International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 03 Issue 04 April 2018, ISSN No. - 2455-8737
Available online at - www.ijirms.in

Open Access Journal | Research Article | DOI: 10.23958/ijirms/vol03-i04/16

Secnidazole Oral Granules: A Novel Drug Formulation and an Effective Alternative in Treatment of Bacterial Vaginosis

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Abstract:

Bacterial vaginosis (BV) is one of the common cause of abnormal vaginal discharge which enhances the acquisition and transmission of a range of sexually transmitted infections. The currently available antibiotics for BV must be administered to patients for 5 to 7 days and studies have shown that nearly 50% patients do not comply with this lengthy treatment regimen. Secnidazole, a second-generation 5-nitroimidazole is developed in a novel oral granule formulation with a broad spectrum of activity against anaerobic bacteria. Based on the phase II and phase III data this molecule received its US FDA approval in September 2017. Secnidazole oral granules offers a valuable advantage since it has longer half-life (~17 hours) which makes it suitable for single-dose therapy and also has a novel method of administration where the granules taken orally by sprinkling onto yogurt or pudding, without regard to the timing of meals. Also, it does not interfere with combined oral contraceptive and spares lactobacilli, a characteristic which is desirable in drugs used to treat BV. The complexity of current treatment regimen can decrease the patient's compliance and a single dose treatment option with secnidazole oral granules may improve treatment adherence, which may be beneficial for both patients and health care practitioners. Secnidazole is the first new oral antibiotic to treat BV in more than a decade and will provide physicians with a new treatment option. This review was conducted by searching the databases of PubMed, EMBASE, and Google Scholar for articles.

Keywords: ***Secnidazole, nitroimidazole, bacterial vaginosis, QIPD, sexually transmitted infections.***

Introduction

Bacterial vaginosis (BV) is one of the diseases which is of global concern as it enhances the acquisition and transmission of a range of sexually transmitted infections. It is also one of the common causes of abnormal vaginal discharge.[1] The prevalence of BV is difficult to determine, since a large proportion of infected women are asymptomatic and do not seek medical care. The prevalence of bacterial vaginosis differs widely from country to country and even within similar population groups. Several studies done in the past decade in India have suggested the prevalence of BV has varied from 10% to as high as 45% in reproductive age group.[2,3] Higher incidences of BV were associated with IUCD use.[3,4] Current antibiotics for BV must be administered to patients for 5 to 7 days, and often more than once a day.[5] Studies have shown that nearly 50 % patients do not comply with 5-7 days treatment regimen for BV.[6] Poor adherence is seen with lengthy and complex drug regimen which can lead to treatment failure and increased chances of disease recurrence. Secnidazole, a second-generation 5-nitroimidazole has been recently introduced in a novel oral granule formulation with a broad spectrum of activity against anaerobic bacteria and a longer half-life (~17 hours) than metronidazole (~8 hours) which makes it suitable for single-dose therapy.[7] Thus, this new formulation offers an effective alternative to metronidazole multiple dose regimen. The advantages of secnidazole over the currently available therapy have prompted for a review of salient features of this drug in treatment of BV.

Literature Search

We searched the databases of PubMed, EMBASE, and Google Scholar for articles using the following search terms: secnidazole and bacterial vaginosis. The various websites providing important updates on the recent guidelines of BV management as well as the regulatory information in relation to secnidazole were also reviewed thoroughly.

Current Management of BV

Besides being troublesome for patients especially when symptoms of discharge and odour occur, BV is also

associated with an increased risk of development of sexually transmitted infections like human immunodeficiency virus (HIV), herpes simplex virus type 2, Trichomonas vaginalis, Neisseria gonorrhoeae and Chlamydia trachomatis.[8-10] BV is also associated with an increased risk of preterm labour, preterm delivery, low birth weight, premature rupture of membranes, intra-amniotic infection.[1,11]

The current available therapy for BV include metronidazole, tinidazole, clindamycin and secnidazole. A study by Thulkar et al[12] did a comparison in women with BV and found high cure rate at the end of 4 weeks who received oral single dose 2g metronidazole (77.9%), 2g tinidazole (97.7%), 2g secnidazole oral tablet (80.2%), and 1.5g ornidazole (97.7%).

Another study by Bohbot et al[13] compared secnidazole and metronidazole in a double-blind, double-dummy, phase III trial in 577 patients who were randomized to receive metronidazole (500 mg, BD for seven days) or secnidazole 2-gram tablet once. The single-dose secnidazole regimen was found to be at least as effective as the multiple-dose regimen of metronidazole (60.1% cured women vs 59.5%) in achieving therapeutic cure at the end of 28 day.

The primary objective of treatment is resolution of symptoms, other potential benefits of BV treatment include reduction in the risk for acquiring sexually transmitted infection. The current management of BV has been summarized in Table 1.

Table 1: Treatment guidelines for management of BV

CDC Treatment Guidelines 2015 [5]		National Treatment Guidelines 2016 (India)[12]
Recommended Management	**Alternatives**	**Recommended Management ***
Metronidazole 500mg Oral BD x 7 days OR	Tinidazole 2 g orally OD for 2 days	Metronidazole 500mg Oral BD x 7 days OR
0.75% Metronidazole vaginal gel one 5 gm applicator intravaginally OD for 5 days OR	Tinidazole 1 g orally OD for 2 days	Metronidazole vaginal gel 1 HS x 5 days OR
2% Clindamycin Vaginal cream one 5 gm applicator intravaginally at bedtime for 7 days	Clindamycin 300 mg orally BD for 7 days	Tinidazole 2 g orally OD x 3 days Or
	Clindamycin ovules 100 mg intravaginally at bedtime for 3 days	2% Clindamycin Vaginal cream 5 gm HS x 5 days

Secnidazole Oral Granules - Dosage and Administration

Currently secnidazole is available in multiple formulations. In India the formulations approved by DCGI are 500mg tablet, 1gm Film Coated tablet and 500mg/15ml suspension for BV.[15] Recently, United States Food and Drug Administration (FDA) has approved a new formulation of secnidazole, which is in the form of 2-gram oral granule, on September 15, 2017.[16]

Secnidazole has a novel method of administration where single 2-gram packet of granules taken once orally by sprinkling onto applesauce, yogurt or pudding, without regard to the timing of meals. The mixture should be consumed within 30 minutes without chewing or crunching the granules.[17]

Pharmacodynamic and Pharmacokinetic of Secnidazole[17]

Secnidazole is a 5-nitroimidazole antimicrobial which acts by entering the bacterial cell as an inactive prodrug. The nitro group of the prodrug is decreased by bacterial enzymes to radical anions. It is hypothesized that these radical anions interfere with the DNA synthesis of the bacteria.

Following an overnight fast, single oral dose of secnidazole 2-gram admixed with (4 oz) of applesauce in healthy adult female subjects had resulted in a mean (SD) secnidazole peak plasma concentration (Cmax) of 45.4 (7.64) mcg/mL. Median (range) time to peak concentration (Tmax) was 4.0 (3.0-4.0) hours. Subsequently after the administration of the 2-gram dose, mean secnidazole plasma concentrations decreased to 22.1 mcg/mL at 24 hours, 9.2 mcg/mL at 48 hours, 3.8 mcg/mL at 72 hours, and 1.4 mcg/mL at 96 hours.

Ingestion of a high-fat meal after administration of 2-gram of secnidazole resulted in no significant change in the rate (Cmax) compared to administration when admixed with applesauce and taken after overnight fasting. There was no effect on Cmax, Tmax and AUC mean (SD) value respectively on admixing secnidazole with pudding {45.6 (5.1), 4.0 (4.0 – 6.0), 1447 (331.0)} and yogurt 43.4 (5.4), 4.0 (4.0 – 8.0), 1478 (335.0)} as compared to admixing with applesauce {44.1 (4.6), 4.0 (3.0 – 6.1), 1523 (372.2)}

The apparent volume of distribution of secnidazole is approximately 42 L while the plasma protein binding is <5%. The total body clearance of secnidazole is approximately 25 mL/min. while the renal clearance is approximately 3.9 mL/min. The plasma elimination half-life for secnidazole is approximately 17 hours.

Efficacy of Secnidazole in Clinical Trial

The FDA approval of secnidazole was supported by a set of studies, including two pivotal trials in BV which established its efficacy in management of BV and an open label safety study. The findings of the phase II trial are mentioned in Table 2.

Table 2: Phase 2, randomized, double-blind, dose-ranging, placebo-controlled study for assessment of secnidazole oral granules in treatment of BV[18]

Name of clinical trial	No. of participants	Treatment regimen given to participants	Duration	Clinical cure rate (primary endpoint)	Microbiologic cure rates (Secondary efficacy endpoint)
NCT02147899 (Phase II study)	215 (24 U.S. centres)	• Secnidazole 1gram • Secnidazole 2 gram • Placebo	21-30 days	• 49.3% for the 1-g group • 65.3% for the 2-g group • 19.4% for the placebo group	• 23.4% for the 1-g group • 40.3% for the 2-g group • 6.5% for the placebo group

Table 3: Phase III, randomized, double-blind, placebo-controlled study for assessment of secnidazole 2-gram oral granules in treatment of BV[19]

Name of clinical trial	No. of participants	Treatment regimen given to participants	Duration	Clinical outcome responder rates (primary endpoint)	Clinical cure rates (secondary endpoint)
NCT02418845 (Phase III study)	189 (21 U.S. centres)	• Secnidazole 2 gram (n=125) • Placebo (n=64)	7-14 days	• 53.3% for the 2-g group • 19.3% for the placebo group (P < .001)	• 64.0% for the 2-g group • 26.4% for the placebo group

Based on the phase II data, the 2-g dose was found superior to 1-g and placebo which was then selected for further evaluation in a phase-3 confirmatory trial for the treatment of BV. (data of Phase III is shown in Table 3)

A notable finding in this trial was that there was no additional requirement of treatment for BV patients receiving single-dose secnidazole 2 g vs placebo (68.0% [68/100] vs 29.6% [16/54]; P < 0.001 based on the investigator's clinical assessment.

Safety Data from Pre-Clinical and Clinical Trial

In vitro,[20] the effect of secnidazole (10 or 300 μM) or control was evaluated on the hERG potassium current using human embryonic kidney cells, and inhibition of the hERG potassium current was examined. The IC50 for secnidazole on hERG potassium current was estimated to be >300 μM, suggesting minimal inhibitory effects.

The cardiac safety of oral granule formulation of secnidazole was evaluated by Darpo et al.[21] This was a 4-way crossover phase 1 study in 52 healthy participants to assess the electrocardiogram (ECG) effects of single dose Secnidazole 2-gram and 6-gram (supra-therapeutic dose) compared with placebo, and with moxifloxacin as a positive control to demonstrate assay sensitivity. Blood samples were taken to determine plasma secnidazole concentrations and serial digital 12-lead ECGs were recorded pre- and post-dose.

A high precision QT technique measured ECGs which showed that single doses of 2 gram and 6-gram secnidazole did not have a clinically relevant effect on the QTcF interval (primary endpoint). This thorough QT study has demonstrated that secnidazole in recommended dose of 2 gram and plasma concentrations up to 3-fold above therapeutically relevant levels does not have a clinically concerning effect on ECG parameters including the QT interval.

Based on the available data from clinical trials[18,19] conducted with secnidazole granules vulvo-vaginal candidiasis (8.4-9.6%) was the most common side effect seen. Other reported side effects were nausea (3.6-5.3%), headache (3.6%), dysgeusia (3.4%), diarrhoea (2.5%), abdominal pain (2%), vulvo-vaginal pruritic (2%).

Advantages of Secnidazole Therapy in Treatment of BV

Secnidazole has longer half-life (~17 hours) which makes it suitable for single-dose therapy and also has a novel method of administration where the granules taken orally by sprinkling onto applesauce, yogurt or pudding, without regard to the timing of meals.[17]

Petrina et al[22] evaluated the antimicrobial susceptibility of vaginal isolates of facultative and anaerobic bacteria to secnidazole, metronidazole, tinidazole and clindamycin. This study has shown that secnidazole spares lactobacilli, a characteristic which is desirable in drugs used to treat bacterial vaginosis.

A phase 1 trial conducted in 54 healthy female subjects by Pentikis et al.[23] has shown that secnidazole oral granules offers a valuable advantage since it does not interfere with combined oral contraceptive. Co-administration of secnidazole and oral contraceptive drugs, ethinyl oestradiol (EE2) 0.035-mg and norethindrone (NET) 1-mg, either on the same day or 1 day apart, had no clinically relevant effects on the bioavailability of EE2 or NET. This finding is important considering that many of the women diagnosed with BV use hormonal contraception and also the current standard treatment which is metronidazole can decrease oral contraceptive efficacy by interrupting the enterohepatic cycling of oestrogens by reducing the bacterial population of the small intestine, which is responsible for hydrolysis of the glucuronide moiety to free drug and thus resulting in lower circulating concentrations of ethinylestradiol.[24]

Use in Specific Populations[17]

Insufficient data is available with use of secnidazole oral granules in pregnancy to inform a drug associated risk of adverse developmental outcomes. Also, no information is available on the presence of secnidazole in human milk, the effects on the breastfed child, or the effects on milk production. To avoid any potential serious adverse reactions, patients are advised not to breastfeed (for 96 hours; based on half-life after administration of secnidazole) during treatment. The safety and effectiveness of secnidazole in paediatric patients below the age of 18 years and in geriatric patients have not been established.

Current Status of Secnidazole Oral Granules

Secnidazole 2-gram oral granules has been designated as a Qualified Infectious Disease Product (QIDP) by the U.S. Food and Drug Administration (FDA) for the treatment of BV. QIDP designation is granted to incentivize the development of new antibiotics in response to the growing threat of antibiotic resistance and a lack of antibiotic products in pharmaceutical manufacturers' pipelines.[25] This makes secnidazole oral granule formulation eligible for certain benefits including at least 10 years of market exclusivity.

Hope for Future

Secnidazole is the first new oral antibiotic to treat BV in more than a decade and will provide physicians with a new treatment option. The complexity of current treatment regimen can decrease the patient's compliance and a single dose treatment option with secnidazole oral granules may improve treatment adherence, which may be beneficial for both patients and health care practitioners. Clinical trials have shown secnidazole therapy is not inferior to the current standard metronidazole and it has no interactions with OCPs unlike metronidazole.

Studies conducted by Saracoglu et al.[26] and Wang et al[27] have shown that oral/vaginal combination groups have significantly higher cure rates as compared to groups which received only oral nitroimidazole. Secnidazole can be the potential candidate for this considering its single time administration. This novel drug is a step ahead in treatment of BV.

Conclusion

Secnidazole, in the oral granule form, seems to be a promising option for the treatment of BV. Currently, only US FDA has recognized the importance of this new formulation, but with more future studies in different regions worldwide, it is possible that the new drug formulation becomes a vital tool in managing an important health concern like BV.

Financial Support and Sponsorship - Nil

Conflicts of Interest - There are no conflicts of interest.

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