Metronidazole Vaginal Gel 0.75% (MetroGel-Vaginal®): A Brief Review

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KEY WORDS
bacterial vaginosis; metronidazole

Metronidazole vaginal gel 0.75% (MetroGel-Vaginal®, 3M Pharmaceuticals, St. Paul, MN) is the intravaginal form of the antibacterial, antiprotozoal agent metronidazole. MetroGel-Vaginal is indicated for the treatment of bacterial vaginosis (BV) and has been shown to be as effective as the oral form of metronidazole for this condition. Recently, a single daily five-day dosing regimen was approved by the Food and Drug Administration. The prior dosing regimen was twice daily for five days. The current product labeling allows for either dosing regimen to be used.

STRUCTURE AND DERIVATION
Metronidazole is a nitroimidazole derivative. Its chemical name is 2-methyl-5-nitroimidazole-1-ethanol. Metronidazole vaginal gel 0.75% is administered as a single 5-g dose via intravaginal applicator. Each gram of MetroGel-Vaginal contains 7.5 mg of metronidazole in a gelled, purified water solution, containing 0.8 mg of methylparaben, 0.2 mg of propylparaben, propylene glycol, carbomer 934p, sodium hydroxide (to adjust pH), and edetate disodium. The gel is formulated at pH 4.0 (normal vaginal pH) and is free of mineral oil. Each applicatorful delivers 5 g of gel, containing approximately 37.5 mg of metronidazole.

MECHANISM OF ACTION
Metronidazole is a small uncharged molecule that exerts its biologic activity through reduction of its nitro group. Anaerobic or microaerophilic conditions promote activation of metronidazole. The action of metronidazole is believed to consist of three successive steps: entry of the drug into target cells, activation by a reduction process, and toxic effects of the reduced product. The reduction of the nitro group of the 5-nitroimidazole results in the formation of toxic derivatives, which kill susceptible bacteria by interacting with DNA. The reduction of metronidazole in anaerobic organisms most likely occurs in a one-electron step and is assumed to lead first to the formation of a free radical anion.

The proposed site of metronidazole reduction is the pyruvate phosphoroclastic reaction in which ferredoxin serves as the terminal electron acceptor. This process, and thus the level of antimicrobial activity, is markedly influenced by the oxygen tension of the environment.

PHARMACOKINETICS
The bioavailability of metronidazole varies according to the route of administration. Intravenous or oral administration of metronidazole results in nearly 100% bioavailability, and the drug diffuses readily to nearly all body tissues. Topical administration (rectal or intravaginal) reduces the bioavailability, resulting in lower serum concentrations of the drug. Metronidazole is metabolized by the liver into acid and hydroxy metabolites. The hydroxy metabolite is present in plasma in
considerable amounts after oral administration. Metronidazole is excreted primarily in the urine as parent drug, oxidative metabolites and conjugates. The half life of metronidazole in plasma and tissues is 8 hours.

The pharmacokinetic characteristics of metronidazole vaginal gel 0.75% were investigated in 12 healthy adult volunteers. A single 5-g dose of gel (37.5 mg of metronidazole) was compared with a single 500-mg dose of oral metronidazole. Results of the study demonstrated a mean maximum serum concentration of 237 ng/ml following a single 5-g dose of metronidazole vaginal gel 0.75% (range: 152–368 ng/ml). A mean maximum serum concentration of 12,785 ng/ml was achieved following a single 500-mg oral dose of metronidazole (range: 10,013–17,400 ng/ml) (Fig. 1). These peak concentrations were achieved 6–12 hours after the gel was used and 1–2 hours after the oral metronidazole was taken. Therefore, the mean peak metronidazole serum concentration following intravaginal administration of a single 5-g dose of gel is less than 2% of that seen following a single 500-mg oral dose of metronidazole. Metronidazole vaginal gel 0.75% is approximately 56% bioavailable, relative to oral metronidazole. However, since only 37.5 mg of metronidazole is delivered in each 5-g dose of gel, total systemic exposure to the drug is dramatically reduced compared with standard doses of oral metronidazole.

A second pharmacokinetic study of metronidazole vaginal gel 0.75% was conducted in patients with BV. The five-day, twice-daily therapeutic regimen was evaluated. The objectives of the study were to determine the amount of drug absorbed and the mean maximum serum concentration achieved relative to normal, healthy volunteers (dose 1) and to determine the multiple dose pharmacokinetics (steady state) in this group of patients (dose 9). Vaginal absorption of the metronidazole gel formulation in patients with BV was similar to that seen in normal, healthy volunteers.

Following single and multiple 5-g doses of metronidazole 0.75% vaginal gel (twice-daily dose) in patients with BV, a mean maximum serum concentration of 214 ng/ml on day 1 and 294 ng/ml on day 9 were reported. Similar steady-state serum concentrations were noted after the first dose and following a full therapeutic course of metronidazole vaginal gel 0.75% in patients with BV. Results from both studies show that minimal concentrations of metronidazole are detected in the systemic circulation after single- and multiple-dose administration of intravaginal metronidazole gel administration in normal, healthy volunteers and in patients with BV, respectively. Metronidazole vaginal gel 0.75% produces only 2% of the mean peak serum concentrations of a standard oral metronidazole dose, with a 96% reduction in total systemic exposure.

SIDE EFFECTS AND INTERACTIONS

Metronidazole vaginal gel 0.75% is associated with a low incidence of adverse effects and is well tolerated. Safety data for the intravaginal administration of the drug was obtained from a total of 800 patients who received the drug in controlled clinical trials. Less than 1% of patients discontinued
therapy due to side effects. The most frequently reported side effects were related to the genital tract, including vaginal discharge (12%), symptomatic candidiasis (6–10%), and vulvovaginal irritation (9%). Gastrointestinal side effects, commonly reported following oral metronidazole therapy, were minimal with intravaginal metronidazole gel (nausea, 2–4%; metallic taste, 1.7–2%).

In a randomized, single-blind controlled trial of metronidazole vaginal gel 0.75% vs. oral metronidazole, the incidence and severity of gastrointestinal adverse events reported by subjects who received the intravaginal gel was lower than those reported by subjects who received oral metronidazole \( (P = 0.014). \)

This is likely due to the minimal systemic exposure metronidazole vaginal gel 0.75% produces relative to oral metronidazole. The product is contraindicated in patients with a prior history of hypersensitivity to metronidazole, parabens, or other ingredients of the formulation. Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. \( ^{13} \) This possible drug interaction should be considered when metronidazole vaginal gel 0.75% is prescribed for patients on this type of anticoagulant therapy.

**SPECTRUM OF ANTIMICROBIAL ACTIVITY**

Metronidazole is a widely used antimicrobial agent that is active against both anaerobic bacteria and protozoa. \( ^{14} \) Unlike other imidazole derivatives, the drug does not possess any antifungal activity. Metronidazole is active not present against most obligate anaerobes but does not possess any clinically relevant activity against facultative anaerobes or aerobes at concentrations achievable with systemic therapy. Against susceptible organisms, metronidazole is generally bactericidal at concentrations equal to or slightly higher than the minimum inhibitory concentration. Metronidazole has been shown to have in vitro and clinical activity against the following organisms: \( ^{16} \)

- Anaerobic gram-negative bacilli: *Bacteroides* species, including the *Bacteroides fragilis* group; *Prevotella* species; *Fusobacterium*

- Anaerobic gram-positive bacilli: *Clostridium* species, *Eubacterium* species

- Anaerobic gram-positive cocci: *Peptostreptococcus* species

**Protozoa: Trichomonas vaginalis, Entamoeba histolytica**

Clinically, metronidazole vaginal gel 0.75% has been shown to decrease the rate of isolation of the BV pathogens *Gardnerella vaginalis*, *Bacteroides* species, and *Mycoplasma hominis*. \( ^{15} \) Increases in vaginal lactobacilli were observed in BV patients following therapy. Metronidazole vaginal gel 0.75% is formulated at a concentration of 7,500 µg/ml of metronidazole, thus high intravaginal concentrations of metronidazole (higher than those achievable with systemic therapy) can be expected during intravaginal therapy.

**CLINICAL APPLICATIONS**

Metronidazole vaginal gel 0.75% is indicated for the treatment of BV. A total of five controlled clinical studies evaluating the efficacy of metronidazole vaginal gel 0.75% have been conducted. \( ^{1,15–18} \) These trials included the following study designs: 1) a randomized, single-blind controlled trial of metronidazole vaginal gel 0.75% daily vs. twice-daily dosing; 2) a randomized, single-blind controlled trial of metronidazole vaginal gel 0.75% (twice-daily dosing regimen) vs. 500 mg of oral metronidazole twice daily for 7 days; 3) Two randomized, double-blind, placebo-controlled trials of metronidazole vaginal gel 0.75% (twice-daily dosing); 4) a randomized, double-blind, controlled trial of metronidazole vaginal gel 0.75% (twice-daily dosing) vs. triple sulfa cream.

A total of 514 patients were enrolled in the study comparing daily vs. twice daily dosing of metronidazole vaginal gel 0.75%; \( ^{18} \) 252 were randomized to the once-a-day dose (at bedtime) for 5 days, and 262 were randomized to the twice-a-day dose (morning and evening) for 5 days. Once- and twice-daily dosing regimens of the gel were equally effective in eradicating BV at both the first return visit (12–17 days after initiation of therapy) and the final return visit (one month after therapy). Clinical cure rates based on patients considered evaluable at the first return visit were 77% and 80% for daily and twice-daily dosing regimens, respectively. Rates of recurrence were also very similar for the two treatment regimens. Of patients deemed cured at the first return visit, 73% and 74% of the patients in the daily and twice-daily treatment groups, respectively, remained cured at the final return visit.

In a study comparing oral metronidazole to met-
ronidazole vaginal gel 0.75%, a total of 112 patients were enrolled; 56 were randomized to receive intravaginal therapy twice a day for 5 days, and 56 were randomized to receive 500 mg of oral metronidazole twice a day for 7 days. Metronidazole vaginal gel 0.75% and oral metronidazole were equally effective in curing BV at both the first return visit (11–17 days after initiation of therapy) and the final visit (one month following therapy). Cure rates of 84% and 85% were noted at the first return visit for patients treated with intravaginal and oral metronidazole, respectively. At the final visit, 71% of patients in each treatment arm were considered cured. Microbiologic efficacy, as assessed by Gram stain, was consistent with clinical findings. At first return visit, 84% of intravaginally treated patients and 85% of orally treated patients were considered cured. Recurrence rates were also similar for both treatment groups. In the intravaginally treated group, 79% of the patients deemed cured at the first return visit remained cured at the final visit, compared with 78% of patients treated with oral metronidazole.

Patients with BV were enrolled in two double-blind multicenter studies of metronidazole vaginal gel 0.75% (twice-daily dosing) vs. placebo gel. A total of 87 patients were enrolled in the first study: 45 patients were randomized to intravaginal metronidazole and 42 to placebo. A total of 69 patients were enrolled in the second study: 41 patients to intravaginal metronidazole and 28 to placebo. In both placebo-controlled trials, metronidazole vaginal gel 0.75% was shown to be superior to placebo gel at both the first return visit and final return visits. In the first study, cure rates at the first return visit (17–21 days after initiation of therapy) were 81% for intravaginal metronidazole and 11% for placebo. Clinical cure rates at the final return visit (one month after therapy) were 76% for intravaginal metronidazole and 6% for placebo. Comparable findings were noted with the second study. Clinical cure rates at the first return visit (9–12 days after initiation of therapy) were 82% for intravaginal metronidazole and 39% for placebo. Cure rates at the final return visit (one month after therapy) were 69% for intravaginal metronidazole and 13% for placebo. These differences were all statistically significant. Recurrence was low in both trials. Of the patients treated with metronidazole vaginal gel 0.75% who were considered cured at the first return visit, 97% and 85% remained cured at the final visit in studies one and two, respectively.

Finally, 247 patients were enrolled in a trial comparing metronidazole vaginal gel 0.75% to triple sulfa cream. A total of 124 patients were randomized to receive intravaginal metronidazole and 123 were randomized to receive triple sulfa cream. Both therapies were administered twice a day for five days. At the first return visit (17–21 days after initiation of therapy), 79% of patients treated with intravaginal metronidazole and 71% of patients treated with triple sulfa cream were considered cured. At the final return visit (one month after therapy), 66% of patients treated with metronidazole vaginal gel 0.75% and only 47% of patients treated with triple sulfa cream were considered cured. The difference at the final return visit was statistically significant ($P < 0.02$). The superior efficacy of metronidazole vaginal gel 0.75% at the final return visit is consistent with the fact that certain BV pathogens, including Gardnerella vaginalis and anaerobic gram-negative rods, are not highly sensitive to triple sulfa cream.

### Table 1. Costs of selected antibiotics for the treatment of bacterial vaginosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Average wholesale prices for a full course of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleocin vaginal cream applicatorful</td>
<td>once or twice daily for 5 days</td>
<td>$30.48</td>
</tr>
<tr>
<td>Cleocin capsules</td>
<td>300 mg twice daily for 7 days</td>
<td>$38.92</td>
</tr>
<tr>
<td>Flagyl tablets</td>
<td>500 mg twice daily for 7 days</td>
<td>$37.81</td>
</tr>
<tr>
<td>Flagyl ER tablets</td>
<td>750 mg daily for 7 days</td>
<td>$39.90</td>
</tr>
<tr>
<td>Generic metronidazole</td>
<td>500 mg twice daily for 7 days</td>
<td>$5.25</td>
</tr>
<tr>
<td>MetroGel-Vaginal®</td>
<td>1 applicatorful once or twice daily for 5 days</td>
<td>$30.48</td>
</tr>
</tbody>
</table>

ing regimens of effective therapy for the treatment of BV. With the exception of generic metronidazole tablets, metronidazole vaginal gel 0.75% is the least expensive of the therapies for BV.

CONCLUSION

There are multiple methods for treating BV. Metronidazole vaginal gel 0.75% is an important option, for it has many advantages over other standard therapies. The advantages of this treatment modality include equal efficacy compared to oral administration, minimal side-effect profile as a result of low serum levels, and a short five-day single dosing regimen which is now approved by the Food and Drug Administration.

REFERENCES

12. Data on file, 3M Pharmaceuticals, St. Paul, MN.
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