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CLINICAL STUDY

The efficacy and safety of a single dose of Clindesse™ vaginal cream versus a seven-dose regimen of Cleocin® vaginal cream in patients with bacterial vaginosis

SEBASTIAN FARO[1] & CAMPBELL K. SKOKOS[2] FOR THE CLINDESSE™ INVESTIGATORS GROUP

[1]*The Woman's Hospital of Texas, Houston, Texas, and* [2]*The Woman's Clinic, Little Rock, Arkansas, USA*

Abstract

Objective. To determine whether a single dose of Clindesse™ vaginal cream is comparable in efficacy and safety to Cleocin® vaginal cream administered once daily for 7 days in the treatment of bacterial vaginosis.

Study design. This multicenter, randomized, single-blind, parallel-group study enrolled 540 patients with BV infections. Treatment consisted of either a single intravaginal dose of Clindesse™ or 7 daily doses of Cleocin®. Efficacy and safety were assessed 21–30 days after the start of treatment. The efficacy endpoints were Investigator Cure, Clinical Cure (a composite of all 4 Amsel's criteria and Investigator Cure), Nugent Cure (Nugent score < 4), and Therapeutic Cure (a composite of Clinical Cure and Nugent Cure). Resolution of individual Amsel's criteria was also evaluated. Treatment-emergent adverse events were monitored throughout the study.

Results. There were no significant differences in cure rates between the Clindesse™ and Cleocin® treatment groups in Investigator Cure ($P = 0.702$), Clinical Cure ($P = 0.945$), Nugent Cure ($P = 0.788$), or Therapeutic Cure ($P = 0.572$). Results were also similar for 3 of 4 and 2 of 4 Amsel's criteria and for each individual Amsel's criterion (all P-values > 0.200). Ninety-five percent confidence intervals for each endpoint were consistent with equivalence between the 2 products. There was no significant difference between the treatment groups in the incidence of treatment-emergent adverse events ($P = 0.386$).

Conclusions. A single dose of Clindesse™ vaginal cream is equivalent in safety and efficacy to a 7-dose regimen of Cleocin® vaginal cream in the treatment of bacterial vaginosis. This represents a significant advance in the treatment of bacterial vaginosis.

Key words: *Bacterial vaginosis, vaginitis, clinidamycin vaginal cream*

Introduction

Bacterial vaginosis (BV) continues to be one of the most common vaginal disorders in reproductive-age women. It represents 40–50% of all cases of vaginitis, surpassing both vaginal candidiasis and vaginal trichomoniasis [1]. It causes significant patient discomfort and has been associated with many disorders of the female reproductive tract, including recurrent urinary tract infections, adnexal tenderness, postpartum endometritis, increased risk of infection after gynecologic surgery, pelvic inflammatory disease, and adverse pregnancy outcomes. BV results from replacement of the normal *Lactobacillus*-dominant vaginal flora with polymicrobial, primarily anaerobic, bacteria. The cause of this microbial shift is not fully understood [2,3].

Recommended antimicrobial treatments for non-pregnant women often include oral or intravaginal therapy with clindamycin. While both oral and intravaginal administrations are effective, intravaginal medications may result in fewer of the adverse side effects associated with oral antibiotic therapy such as nausea, vomiting, and taste perversion [4,5]. In addition, patients treated with intravaginal therapies report increased treatment satisfaction compared with those treated with oral therapies [6]. Most intravaginal therapies for BV, like oral therapies, require the inconvenience of daily use for multiple days, and this inconvenience may have a negative effect on treatment compliance and satisfaction [7]. Thus, an effective single-dose vaginal treatment for BV might be beneficial to women from a number of different points of view.

Correspondence: Sebastian Faro, MD, PhD, 7400 Fannin, Ste. 840, Houston, TX 77054, USA. Tel: 713 799 8994. Fax: 713 799 9931.

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Clindesse™ (clindamycin phosphate) vaginal cream 2% is a single-dose intravaginal therapy recently approved for use in the treatment of BV in nonpregnant women. Clindesse™ uses a patented, sustained-release, single-dose, topical cream emulsion. In vitro studies with this cream technology have shown that in an acetate buffer of pH 4.3, which simulates normal vaginal fluid, the sustained release cream is highly stable and remains intact for a prolonged period of time. Under the same conditions, a conventional cream rapidly disintegrates and releases the active ingredient into the medium (data on file, KV Pharmaceutical Company, St. Louis, Missouri). Clinical studies demonstrated that butoconazole nitrate 2% in this sustained-release formulation remains in the vagina 63% longer than butoconazole nitrate 2% in a conventional formulation (median retention time 4.2 days versus 2.6 days) [8].

Given the ability of Clindesse™ to maintain therapeutic levels of clindamycin in the vagina for a prolonged period of time, we hypothesize that a single dose of Clindesse™ would be equivalent to a 7-day course of a conventional clindamycin phosphate intravaginal cream. Such reductions in dosing frequency have been shown to increase treatment compliance, patient satisfaction, and quality of life [7]. Thus, the purpose of the current study was to determine whether a single dose of Clindesse™ is equivalent in safety and efficacy to a 7-day regimen of Cleocin® vaginal cream in the treatment of BV.

Material and methods

The study was designed in accordance with the United States Food and Drug Administration FDA Center for Drug Evaluation and Research (CDER) 1998 draft guidelines for developing effective treatments for BV [2]. This was a multicenter, single (Investigator)-blind, active-controlled study. Patients were recruited at 28 clinics in the United States, each with its respective IRB/ethics board approval. All patients provided signed informed consent before any study-related procedure was performed.

Eligible patients were nonpregnant women at least 18 years of age with a clinical diagnosis of BV, which was defined as meeting all of Amsel's criteria [9] ($\geqslant 20\%$ clue cells, off-white [milky or gray], thin, homogenous vaginal discharge, vaginal pH > 4.5, a fishy amine odor upon the addition of 10% KOH to vaginal fluid [''whiff'' test]). Patients were excluded if they were pregnant or nursing; had sexually transmitted infections, had vulvovaginal infections other than BV, had vulvovaginal or cervical abnormalities or disorders; were actively menstruating; had received antifungal or antimicrobial treatment within 14 days of the study; were using intrauterine devices (IUDs); were taking anticoagulants, lithium, disulfiram, or neuromuscular blocking agents; or were hypersensitive to clindamycin, lincomycin, or to any excipient in the drug formulation.

Eligible patients were randomly assigned to 1 of 2 treatment arms (Clindesse™ or Cleocin®) in a single (Investigator)-blind fashion according to a computer-generated randomization schedule. Patients were instructed in the appropriate study medication administration techniques, which were to be performed or started within 48 hours after leaving the clinic.

Clindesse™ vaginal cream consisted of 2% clindamycin phosphate formulated in 5 g of the sustained-release vaginal cream, for a total of 100 mg clindamycin phosphate. Clindesse™ was self-administered by patients in a single dose. Cleocin® vaginal cream also consisted of 2% clindamycin phosphate, but formulated in 5 g of a conventional vaginal cream. Cleocin® was self-administered by the patient once daily for 7 consecutive days.

Treatment effectiveness was evaluated and compared at a Test-Of-Cure (TOC) visit 21–30 days following the start of treatment, using several clinical and microbiologic indices. Investigator Cure was based on the Investigator's response (Yes/No) to a question at the TOC visit regarding the need for additional BV treatment. Clinical Cure was a composite endpoint including resolution of all 4 Amsel's criteria and Investigator Cure. Nugent Cure was defined as a Gram stain Nugent score [10] < 4 (on a 10-point scale). Therapeutic Cure was a composite endpoint defined as both Clinical Cure and Nugent Cure. In addition, the 4 Amsel's criteria were each evaluated individually. The TOC visit was selected to demonstrate both status and duration of outcome. The per-protocol (PP) population was selected for the efficacy analyses in accordance with demonstration of equivalence between treatments.

The safety of the 2 treatments was evaluated by monitoring treatment-emergent adverse events (AEs) throughout the study.

Statistical methods

Efficacy endpoints were analyzed using the center-stratified Cochran-Mantel-Haenszel (CMH) estimate of the difference in cure rates and corresponding confidence interval [11]. Clindesse™ was to be considered equivalent to Cleocin® if the 2-sided 95% confidence interval (CI) for the difference in cure rates (Clindesse™ minus Cleocin®) had a lower limit greater than -20% and an upper limit less than $+20\%$. Efficacy analyses were performed using a PP population, which included patients who administered study medication, had baseline Nugent scores $\geqslant 4$, had assessment results at the TOC visit or discontinued participation in the study prior to the

TOC visit due to lack of efficacy, had no antimicrobial therapy for conditions other than BV during the study, started study medication within 48 hours of the entry visit, and had no major violations of the study protocol. All patients who administered at least 1 dose of study medication were included in the safety analyses.

Results

Of the 540 patients enrolled in the study (271 in the Clindesse™ group and 269 in the Cleocin® group), 253 (46.9%) were considered evaluable for the PP population (128 in the Clindesse™ group and 125 in the Cleocin® group). Of the 287 patients who were not evaluable in the PP population, 92 had baseline Nugent scores < 4, 64 participated in the study for less than 21 days but were not treatment failures, and 52 did not start study medication within 48 hours of the Entry Visit. These 3 reasons account for approximately 75% of the patients who were not evaluable in the PP population. The percentages of patients with each primary reason for non-evaluability were similar between the treatment groups. A complete listing of the primary reasons for non-evaluability in the PP population by treatment group is in Table I.

Cure of BV was evaluated by a number of different measures. Frequencies of Investigator Cure, Clinical Cure, Nugent Cure, and Therapeutic Cure are presented in Table II.

The Investigator Cure represents the Investigator's assessment of the need for additional therapy for BV at the TOC Visit. Investigator Cure (no additional therapy required for BV) was achieved in 89.1% of Clindesse™ patients and 86.4% of Cleocin® patients at the TOC visit. There were no statistically significant differences in Investigator Cure rates between treatment groups ($P = 0.702$) and the 95% CIs for the differences were consistent with equivalence with regard to the need for additional treatment of BV as assessed by the Investigator.

Clinical Cure, which represents both alleviation of BV signs and symptoms and alleviation of the need for additional BV therapy at the TOC visit, was achieved in 64.3% of Clindesse™ patients and 63.2% of Cleocin® patients. There were no statistically significant differences in Clinical Cure rates between treatment groups ($P = 0.945$).

Similar cure rates were also observed in the 2 treatment groups when less stringent criteria were used to define cure. If 3 of the 4 Amsel's criteria are used to define cure, 87.5% of Clindesse™ patients and 83.2% of Cleocin® patients are cured ($P = 0.399$). When 2 of the 4 Amsel's criteria are used to define cure, cure rates increase to 90.6% of Clindesse™ patients and 91.2% of Cleocin® patients ($P = 0.792$). There were no statistically significant differences in cure rates between treatment groups and the 95% CIs for the differences were consistent with equivalence in the alleviation of BV signs using both 2 and 3 of the 4 Amsel's criteria. In addition, there were no statistically significant differences in resolution of Amsel's criteria between the treatment groups when the criteria for clue cells ($< 20\%$) and a negative ''whiff'' test were evaluated together ($P = 0.965$) or when the criteria for clue cells, ''whiff'' test, and vaginal pH (< 4.7) were evaluated together ($P = 0.539$). The cure rates associated with each Amsel's criterion and selected groups of criteria are presented in Table III.

Table I. Primary reasons for non-evaluability in the per-protocol population by treatment group.

	Clindesse™ ($N = 271$)‡		Cleocin® ($N = 269$)‡		Overall† ($N = 540$)‡	
Reason	n§	(%)§	n§	(%)§	n§	(%)§
Did not take study medication	8	(3.0)	4	(1.5)	12	(2.2)
Did not take Cleocin® on 3 consecutive days	-	-	18	(6.7)	18	(3.3)
Baseline Nugent score < 4	42	(15.5)	50	(18.6)	92	(17.0)
Did not take study medication with 48 hours of the entry visit	34	(12.5)	18	(6.7)	52	(9.6)
Participated in the study for < 21 days without treatment failure	37	(13.7)	27	(10.0)	64	(11.9)
Received antimicrobial therapy for reasons other than bacterial vaginosis	7	(2.6)	14	(5.2)	21	(3.9)
Used other intravaginal products or had intercourse within 7 days of start of treatment	11	(4.1)	9	(3.3)	20	(3.7)
Did not meet all inclusion and exclusion criteria	3	(1.1)	3	(1.1)	6	(1.1)
Participated in the study for > 40 days	1	(0.4)	1	(0.4)	2	(0.4)
Total patients not evaluable	143	(52.8)	144	(53.5)	287	(53.1)
Total patients evaluable	128	(47.2)	125	(46.5)	253	(46.9)

† ''Overall'' refers to the total number of patients enrolled; ‡ Denotes total number of patients enrolled by and across treatment group; § n and % denote the number and percentage of evaluable and nonevaluable patients by reason for each treatment group.

Table II. Efficacy outcomes at the Test-of-Cure Visit (number and % of evaluable patients cured).

	Clindesse™		Cleocin®		Treatment differences§		
Endpoint	N†	n (%)‡	N†	n (%‡)	%	95% CI	P-value
Investigator Cure	128	114 (89.1)	125	108 (86.4)	2.7	[−5.4, 10.7]	0.702
Clinical Cure|	126	81 (64.3)	125	79 (63.2)	1.1	[−10.8, 13.0]	0.945
Nugent Score < 4	124	70 (56.5)	123	71 (57.7)	−1.3	[−13.6, 11.1]	0.788
Therapeutic Cure|	126	53 (42.1)	125	57 (45.6)	−3.5	[−15.8, 8.7]	0.572

† Denotes the number of patients with non-missing data in each treatment group; ‡ n and % denote the number and percentage of patients cured within each endpoint for each treatment group; § Clindesse™ minus Cleocin® cure rates; | Subjects were considered evaluable (included in N) and to have achieved cure if data for 1 Amsel's criterion were missing, but all other criteria were consistent with cure.

Table III. Number and percent of patients with resolution of individual Amsel's criteria at the Test-of-Cure Visit.

	Clindesse™		Cleocin®		Treatment difference§		
Endpoint	N†	n (%)‡	N†	n (%)‡	%	95% CI	P-value
3 of 4 Amsel's criteria resolved	128	112 (87.5)	125	104 (83.2)	4.3	[−4.4, 13.0]	0.399
2 of 4 Amsel's criteria resolved	128	116 (90.6)	125	114 (91.2)	−0.6	[−7.7, 6.5]	0.792
< 20% Clue cells	128	112 (87.5)	125	105 (84.0)	3.5	[−5.1, 12.1]	0.480
Negative "whiff" test	128	116 (90.6)	125	118 (94.4)	−3.8	[−10.2, 2.7]	0.205
Normal discharge	128	108 (84.4)	125	108 (86.4)	−2.0	[−10.7, 6.7]	0.545
pH < 4.7	127	94 (74.0)	122	87 (71.3)	2.7	[−8.4, 13.8]	0.668
Clue cells + "whiff" test	128	108 (84.4)	125	105 (84.0)	0.4	[−8.6, 9.4]	0.965
Clue cells + "whiff" test + pH	127	87 (68.5)	122	79 (64.8)	3.7	[−8.0, 15.5]	0.539

† Denotes the number of patients with non-missing data in each treatment group; ‡ *n* and % denote the number and percentage of patients cured within each endpoint for each treatment group; § Clindesse™ minus Cleocin® cure rates.

The Nugent score represents a microbiologic diagnostic measure of BV. Nugent Cure (Nugent score < 4) was achieved in 56.5% of Clindesse™ patients and 57.7% of Cleocin® patients at the TOC visit. There were no statistically significant differences in Nugent Cure rates between treatment groups ($P = 0.788$) and the 95% CIs for the differences were consistent with equivalence in Nugent Cure rates at the TOC Visit.

Therapeutic Cure represents the composite of Clinical Cure and Nugent Cure at the TOC visit. Analysis results demonstrate that 53 (42.1%) patients in the Clindesse™ group achieved Therapeutic Cure compared with 57 (45.6%) patients in the Cleocin® group. Therapeutic Cure results indicate that a single dose of Clindesse™ is statistically equivalent in effectiveness to 7 daily doses of Cleocin® in the treatment of BV ($P = 0.572$).

Among the 263 patients in the Clindesse™ group and the 265 patients in the Cleocin® group that received at least 1 dose of study medication, 80 Clindesse™-treated patients (30.4%) and 71 Cleocin®-treated patients (26.8%) had a total of 115 and 97 treatment–emergent AEs, respectively, during the study. The most commonly reported AEs are shown in Table IV. Twenty-seven patients (10.3%) in the Clindesse™ group reported 29 study medication-related AEs compared with 21 patients (7.9%) in the Cleocin® group who reported 22 study medication-related AEs. The number of patients who reported AEs and study medication-related AEs were not statistically different between the 2 treatment groups ($P = 0.386$ for overall AEs and $P = 0.336$ for study medication-related AEs). Overall, among the 528 patients who received study medication, 5 (0.9%) were discontinued from the study due to AEs. Three (1.1%) Clindesse™-treated patients were discontinued due to Vaginal Yeast Infection, Candidiasis, and Allergic Reaction to Study Drug (1 patient each). Two patients (0.8%) in the Cleocin® group were discontinued due to Vaginal Yeast Infections. There was 1 serious AE (cellulitis) reported by a patient receiving Cleocin® during the study. The event was judged to be unrelated to the study medication by the investigator.

Discussion

As we hypothesized, analyses of interpretive, symptomatic, and diagnostic efficacy variables revealed no statistically significant differences between use of clindamycin phosphate 2%, administered in a single-dose vaginal cream (Clindesse™), and in a standard 7-day vaginal cream (Cleocin®).

Investigator Cure is an interpretive measure representing the requirement for additional therapy

Table IV. Most commonly reported adverse events (intent-to-treat population)[†].

Endpoint	Clindesse™ ($N = 263$)[§] *n* (%)[§]	Cleocin® ($N = 265$)[§] *n* (%)[§]	Treatment difference[‡] 95% CI	*P*-value[|]
Infections and infestations				
Urinary tract infection	2 (0.8)	3 (1.1)	[−2.0, 1.3]	1.000
Vaginosis, fungal	38 (14.4)	27 (10.2)	[−1.3, 9.9]	0.146
Nervous system disorders				
Headache	4 (1.5)	4 (1.5)	[−2.1, 2.1]	1.000
Pregnancy, peurperium, and perinatal conditions				
Pregnancy	3 (1.1)	1 (0.4)	[−0.7, 2.2]	0.371
Reproductive system and breast disorders				
Vaginal discharge	2 (0.8)	3 (1.1)	[−2.0, 1.3]	1.000
Vaginal hemorrhage	0 (0.0)	3 (1.1)	[−2.4, 0.1]	0.248
Vulvovaginal pruritus	11 (4.2)	8 (3.0)	[−2.0, 4.3]	0.494

[†] Reported by > 1% of patients in any treatment group; [‡] Clindesse™ minus Cleocin® cure rates; [§] N Denotes the number of patients with non-missing data in the PP population for each treatment group. n and % denote the frequency of patients cured in the PP population within each endpoint for each treatment group; [|] P-value was derived using FET to determine if rates of events differed between treatment groups.

for BV in the medical opinion of the clinical Investigator. Clinical Cure is a conservative symptomatic measure representing resolution of all 4 of the Amsel's criteria as well as a favorable assessment of cure by the Investigator. The Nugent score represents a diagnostic evaluation of BV that is not often used in clinical practice. Therapeutic Cure, which requires both Clinical Cure and Nugent Cure, represents a very conservative composite outcome combining symptomatic, interpretive, and diagnostic measures of BV that has not previously been used as an endpoint. The definitions of Clinical Cure and Therapeutic Cure used here are considerably more conservative than definitions used in previous studies. Although these more conservative criteria for cure are compliant with the 1998 CDER guidance for the evaluation of BV in clinical studies, they may result in lower cure rates than reported in previous studies.

Resolution of 3 of the 4 Amsel's criteria may be more representative of the evaluation of BV in clinical practice. Cure rates using this endpoint were comparable between the Clindesse™ and Cleocin® groups. A study evaluating a 7-day dosing regimen with Cleocin® and a 7-day, twice-daily dosing regimen with MetroGel® (0.75% metronidazole) vaginal gel defined BV cure as resolution in this manner and reported 86.2% and 75.0% cure rates for Cleocin® and MetroGel®, respectively [5]. Although there may be some differences between these studies (e.g., study populations, inclusion criteria, patient evaluability), the cure rates observed were comparable to the 87.5% and 83.2% rates observed using the same definition of cure with Clindesse™ and Cleocin®, respectively, in this study. Previous clinical studies performed with Cleocin® defined BV cure as resolution of 2 of Amsel's criteria (the ''whiff'' test and clue cell criteria) and reported a cure rate of 86% for a 7-day dosing regimen [12]. This is comparable to the 84.4% and 84.0% cure rates observed using these 2 criteria with Clindesse™ and Cleocin®, respectively, in this study.

In the study reported here, there were no significant differences in the incidence of AEs between the treatment groups, and AEs commonly associated with oral therapy (e.g., nausea, taste perversion) were reported in less than 1% of the patients in either treatment group.

Conclusions

Overall, a single-dose regimen of Clindesse™ was shown to be comparable with respect to both efficacy and safety to Cleocin®. Clindesse™, however, provides equivalent efficacy and safety in a single dose, compared with a 7-dose regimen of Cleocin®. It has been shown that reducing dose frequency increases the patient's compliance with treatment, symptom control, satisfaction with treatment, and quality of life in a number of disease states [7]. Clindesse™ offers these advantages, and therefore represents an important therapeutic advance in the treatment of BV.

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