Expert Opinion

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Advancing vaginal drug delivery

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Bacterial vaginosis and vulvovaginal candidiasis are the two most common forms of vaginitis in female patients. Although a variety of effective treatments have been available to eradicate these infections, limitations have lessened the utility of previously available products. Oral therapies are often fraught with systemic adverse reactions, as well as the potential to interact with concomitant medications. Vaginal preparations, although generally perceived as safer, have historically been undesirable for women to use due to their multiple days of dosing; messy, dripping creams; and requisite night-time dosing. Recognising that the therapeutic delivery of the active agent plays a critical role in the overall success of therapy, and attempting to circumvent the weaknesses of traditional vaginal drug delivery while maintaining and even improving safety profiles, a new form of vaginal drug delivery was developed. This unique and proprietary delivery system, with both bioadhesive and sustained release properties, introduces the convenience of a single dose of medication that can be applied at any time, with efficacy rates equivalent to lengthier durations of treatment. This advance in science and technology has now been successfully applied to two products, Gynazole-1® (butoconazole nitrate 2%) and Clindesse™ (clindamycin phosphate 2%) indicated for the treatment of vulvovaginal candidiasis and bacterial vaginosis, respectively, in order to enhance convenience and compliance for the treatment of two very common clinical conditions.

Keywords: bacterial vaginosis, bioadhesion, butoconazole, clindamycin, sustained release, vaginal drug delivery, vaginitis, vulvovaginal candidiasis

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1. Introduction

Vaginitis, the broad term that is typically applied to any condition causing an inflammation of the vagina, includes three primary causes: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV) and trichomoniasis. In the US alone, vaginitis accounts for an estimated 10 million office visits per year [1]. In Europe, VVC is diagnosed more frequently than BV, whereas the US has a higher incidence of BV, followed by VVC. Worldwide, trichomoniasis is on the decline [2]. Available treatments for VVC include vaginal antifungal preparations, along with one oral medication indicated for the treatment of VVC. Similarly, BV is most often treated with one of two available antibiotics, either of which may be administered systemically or vaginally in various preparations.

The perceived convenience of oral medications is shadowed by the risk of systemic adverse drug reactions and the potential to interact seriously with concomitant medications [3]. Furthermore, the decision to treat localised infections with a topical treatment (provided equivalent efficacy) is one often advocated by various healthcare practitioners. Criticisms for the vaginal delivery of existing medications have often included the inconvenience of multiple days of dosing, coupled with the messiness associated with product leakage from the vaginal cavity. To minimise leakage, most traditional creams advise applying while in the supine position (i.e., at bedtime). In addition to delaying the time to onset of relief, night-time application can further inconvenience the patient's lifestyle. In order to achieve and maintain

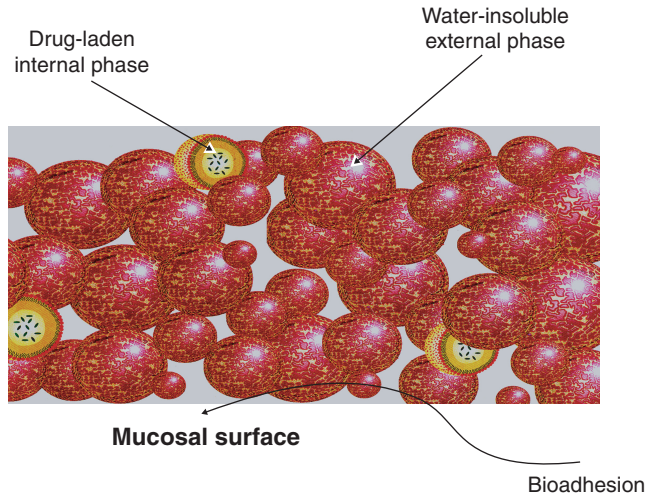

Figure 1. Site release: high internal phase emulsion. Reprinted with permission from Thompson D, Levinson RS: A bioadhesive topical drug delivery system. *Drug Delivery Systems & Sciences* (2002) **2**(1):17-19 [4], courtesy of the publishers of Drug Delivery Systems & Sciences.

the desired drug concentrations in the vagina, sequential dosing is often necessitated. Products using reduced or single-day treatment may employ substantially increased drug concentrations, which can increase the risk of vaginal irritation. In addition, some commercially available vaginal preparations require cleansing of the applicator and reuse during the course of treatment, which women may find undesirable.

2. SITE RELEASE® vaginal delivery system: advancing technology

The lack of optimal treatments available for two extremely common forms of vaginitis served as the impetus to develop a unique drug delivery system, designed to eliminate the inconveniences of conventional vaginal delivery systems, while maintaining safety profiles and still providing the same high level of therapeutic treatment. The SITE RELEASE® (SR) vaginal delivery system was introduced in the marketplace in the US in 2000 as a unique and proprietary delivery system, covered by several worldwide patents, designed for bioadhesion to the mucosal surfaces of the vagina, allowing for a sustained and controlled delivery of drug over time. The design advantages of the bioadhesive topical drug delivery system include minimisation of vaginal cream leakage; administration of therapy during anytime of the day; less total drug exposure per course of therapy; continuous drug release; and more rapid relief of symptoms than the conventional cream, all in a single-dose therapy.

SR technology distinguishes itself from other vaginal preparations due to its unique formulation approach and the resultant bioadhesion and the controlled release of the active drug moiety. SR is a dual-phase emulsion with an internal hydrophilic phase, into which the active drug moiety is incorporated. The water-in-oil design contains an internal phase concentration of up to 90%, considerably higher than other commercial emulsions yet remarkably stable (**Figure 1**). This high internal phase concentration confers a twofold purpose: first, the external lipid phase repels moisture, thereby resisting dilution and removal of the preparation with normal vaginal secretion; second, the lipid layer serves to sequester the dispersed water phase containing the active drug payload, allowing for the release of the active drug to be metered out slowly over time.

2.1 Bioadhesion

Clinically, the bioadhesive properties of SR have been demonstrated in two separate studies. Weinstein *et al.* studied the vaginal retention time of cream delivered via SR and a standard vaginal cream, each containing butoconazole nitrate 2% [4]. A total of 16 healthy females were treated intravaginally with either the standard cream or the SR bioadhesive delivery system and monitored daily over 7 days for the amount of residual cream detected within the vaginal cavity following a gynecological swab. Analysis of the data demonstrated a median vaginal retention time of ~ 2.5 days for the standard cream. The median vaginal retention time of the SR delivery system in treated patients was 4.2 days ($p = 0.0024$), 63% longer than a standard formulation containing the same active ingredient, butoconazole nitrate.

A second study demonstrating bioadhesion is available in 44 healthy volunteers randomised to a single dose of conventional antifungal cream, or a single dose of the same antifungal delivered with the enhanced SR technology [5]. After application of a single-dose of either treatment, women were required to wear mini-pads for a 48-h period to evaluate product leakage from the vaginal cavity. A total of 28 women were available for analysis to provide information regarding product leakage. At every data point, significantly more cream was

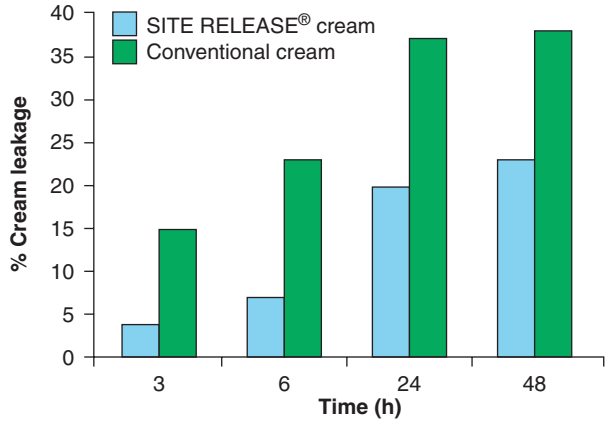

Figure 2. Bioadhesive technology. Percentage of accumulated cream in sanitary towels following vaginal application of equivalent doses captured at different controlled times (3, 6, 24 and 48 h). N = 28 healthy volunteers. At all times the differences are statistically significant ($p < 0.05$). Data on file, KV Pharmaceutical.

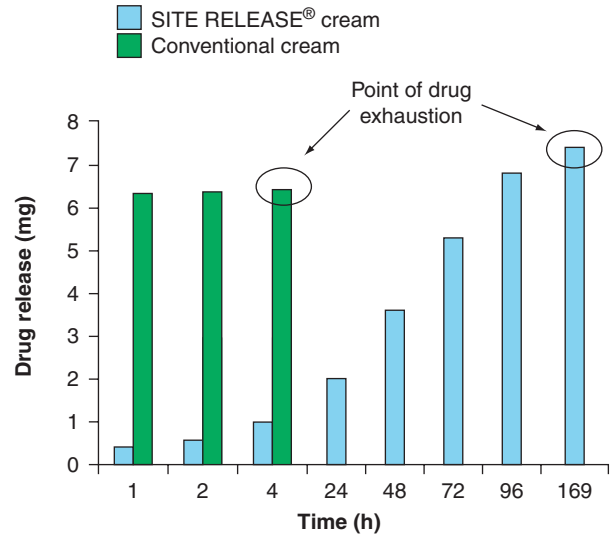

Figure 3. *In vitro* comparison of medication release from a conventional cream versus a site release cream. Approximately 6 – 8 mg of active drug. Data on file, KV Pharmaceutical. Reprinted with permission from Thompson D, Levinson RS: *A bioadhesive topical drug delivery system. Drug Delivery Systems & Sciences* (2002) **2**(1):17-19 [4], courtesy of the publishers of Drug Delivery Systems & Sciences.

found to leak from the traditional formulation versus the SR emulsion (**Figure 2**). Importantly, almost 25% of the total administered amount of cream had escaped from the vagina between 3 and 6 h after initial administration with a conventional vaginal cream. In contrast, < 5% of the cream had leaked from the vaginal cavity during this same time frame using the unique SR formulation. Overall, leakage was reduced by > 50% with this novel vaginal emulsion vehicle in comparison to the conventional cream.

2.2 Controlled release

In vitro analysis using the SR technology with butoconazole has also revealed continuous release of the active drug moiety while shaken in a pH 4.3 acetate buffer, designed to simulate vaginal fluid [6]. The active ingredient was released continuously throughout a 7-day study period when delivered via SR (**Figure 3**). In marked contrast, a conventionally marketed vaginal cream was used as a control and was found to disintegrate rapidly and begin to release its active drug immediately. In fact, the conventional vaginal cream released its entire payload of active drug (butoconazole nitrate) within the first several hours. The rapid and complete release of the active drug moiety in the conventional carrier differs significantly from the SR vehicle, which slowly metered out release of the same active drug moiety over a considerably longer period of time: 7 days.

2.3 Clinical benefits

The SR delivery system, with its characteristic bioadhesion and controlled release delivery of the active drug moiety, allows for the resolution of symptoms associated with VVC more rapidly than both oral fluconazole and vaginal miconazole. Traditional vaginal creams commonly require application at bedtime so that the supine position of the patient will help maintain the cream within the vaginal cavity. Following this application, such conventional creams, as represented in **Figure 3**, deliver a rapid and complete release of the active medication from the vehicle in which it is carried. Essentially, the patient is actively treated for ~ 4 h with the available medication from a conventional cream, and must then remain without exposure to the active drug moiety for ~ 20 h until the next dose of drug can be applied, and the sequence is repeated until completion of the treatment regimen. Conversely, the SR system enables the patient to use the product immediately, as the technology is designed to adhere to the vaginal wall. During the ~ 4 days of vaginal retention, the active drug moiety is designed to be slowly released over time, enabling the actual drug to remain in constant contact with the mucosal tissues to continuously treat the infection.

Furthermore, the bioadhesive and sustained release properties allow for a low dose of active drug to achieve a clinical cure equivalent to treatments using significantly larger doses of medication. Adverse drug reactions are often dose related, with either the appearance of new adverse events or the exacerbation of existing side effects as the dose is escalated. Therefore, the lowest available dose that can effectively result in a clinical cure should be used to minimise the risk of untoward effects. Because the SR technology is designed for the chosen active drug moiety to stay directly at the site where it is needed, an extremely low dose of the medication can be used, yet can still provide comparable rates of therapeutic cure.

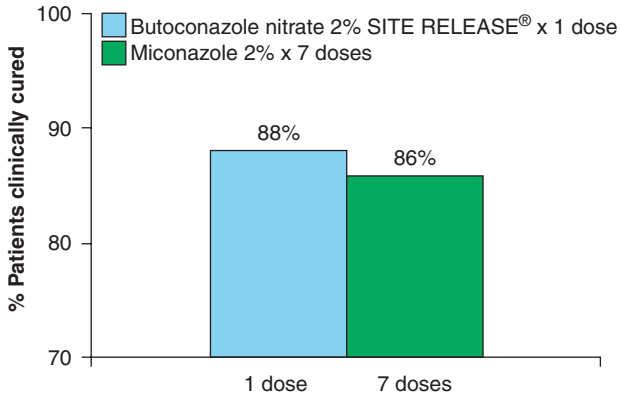

Figure 4. Post-treatment clinical cure rates (30 – 45 day follow-up visit). The clinical cure rate for seven doses of miconazole at 8 – 10 days was 96%. Therapeutic efficacy is based on clinical cure rate (relief of symptoms) and microbiological cure (pathogen eradication). The therapeutic efficacy rate after 30 days for the one dose treatment of butoconazole nitrate was 62% as compared with 68% for the 7-day treatment of miconazole-7. Based on these results, there is no statistically significant difference between these treatments. Adapted from Brown D, Henzl MR, Kaufman RH: Butoconazole nitrate 2% for vulvovaginal candidiasis: new, single-dose vaginal cream formulation vs. seven-day treatment with miconazole nitrate. *J. Reprod. Med.* (1999) **44**:933-938.

3. Clinical profile

The SR technology is currently available in two commercial products in the US: Gynazole-1® (butoconazole nitrate 2% SR) and Clindesse™ (clindamycin phosphate 2% SR) indicated for the treatment of VVC and BV, respectively.

3.1 Vulvovaginal candidiasis treatment

Currently, there are various antifungal medications designed for vaginal drug delivery available both over-the-counter and by prescription. In addition, one medication, fluconazole, is indicated for the oral treatment of VVC.

Butoconazole nitrate 2% SR has demonstrated efficacy comparable to other VVC treatments. Brown *et al.* confirmed the efficacy of a single dose of butoconazole nitrate 2% SR vaginal cream and seven doses of miconazole nitrate 2% in a conventional vaginal cream when studied in 205 infected patients [7]. All 205 patients were confirmed both clinically and by potassium hydroxide smear to have VVC. The clinical cure rates at 7 – 10 days post-therapy initiation were comparable between the single dose of butoconazole nitrate 2% SR vaginal cream and seven doses of the conventional miconazole 2% vaginal cream at 92 and 96%, respectively. There was no statistical difference in the cure rates between the two therapies. Similarly, 30 days after treatment completion, cure rates were 88 and 86% for butoconazole nitrate 2% SR vaginal cream and the seven doses of the conventional miconazole 2% vaginal cream, respectively (**Figure 4**). The *in vitro* microbiological cure rates were also comparable between therapies at both the initial follow up and 30-day follow-up visits.

More significant from a patient satisfaction standpoint is the data analysis of a subset of the aforementioned 205-patient study. Of the patients randomised to either butoconazole nitrate 2% SR or the seven doses of miconazole vaginal cream ~ 23% were suffering from severe or very severe symptoms of VVC (pruritus, irritation and so on) at baseline. Patients treated with butoconazole nitrate 2% SR vaginal cream experienced a rapid relief of the signs and symptoms of VVC after only the first day of therapy [7]. There was a statistically significant difference ($p = 0.01$) in this relief when compared with conventional therapy with seven doses of miconazole 2% conventional vaginal cream (**Figure 5**). After only 1 day, the percentage of butoconazole nitrate 2% SR vaginal cream treated patients with severe symptoms declined from 23 to 6%. Comparable relief between therapies was not achieved until after 3 days of therapy with the conventional miconazole 2% vaginal cream, an important feature potentially leading to improved patient satisfaction with butoconazole nitrate 2% SR vaginal cream. Hence, with comparable efficacy and rapid relief of severe symptoms after only 1 day of therapy, treatment with butoconazole nitrate 2% SR vaginal cream addresses an important patient expectation. In addition, patient compliance is simultaneously enhanced by the mere fact that one application of butoconazole nitrate 2% SR vaginal cream fulfills the total dosing requirement for a full course of therapy.

Similarly, a study was recently conducted comparing the rate of relief experienced by patients using butoconazole nitrate 2% SR vaginal cream versus oral fluconazole 150 mg [8]. Intuitively, it stands to reason that a topical therapy applied to a site of infection would start to mitigate the itching and burning associated with VVC more rapidly than a systemic medication that must travel throughout the body before reaching the site of infection; this premise was indeed verified in an open-label, randomised parallel study of 181 patients. The time to first relief of symptoms exhibited by 50% of patients occurred at 17.5 h for women in the butoconazole nitrate 2% SR group versus 22.9 h for the fluconazole patients. At 12- and 24-h post-treatment, 44.4 and 72.8% of patients in the butoconazole nitrate 2% SR vaginal cream group reported first relief of symptoms versus only 29.1 and 55.7% in the fluconazole group at these same times ($p = 0.044$ and 0.024, respevtively).

Two additional studies of butoconazole nitrate 2% SR vaginal cream against a single-dose 500-mg clotrimazole vaginal tablet serves to reinforce this data, in that a single dose of butoconazole in the SR vaginal cream provides equivalent or superior rates of cure for VVC as compared with the single dose clotrimazole vaginal tablet [9].

The approval of fluconazole, a triazole antifungal, for the oral treatment of VVC provided women with a convenient alternative to the messy and repetitive vaginal creams that

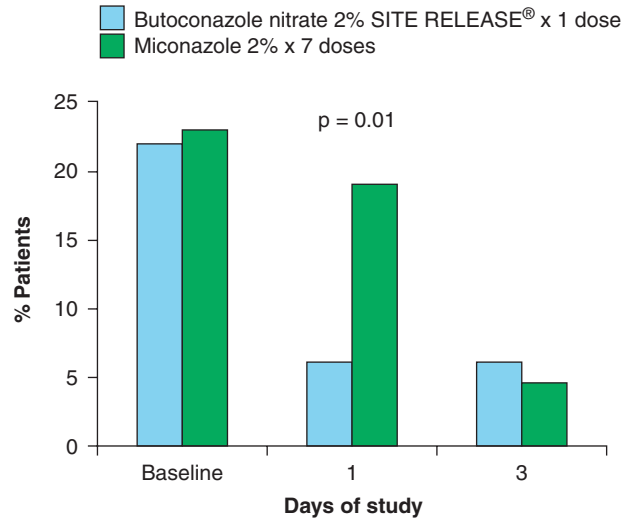

Figure 5. Proportion of patients with severe/very severe symptoms of vulvovaginal candidiasis. Adapted from Brown D, Henzl MR, Kaufman RH: Butoconazole nitrate 2% for vulvovaginal candidiasis: new, single-dose vaginal cream formulation vs. seven-day treatment with miconazole nitrate. *J. Reprod. Med.* (1999) **44**:933-938.

were previously the only option. However, fluconazole, like any other systemic medication, cannot be presumed innocuous and wholly devoid of safety concerns. The product labelling for a single dose of fluconazole 150 mg denotes a 26% incidence of adverse events, including headache (13%), nausea (7%) and abdominal pain (6%) [10]. Rare reports of angioedema and anaphylactic reactions are available from postmarketing surveillance. Furthermore, fluconazole is recognised as an inhibitor of the cytochrome P450 system, and thus can interact with other medications a patient may be taking, including certain medications that have extremely narrow therapeutic ranges. Fluconazole is recognised to interact with oral hypoglycaemics, phenytoin, carbamazepine, cyclosporin, tacrolimus and warfarin. Drug interactions must also be considered with vaginal medications: in 2001 the FDA required miconazole-containing vaginal products to bear a warning that they may potentiate the effect of anticoagulants, increasing the risk of bleeding [101]

. Conversely, the SR technology has been demonstrated to have a remarkably low systemic exposure, even when compared with other vaginal treatments. When utilised to deliver the antifungal butoconazole, the systemic absorption has been measured to be only 1.7% of the single 100-mg dose. Consequently, there is a low expectation of drug interactions and currently no known drug interactions exist with this butoconazole nitrate 2% SR. Furthermore, butoconazole nitrate 2% SR was well tolerated in clinical trials with 5.7% of patients reporting complaints such as vulvar/vaginal burning, itching, soreness and swelling, pelvic or abdominal pain or cramping, or a combination of two or more of these symptoms [9]. Only 1% of these adverse events were deemed treatment related [9].

In addition to high rates of efficacy from both a clinical and an exemplary safety profile, patient satisfaction with this enhanced technology has also been assessed. In a survey conducted in almost 2000 women who used the SR technology for the treatment of VVC, 97% of women stated that they would use that product again [11]. In order to garner approval ratings this high, women cited the fast symptom relief as being the most important attribute in treating a yeast infection. Women also cited a desire for a single-dose product and one that was not messy compared with other products; all properties found with the SR delivery system.

3.2 Bacterial vaginosis treatment

Currently, two antibiotics, metronidazole and clindamycin, are used to treat BV. Both antibiotics may be taken either orally or dosed vaginally in various preparations [12]. All treatments require a prescription, and are usually diagnosed by a clinician finding the appearance of three out of four of Amsel's criteria: homogenous discharge that adheres to the vaginal walls; amine odour before or after vaginal secretions are applied to KOH ('whiff' test); a pH > 4.5; and clue cells following microscopic examination [13]. BV, unlike vaginal yeast infections, can have negative consequences if left untreated including pelvic inflammatory disease, which can progress to infertility; enhanced transmission of sexually transmitted diseases, including HIV; and complications in pregnant women, including premature delivery [1,14].

Clinical studies have demonstrated approximate equivalence between oral and vaginal therapies of both metronidazole and clindamycin, when dosed between 3 and 7 days of therapy [2,15-17]. Because efficacy rates are presumed to be equivalent, therapy is often chosen based on clinician preference and individual patient considerations (i.e., potentially interacting medications).

Both metronidazole and clindamycin have a long history of use for bacterial infections and excellent coverage against the common pathogens implicated in BV; likewise, both medications have certain limitations that may constrain their clinical utility. Metronidazole is widely recognised to interact with alcohol and certain medications [18]. Patients must be warned to avoid alcohol, even minute amounts, due to the potential development of a disulfiram reaction, in which the patient becomes violently ill (alcohol should be avoided for ≥ 24 h after the last metronidazole dose, although the exact prevalence of disulfiram-like reactions is not specifically known). Metronidazole greatly potentiates the effect of warfarin, and increases the patient's chance of bleeding; metronidazole may also increase the level of lithium; phenobarbital and phenytoin increase the metabolism of metronidazole, thus decreasing metronidazole serum levels; and cimetidine may increase metronidazole levels. In addition, metronidazole should be used cautiously in

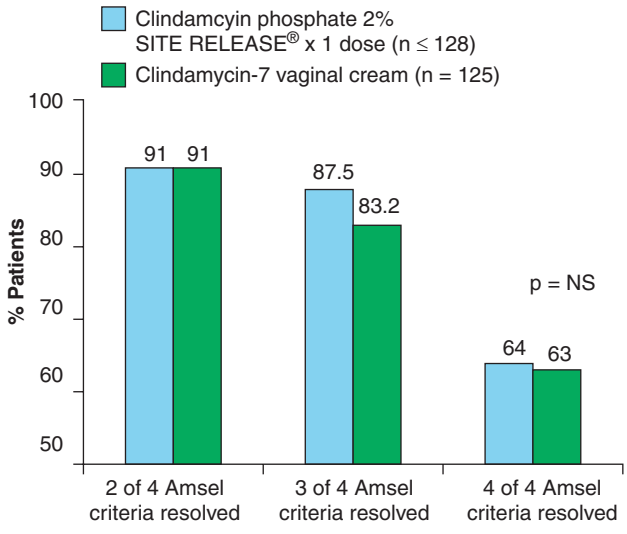

Figure 6. Post-treatment clinical cure rates. Multi-centre, randomised, parallel-group study of 253 per-protocol patients with bacterial vaginosis . Patients were considered clinically cured, with the resolution of at least three of the four signs and symptoms of bacterial vaginosis as defined by Amsel criteria, at 21 – 30 days post-dosing. No significant difference between either product in clinical cure rates.

patients with hepatic insufficiency and CNS diseases, as convulsive seizures and peripheral neuropathy have been reported, albeit rarely, with metronidazole use.

Clindamycin also has broad coverage against the pathogens implicated in BV, and appears, both orally and vaginally, to be better tolerated than metronidazole. One potentially serious side effect associated with clindamycin is the rare possibility of clindamycin-induced overgrowth of *Clostridium difficile* leading to pseudomembranous colitis [19]. Clindamycin may precipitate the actions of neuromuscular blocking agents, which are generally reserved for use prior to surgical procedures. Clindamycin, like metronidazole, may be associated with gastrointestinal side effects when taken orally; however, the incidence is less than metronidazole.

Vaginal preparations are generally better tolerated than their oral counterparts, likely as a result of their low systemic circulation of drug [2]. However, it must be recognised that significant amounts of the active drug moiety may be absorbed via the vagina, particularly with the gel-based preparation of metronidazole, in which as much as 56% of the intravaginal dose may be absorbed systemically [20]. Among the vaginal products, the same drug interactions and systemic adverse events are possible as a function of the active drug moiety, but are less likely to appear due to lower doses and less systemic exposure. In instances in which the intravaginal dose is particularly low, especially in conjunction with minimal systemic absorption, the likelihood of systemic adverse reactions is fairly remote. As with all antibiotics, both metronidazole and clindamycin can precipitate an overgrowth of yeast, resulting in a vaginal yeast infection. Thus, VVC can appear following the administration of either metronidazole or clindamycin, with both oral and vaginal use.

Due to enhanced tolerability and safety, clinicians may feel that the vaginal delivery of either metronidazole or clindamycin is the better choice to treat BV; however, some patients and clinicians may have the perception that oral medication is advantageous with respect to ease of use, convenience and decreased mess. Contrary to this perception, patient preference for vaginal drug treatment was documented in a study examining three different treatments of BV. In this study of 101 patients, randomisation to oral metronidazole, vaginal metronidazole or vaginal clindamycin cream, there was no statistically significant difference in cure (oral metronidazole 84.2%; vaginal metronidazole 75.0%; vaginal clindamycin 86.2%) [16]. In addition, post-treatment rates of VVC were seen in 12.5% of oral metronidazole patients; 14.8% of vaginal clindamycin patients; 30.4% of vaginal metronidazole patients, results of which were not statistically significant when compared between the groups. Although clinical cure rates and post-treatment VVC were not statistically different, women reported a higher level of satisfaction with the vaginal treatments compared with the oral treatment.

A multi-centre, randomised, parallel-group study of 253 patients with BV was recently conducted to compare the efficacy of clindamycin phosphate 2% SR, the unique single-dose treatment, with that of a conventional clindamycin 2% vaginal cream, which requires seven nightly vaginal doses of clindamycin [21]. The clinical cure rates (when defined as resolution of three out of four of Amsel's criteria) between the two treatments were 87.5% with clindamycin phosphate 2% SR and 83.2% with the conventional clindamycin 2% vaginal cream ($p = 0.399$) in participants meeting study protocol (**Figure 6**). Thus, a single dose of clindamycin, given via the SR system, achieves a clinical cure rate equivalent to seven doses of clindamycin given as the traditional vaginal cream.

Likewise, when the Nugent criterion was applied to determine clinical cure (defined as a score < 4) the percentage cure was also equivalent between the two groups: 56.5% for clindamycin phosphate 2% SR versus 57.7% for the conventional clindamycin vaginal cream ($p = 0.788$). Patients were also evaluated according to investigator cure in which the investigator determined whether the patient needed an additional treatment for BV. The study investigators deemed a very high rate of efficacy for both treatments.

From this same study, one can also examine the resolution of each of the primary individual symptoms of BV: whiff test, percentage clue cells, discharge and vaginal pH. Again, all data gathered demonstrated no statistically significant differences between a single dose of clindamycin phosphate 2% SR versus seven doses of the conventional clindamycin 2% vaginal cream (**Figure 7**).

Beyond the greatly enhanced convenience to patients treating BV, the SR system also allows for significantly decreased exposure to the active medication in comparison to various other treatment regimens on the market with the same active

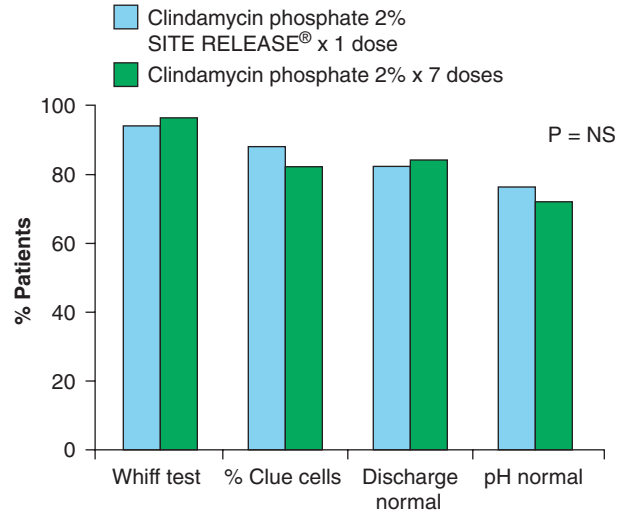

Figure 7. Normalisation of individual symptoms of bacterial vaginosis. Normalisation of Amsel criteria included a negative whiff test; clue cells < 20%; return of vaginal discharge to normal; and vaginal pH < 4.7.

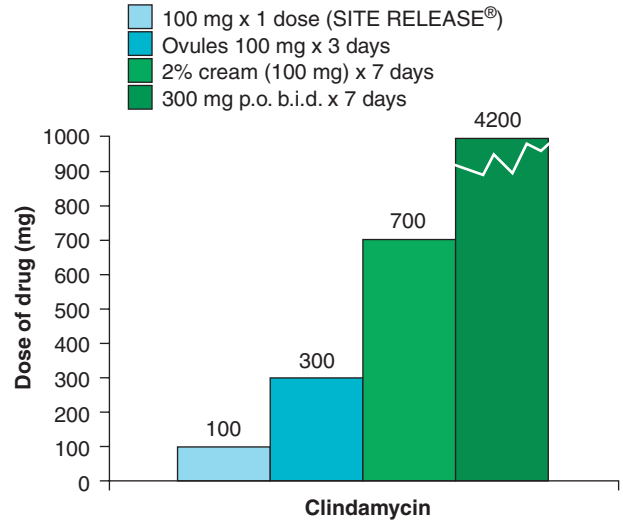

Figure 8. Dose of drug per treatment regimen.

ingredient (**Figure 8**). The next lowest available amount of clindamycin to treat BV still requires a dose of clindamycin that is threefold the amount found when the SR system is applied [22]. Furthermore, the SR delivery system has demonstrated a minimal (1.7%) system absorption when incorporating an antifungal as the active pharmaceutical ingredient and would be expected to behave similarly when using other compounds. In fact, clinical studies have demonstrated systemic blood levels of clindamycin to be 88% lower with the SR system when compared with a conventional 7-day vaginal cream containing the same active drug moiety.

With regards to safety, both clindamycin phosphate 2% SR cream and seven doses of clindamycin vaginal cream were well tolerated, with an incidence of side effects similar to placebo. The most common side effects were VVC (14.1%); vulvovaginal pruritus (3.3%) and headache (2.7%), which were not statistically different from the seven doses of clindamycin cream [23].

4. Future treatment

Currently, SR is commercially employed in two separate products, using two different active drug moieties for the treatment of BV and VVC, the two most common types of vaginitis. Other medical conditions that necessitate localised vaginal treatment are being evaluated for applications of the SR technology. This technology need not be limited to infectious disease states; it also provides an ideal drug delivery vehicle for other therapeutic needs applicable to vaginal drug delivery platforms.

4.1 Alternative technologies

Previously, the only modifications to BV and VVC treatment was the realisation that the duration of treatment could be shortened from 10 to 3 – 5 days, without compromising efficacy in the general population. Whereas this shortened time frame undoubtedly made treatment more convenient for patients, women still disliked the need for a minimum of 3 nights of application with messy vaginal creams. Vaginal tablets and ovules were introduced to the marketplace as an alternative, less messy formulation; however, many women are uncomfortable with the insertion of a solid dosage form or experience problems with expulsion of the entire ovule or tablet. The need to overcome these problems was resolved with the introduction of SR, a technology unlike any previously available. Advances in technology are recognised as beneficial to patients in terms of enhancing compliance rates; increasing the likelihood of therapeutic efficacy, and possibly decreasing healthcare costs associated with nonadherence [24]. In the aforementioned clinical study, women who received clindamycin phosphate 2% SR were found to be 95.4% compliant with the whole treatment duration (i.e., one dose). Conversely, women randomised to the 7-day treatment of clindamycin had a decrease in compliance correlated to days of dosing of therapy. By day 3 of therapy, compliance with 7-day clindamycin was 89.1%, a statistically significant decrease in compliance compared with the 95.4% found with one-dose of clindamycin phosphate 2% SR. Compliance with the 7-day treatment of clindamycin continued to decrease, and was determined to be only 65.3% on day 7, the final day of therapy. Furthermore, this data were obtained via a clinical study, under circumstances where compliance is expected to be higher than real-life use when patients may abandon therapy after a few days worth of treatment. Regardless of the means to decrease the frequency of dosing, the result must be medication that has not been compromised with regards to therapeutic efficacy or increased side effects. SR is the first and only vaginal drug delivery system that has accomplished these

goals of advancing technology without compromising efficacy or safety.

5. Conclusion

The introduction of SR, a novel vaginal delivery system that employs bioadhesion and controlled release, has optimised delivery of drug in the vaginal cavity, eliminating or greatly minimising the drawbacks once associated with conventional vaginal creams. SR provides a safe and effective alternative, enhancing compliance and greatly improving convenience for the patient. One-dose treatment becomes achievable, a considerable advance when compared with other regimens requiring anywhere from 3 to 10 doses for VVC and BV. Due to the tenacious adherence of this system to moist mucosal tissue, minimal leakage occurs, which means a woman can use this product immediately after receiving it, rather than suffering through symptoms or delaying treatment until bedtime. Patient compliance is virtually ensured to a 100% level of confidence. This extraordinary technology also allows the product to be dosed in the doctor's office, without any interruption to the women's daily routine. The significant decrease of both active drug used and absorbed with this system, and the decreased amount of overall cream required for use, means less drug exposure and less mess for the patient to contend with, compared with other vaginal creams. The clinical correlations of this observation lead to a one-time treatment for a full course of therapy for both VVC and BV, a dosing regimen designed to lead to improved patient compliance, convenience and satisfaction.

6. Expert opinion

In the almost 2000 years since Galen (131 – 201 AD), conventional topical pharmaceuticals have not undergone significant changes. Ultimately, the same preparations described by Galen in his famous 'Materia Medica' consisted of oleaginous (grease-based) ointments, water-in-oil and oil-in-water emulsions and liquid lotions. Up to the advent of SR technology by KV Pharmaceutical Company, little had changed with regard to topical drug delivery.

The development of SR bioadhesive delivery system represents a major advance in topical drug delivery technology in that both controlled release of the active principle(s) and the presence of a bioadhesive drug delivery platform is provided. These important attributes result in several advantages in the delivery of topical medicaments, including:

- The preparation does not need to be applied as often as a conventional topical pharmaceutical due to the 'substantivity' or bioadhesion of the delivery platform.
- The controlled release of the active drug(s) can afford a substantial drug sparing effect as seen with other controlled release systems, such as oral or parenteral controlled release products. This means that a therapeutic effect can be achieved with less drug exposure to the patient.
- The bioadhesive nature of the technology can result in a substantial reduction in the number of re-applications of the product in order to obtain a desired therapeutic response, thus greatly enhancing the likelihood of compliance. In some cases, one-dose-to-cure has been achieved.

The attributes of KV's SR technology are significant and represent a major advancement in pharmaceutical technology bearing not only therapeutic advantages but also advantages in compliance, convenience to the patient and in reduction of material that needs to be applied topically to affect the desired therapeutic response. All of these attributes can easily be related to improved therapy and a potential reduction of cost as compared with conventional topical pharmaceutical technologies.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. SCHWEBKE JR: Gynecologic consequences of bacterial vaginosis. Obstet. Gynecol. Clin. N. Am. (2003) 30(4):685-694.

•• **Excellent review underscoring the importance of proper diagnosis and treatment of BV.**

2. SOBEL JD: Vaginitis. *N. Engl. J. Med.* (1997) **337**(26):1896-1902.

3. MIKAMO H, KAWAOE K, IZUMI K, WATANABE K, UENO K, TAMAYA T: Comparative study on vaginal or oral treatment of bacterial vaginosis. *Chemotherapy* (1997) **43**(1):60-68.

• **Provides an understanding to support rationale for local treatment of vaginal infections.**

4. WEINSTEIN L, HENZEL MR, TSINA IW: Vaginal retention of 2% butoconazole nitrate cream: comparison of a standard and a sustained-release preparation. *Clin. Ther.* (1994) **16**(6):930-934.

• **The first clinical study to demonstrate increased vaginal retention of medication with proprietary drug delivery system.**

5. THOMPSON DJ, LEVINSON RS: A bioadhesive topical drug delivery system. *Drug Delivery Systems & Sciences* (2002) **2**(1):17-19.

•• **An excellent review highlighting clinical advantages with a unique bioadhesive delivery system for the treatment of VVC.**

6. Data on File, KV Pharmaceutical.

7. BROWN D, HENZL MR, KAUFMAN RH: Butoconazole nitrate 2% for vulvovaginal candidiasis. New, single-dose vaginal cream formulation vs. seven-day treatment with miconazole nitrate. Gynazole 1 Study Group. *J. Repr. Med.* (1999) **44**(11):933-938.

• **Pivotal clinical trial demonstrating equivalent efficacy with a low, single-dose of butoconazole nitrate compared with traditional 7-day treatment for VVC.**

8. Data on File, KV Pharmaceutical.

9. Gynazole-1® Package Insert. Ther-Rx Corporation.

10. Diflucan® Package Insert. Pfizer Pharmaceuticals.
11. Data on File, KV Pharmaceutical.
12. SCHLICHT JR: Treatment of bacterial vaginosis. *Ann. Pharmacother.* (1994) **28**(4):483-487.
13. AMSEL R, TOTTEN PA, SPIEGEL CA, CHEN KC, ESCHENBACH D, HOLMES KK: Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. *Am. J. Med.* (1983) **74**(1):14-22.
14. CAREY JC, KLEBANOFF MA: Bacterial vaginosis and other asymptomatic vaginal infections in pregnancy. *Curr. Womens Health Rep.* (2001) **1**(1):14-19.
15. PAAVONEN J, MANGIONI C, MARTIN MA, WAJSZCZUK CP: Vaginal clindamycin and oral metronidazole for bacterial vaginosis: a randomized trial. *Obstet. Gynecol.* (2000) **96**(2):256-260.
16. FERRIS DG, LITAKER MS, WOODWARD L, MATHIS D, HENDRICH J: Treatment of bacterial vaginosis: a comparison of oral metronidazole, metronidazole vaginal gel, and clindamycin vaginal cream. *J. Fam. Pract.* (1995) **41**(5):443-449.
17. ANDRES FJ, PARKER R, HOSEIN I, BENRUBI GI: Clindamycin vaginal cream versus oral metronidazole in the treatment of bacterial vaginosis: a prospective double-blind clinical trial. *South. Med. J.* (1992) **85**(11):1077-1080.
18. Metro-Gel® Package Insert. 3M Pharmaceuticals.
19. Cleocin® Vaginal Cream. Pfizer Pharmaceuticals.
20. CUNNINGHAM FE, KRAUS DM, BRUBAKER L, FISCHER JH: Pharmacokinetics of intravaginal metronidazole gel. *J. Clin. Pharmacol.* (1994) **34**(11):1060-1065.
21. Data on File, KV Pharmaceutical
22. Cleocin Vaginal Ovules. Pfizer Pharmaceuticals.
23. Clindesse. Ther-Rx Corporation/KV Pharmaceuticals.
24. RICHTER A, ANTON SE, KOCH P, DENNETT SL: The impact of reducing dose frequency on health outcomes. *Clin. Ther.* (2003) **25**(8):2307-2335.

•• **An excellent and comprehensive discussion on the importance of a reducing dose frequency can positively have on compliance and ultimately, overall health objectives.**

Website

101. http://www.fda.gov/cder/drug/infopage/miconazole/default.htm
Science background: safety of miconazole vaginal cream and suppositories (2001). FDA talk paper.

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