, it is hypothesized that the absorption of clindamycin into the bloodstream would be reduced and that systemic clindamycin exposure would, therefore, be lower when administered as CSDVC than when administered as a single dose of 7-day CVC. The marketed dosage for CSDVC is 100 mg of clindamycin phosphate in 5 g of vaginal cream applied in a single dose. The marketed dosage for the CVC formulation used in this study§ is 100 mg of clindamycin phosphate in 5 g of vaginal cream applied once daily for 3 or 7 days. In this study, 1 dose of CSDVC at the marketed drug concentration and volume was directly compared with 1 dose from a 7-day regimen of CVC at the marketed drug concentration and volume to clarify the release potential of CSDVC in terms of systemic bioavailability in healthy women.

SUBJECTS AND METHODS

This was a single-center, open-label, randomized, 2-period, 2-sequence crossover study. Healthy adult volunteers were enrolled in the study, with an equal number of subjects randomly assigned to each of the 2 treatment sequences. Each subject received a single 5-g intravaginal dose of either CSDVC or CVC, underwent a 14-day washout period, and then received a single 5-g intravaginal dose of the other study medication. The study was conducted according to the principles set forth in the Declaration of Helsinki,[13] and the protocol was approved by LeeCoast Institutional Review Board, Fort Myers, Florida, before the start of the study. All subjects were voluntary participants and provided signed informed consent before any study-related procedure was performed.

Eligible subjects were healthy, nonpregnant women aged ≥18 years with body mass indices of 19 to 35 kg/m^2 who were willing to refrain from sexual intercourse and the use of intravaginal products (eg, douches, tampons) for ≥96 hours after each study medication ad-

*Trademark: VagiSite™ (KV Pharmaceutical Company, St. Louis, Missouri).

†Trademark: Femstat® (Syntex Laboratories, Palo Alto, California).

‡Trademark: Clindesse™ (Ther-Rx Corporation, St. Louis, Missouri).

§Trademark: Cleocin® (Pharmacia & Upjohn, Kalamazoo, Michigan).