

Proof of concept study of a novel bioadhesive clindamycin phosphate 2% vaginal gel to treat bacterial vaginosis

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Summary

The objective of the study was to evaluate the efficacy and safety of a novel single 2% clindamycin phosphate vaginal gel for the treatment of bacterial vaginosis (BV). The vaginal gel, a thermosetting bioadhesive formulation containing 2% clindamycin phosphate, was studied in a single center, single arm, open-label study. Patients ($n = 30$) were screened for BV using the four Amsel criteria (visit 1). A subset of ten women were also assessed using Nugent scores. Eligible patients were consented and provided a single dose of 2.0% clindamycin phosphate gel in a prefilled vaginal applicator (5-gram total dose). Patients returned to the clinic 7 to 14 days (visit 2) after dosing and again between 21 and 30 days (visit 3). Two subjects were excluded from cure rate calculations. Of the evaluable 28 patients, 24 (86%) were successfully treated (clinical cure) with a single dose of 2% clindamycin gel at visit 2. Of the ten patients evaluated for Nugent scoring, seven subjects were evaluable for bacteriologic cure. After a single dose of 2% clindamycin gel, four of seven (57%), and four of seven (57%) had a bacteriologic and therapeutic response, respectively. Of the 24 women who completed visit 2 and were cured based on Amsel criteria, 23 (96%) remained cured at visit 3. Of the subset of ten patients evaluated using Nugent scoring (bacteriologic evaluation), seven of nine (78%) had a score of 3 or less at visit 3. In this group, six of nine women were considered therapeutically cured (67%). There were no reports of adverse reactions, including local reactions to the vaginal gel product over the course of the study. These data support the expanded clinical evaluation of 2% clindamycin gel.

Key words: Bacterial vaginosis; Clindamycin phosphate; Vaginal gel.

Introduction

Clindamycin has been used both orally and vaginally to treat bacterial vaginosis (BV) [1-9]. It has specifically been found to eradicate a number of organisms associated with BV [10]. The most recent vaginal clindamycin product introduced to treat BV was 2% clindamycin phosphate vaginal cream, originally approved in the US in late 2004. In a head-to-head comparison, a single dose of 2% clindamycin phosphate vaginal cream was found to be as effective as a seven-dose regimen of another clindamycin-based BV treatment [11]. The basis of the formulation used in 2% clindamycin phosphate vaginal cream has been summarized [12].

More recently, a vaginal gel containing 2% clindamycin phosphate has been developed as a potential new product to treat women diagnosed with BV [13]. This gel is designed to take advantage of body temperature to undergo sol-to-gel transition that can be utilized in several different states, for example, as a liquid (viscous or dilute) or a semi-solid (gel/paste). The gel also possesses bioadhesive properties, erodes slowly, and releases drug over several days. All these properties should increase the duration of action and potentially improve the effectiveness of clindamycin relative to existing vaginal products [13].

To evaluate the ability of this gel to treat BV, a proof-

ofconcept study was conducted in 30 women diagnosed with BV. The investigation was designed as a single-center, open label study. The gel was administered as a single dose (5 g) containing 100 mg clindamycin. The overall study design was generally consistent with the current draft US FDA Guidance for the treatment of BV [14].

Materials and Methods

The gel, containing 2.0% clindamycin phosphate as the free base, is composed of Poloxamer 407, xanthan gum, citric acid, sodium citrate, and benzyl alcohol in purified water, and was packaged in pre-filled vaginal applicators (5.0 g). The gel was prepared under current Good Manufacturing Practices.

The clinical study was conducted at a single-site (OBGYN Associates of Montgomery, Montgomery, AL, USA). Clindamycin phosphate, the active ingredient in the vaginal gel, is an approved drug indicated for vaginal treatment of BV and the excipients are all used in other vaginal products. These aspects allowed conduct of the study without IRB approval. All patients consented prior to treatment. Patient information was collected and a pelvic examination was performed to establish eligibility. Caucasian and African American women ($n = 30$) between the ages of 17 and 51 were enrolled. If all study requirements were met

Table 1. — Summary of clinical, bacteriologic, and therapeutic cure.

Study Visit	Clinical Cure	Bacteriologic Cure	Therapeutic Cure
Visit 2	24 of 28 (86%)	4 of 7 (57%)	4 of 7 (57%)
Visit 3	23 of 24 (96%)	7 of 9 (78%)	6 of 9 (67%)

and the patient consented for enrollment, a single dose clindamycin phosphate 2% vaginal gel was provided (visit 1). Subjects met the inclusion criteria if all four Amsel criteria were observed [15]: 1) off-white (milky or gray), thin, homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina, 2) vaginal secretion pH of > 4.5 , 3) the presence of clue cells $> 20\%$ of the total epithelial cells on microscopic examination of the saline wet mount, and 4) a fishy odor (i.e., a positive whiff test) of the vaginal discharge with addition of a drop of 10% KOH. A microscopic evaluation of the vaginal smear was performed in the last ten subjects and scored as per the Nugent method [16]. The Nugent scoring was based upon microscopic examination of the Gram stained vaginal smears for quantification of specific bacterial morphotypes. Women returned to the clinic approximately days 7–14 following single administration of the vaginal gel (visit 2). Following pelvic examination, the tests listed above were repeated. The subjects were questioned about the comfort level after the initial treatment and then re-examined. The subjects returned to the clinic for a final visit (visit 3) 21–30 days following drug administration. The tests listed above were repeated following pelvic examination. The subjects were again questioned about the comfort level after the initial treatment.

The primary efficacy endpoint of the study was clinical cure, which includes the clinical response of subjects at visit 2. Clinical cure was defined as resolution of the clinical findings from visit 1. Subjects had to have all of the following: 1) resolution of abnormal vaginal discharge, 2) negative whiff test, and 3) presence of clue cells at less than 20 percent of the total epithelial cells on microscopic examination of the saline wet mount. Secondary efficacy endpoints were proportions of subjects with bacteriologic cure (Nugent scores < 4) and therapeutic cure (a composite endpoint of clinical cure plus a Nugent score < 4).

Results

Patients diagnosed with BV were recruited into the study and given the 2% clindamycin vaginal gel in prefilled vaginal applicators. They were instructed to administer a single dose (5.0 g) and return to the clinical within the next seven to 14 days (visit 2). Of the 30 patients, two were unevaluable (one missed visit 2 and a second was subsequently diagnosed with *Chlamydia trachomatis*). Thus, these two patients were excluded from the clinical cure assessment at visit 2. Of the remaining 28 patients, 24 (86%) were successfully treated based on resolution of discharge, whiff test of vaginal discharge, and presence of less than 20% clue cells of total epithelial cells on microscopic of saline wet

mount. Of the subset of ten patients evaluated for Nugent score, nine were evaluable (the one patient diagnosed with *Chlamydia* was in this subset) at visit 2. Of these, two patients did not have swabs taken and were excluded from the analysis. Of the remaining, three women had Nugent scores of greater than 3 (two had a score of 4 and one scored 7). Thus, the bacteriologic cure was observed in four of seven (57%) women. Therapeutic cure was the same (four of seven women or 57%).

The women returned to the clinic for visit 3 to evaluate the continued efficacy of treatment on days 21 to 30 following product administration. Of the 24 women who completed visit 2 and were cured based on Amsel criteria, 23 (96%) remained cured at visit 3. Of the subset of ten women evaluated using Nugent scoring (bacteriologic evaluation), seven of nine (78%) had a score of 3 or less. The other two patients had Nugent scores of 6 and 9. In this group, six of nine were considered therapeutically cured (67%). Results of this study are summarized in Table 1.

There were no reports of adverse reactions including local reactions to the gel over the course of the study. Women did not complain of gel leakage and they generally found the gel to be acceptable.

Discussion

Clindamycin phosphate products currently marketed for intravaginal use in the US are (a) 2% single dose cream, (b) 2% cream dosed daily for three or seven days, and (c) 100 mg ovules dosed once daily for three days. Of these products, 2% single dose cream is similar to the experimental product reported herein based on dosing regimen. In a head to head study against 2% vaginal cream (seven once-daily doses), a single dose of 2% single dose cream had a clinical cure of 64.3% compared with that of 2% vaginal cream (seven once-daily doses) which had a clinical cure of 63.2% [11]. In the pivotal, placebo-controlled study, 2% single dose cream had a clinical cure of 41% compared with 19.7% in the placebo group. In another study comparing seven once daily doses of 2% single dose cream, the clinical cure was 53.4% (single dose) compared with 54.0% (seven doses). In all these studies, clinical cure was defined as resolution of all four Amsel criteria. Current FDA guidance of clinical cure is defined as resolution of three Amsel criteria (exclusive of pH) [14].

Two percent single dose is a cream-based product designed with bioadhesive and sustained release properties [12]. The vaginal gel used in this study is also a bioadhesive composition with the added feature of increased gelation leading to increased viscosity at body temperature compared with room temperature [13]. Under in vitro condi-

tions, the vaginal gel was also found to release clindamycin over an eight-day period and the gel was slow to erode. These features should increase the efficacy of the active ingredient, clindamycin, by providing a vaginal reservoir of drug that is released slowly over time.

While there are some short comings with this study (open label, small sample size, single center/investigator), the data collected suggest that this new vaginal gel may provide efficacy equal to or possibly greater than observed with 2% single dose cream. The data are consistent with a single dose product that could provide a simple to use, efficacious product that should be well-received by women requiring treatment of BV. These findings support expanded clinical investigation of the efficacy and safety of this thermosetting bioadhesive clindamycin vaginal gel.

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Conflict of Interest

The authors declare no conflict of interest.

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