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Review Article

ANTIFUNGAL PESSARIES: A REVIEW

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Abstract

The incidence and spectrum of local as well as systemic fungal infections have increased dramatically over the past two decades. Various factors which predispose patient to invasive fungal infections are advances in medical technology, use of invasive monitoring devices, mechanical ventilation, parenteral nutrition, broad spectrum antimicrobial agents, intensive cancer chemotherapies, corticosteroid and other immunosuppressive. Traditionally, many invasive fungal infections were associated with a poor prognosis, because effective therapeutic options were limited. The recent development of new antifungal agents has significantly contributed to the successful treatment of fungal diseases. These drugs offer novel mechanisms of action and expanded spectrums of activity over traditional treatment options. However, with these new agents comes the need for increased awareness of the potential interactions and toxicities associated with these drugs. This review provides a summary of the pharmacologic principles involved in treatment of fungal diseases.

Some drugs are poorly absorbed after the oral administration. Over the last twenty years, extensive efforts have been made towards the administration of poorly absorbed drugs through different delivery systems and routes but the presence of a mucus laden cervix (vagina) in women provides an opportunity as a conjoint site for such drug delivery. The vaginal route has been rediscovered as a potential route for systemic delivery of various therapeutically important drugs avoid first pass metabolism. In the current study, further attention has been made on various polymers which are used in hydrogel which provide bioadhesive property to the vaginal formulations, so that the formulation remains vaginal tissues for proper time. The main objective of the present review is to summarize various vaginal drug delivery systems with an special emphasis an vaginal physiology, factors affecting the vaginal drug absorption, mechanism of vaginal epithelium drug absorption including the advances in the current approaches in vaginal drug delivery systems.

Keywords: Spectrum, Pessary, Fungal Infection, Yeast Infection

INTRODUCTION

Vaginal drug delivery systems are traditionally used to deliver contraceptive and drugs to treat the vaginal infections. However, vaginal drug delivery is not limited to these drugs as a the vagina has promise as a site to topically deliver drugs which will be absorbed systemically because of the dense network of blood vessels in the vaginal wall [1-4]. A formulation given by this route as pessaries, vaginal tablets, inserts, cream, powders, douches, gel, etc. The first truly controlled drug delivery systems for use in the vagina were developed in 1970, when the first vaginal ring was used for delivery of medroxy progesterone acetate for

contraception. Still, tablets, creams and counter (OTC) vaginal medications while vaginal rings are the most common long-term drug delivery systems currently used. In recent years vaginal Bioadhesive preparations have been developed as a new type of controlled release form for the treatment of both topical and systemic diseases [5-9]. The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for an extended period of time including day hours and night, thereby enabling lower dosing frequencies. The concept of controlled-release drug delivery has also been successfully applied to the intra-vaginal administration of a systemic prostaglandin derivative for abortion indication. Intra-vaginal controlledrelease drug delivery system is an effective means of continuing delivery of therapeutically active agents such as a contraceptive steroids and prostaglandins. Advantages of Vaginal Drug Delivery System This route is the most preferred and targeted goal of new drugs and dosage forms, vaginal administration can be used as an alternative route in certain cases of therapeutic importance: In cases of nausea and vomiting, the act of taking medication orally may induce emesis so that the drug is vomiting before it is absorbed. Irritation to the stomach and small intestine associated with certain drugs can be avoided. Hepatic first pass elimination of high clearance drugs may be avoided partially [9]. Contact with digestive fluid is avoided, thereby preventing enzymatic degradation of some drugs. Drug delivery can be stopped by removing the dosage form e.g. Vaginal rings. Drugs which traditionally are only given parental may be administered vaginally either as such or in combination with absorption-promoting additives. Rapid drug absorption and quick onset of action can be achieved.

The number of agents available to treat invasive fungal infections has increased by 30% since the turn of the millennium. Although that statistic is impressive, it brings the total number of approved systemic antifungal drugs to only 14 [10], with the potential for 1 more product to possibly emerge this year. These recent additions have provided clinicians with a tool previously lacking in the management of these life-threatening infections: therapeutic alternatives. Along with new options, however, comes the need to understand the uniqueness of each agent, including its role in therapy, toxicity profile, and interactions with concomitant medications. To attain the maximum effect from these agents, clinicians should also become familiar with strategies to optimize efficacy through an understanding of pharmacokinetic and pharmacodynamic properties. These characteristics are unique for each class of antifungal drug and even for each member within a class. In many cases, this variability is not subtle and merits careful attention. An additional concern related to the increasing number of antifungal drugs is the rapid increase in expenditures associated with their use. Many institutions throughout the United States are struggling with the increased financial burden related to the prescribing of these antifungal drugs [11]. Optimization of therapies through targeted application of various kinetic and dynamic principles may be one strategy to maximize the costeffectiveness of treatment of invasive fungal infections. This review focuses on the pharmacologic principles involved in treatment of fungal disease and compares and contrasts the differences among the available agents. Given its role as an agent used primarily to treat superficial infections, terbinafine will not be included in this discussion.

Suppositories

A large number of vaginal medications are available in the form of tablets or suppositories. Some authors use the terms pessaries and suppositories interchangeably and consider vaginal tablets as a separate dosage form. These vaginal formulations are designed to melt

in the vaginal cavity and release the drug for several hours. Suppository systems are now most commonly used to administer drugs for cervical ripening prior to childbirth and local delivery of drugs. Drugs that are administered as suppository include dehydroepiandrosterone sulfate for ripening effect on the uterine cervix, Miconazole for vaginal candiasis and progesterone for hormone replacement therapy. Vaginal tablets may contain binders, disintegrant and other excipients that are used to prepare conventional oral tablets. It has the advantage of easy of manufacture and insertion. Mucoadhesive polymers are sometimes used in vaginal tablet formulation to increase vaginal residence time. Drugs that are administered as vaginal tablets include itraconazole, clotrimazole and prostaglandins. Presence of hydrophobic and release retarding materials may decrease the absorption of a drug from a vaginal formulation. Too hydrophobic drugs may not be suitable for vaginal tablets. Presence of penetration enhancers such as surfactants, bile salts can significantly enhance absorption.

Vaginal Yeast Infection during Pregnancy

During pregnancy, up to 50% of women experience vulvovaginal candidosis [12]. In addition, in pregnant women, recurrent vaginal yeast infections and insufficient therapeutic responses are more frequently recorded than in non-pregnant women [13,14]. An increased content of glycogen and lower pH value in the vagina as well as an intensified binding of yeast cells to the vaginal mucosa have been made accountable for this observation [13,12]. During pregnancy, the therapy of symptomatic vaginal yeast infections should be intense, but restricted to topical preparations; oral antifungals should be avoided [13,15]. Specifically, topical azoles can be used at all stages of pregnancy because there is no or only minimal systemic exposure following intravaginal administration [16]. The FDA assigned topical clotrimazole to pregnancy category B. The other topical imidazoles and triazoles have been assigned to category C. In fact, several clinical trials confirmed the safety of clotrimazole in pregnancy; no association was observed between vaginal application of clotrimazole and congenital abnormalities [17].

Intravaginal Antifungal Agents

Intravaginal antifungal agents are the most commonly used for initial treatment of uncomplicated vulvovaginal candidiasis. They have few adverse effects. Occasionally, local effects such as vaginal burning, stinging or irritation may occur [18] . Intravaginal antifungal agent is the therapeutic agent of choice in pregnancy. Both intravaginal azoles and intravaginal nystatin can be used in the first trimester of pregnancy [19, 20].

Oral antifungal maintenance therapy

Fluconazole

Fluconazole is effective for candida albicans and some non albicans, but is only 50% effective for candida glabrata [18]. Side effects include nausea, vomiting (3-4%), hepatotoxicity (hence liver function test should be checked after six months) and alopecia. In a randomised double blind placebo controlled study by [13], it found that long term weekly fluconazole suppresses but does not cure recurrent vulvovaginal candidiasis. The study included women with active acute vulvovaginal candidiasis with a minimum of four documented episodes in the previous 12 months. The result of vaginal cultures revealed no cases of fluconazole-resistant Candida albicans infection, and no evidence of superinfection with candida glabrata. Fluconazole was well tolerated. Therapy was discontinued only for one patient because of headache. Liver function test was monitored, only one participant had mildly elevated serum aminotransferase level. The study concluded that recurrent VVC can be successfully and safely controlled by weekly suppressive therapy with fluconazole. However, long term cure is difficult to achieve as most patients

(57.1%) had recurrent symptoms within six months of discontinuing therapy

Ketoconazole

The side effects include hepatotoxicity, which is estimated to be 1/10,000 patients [18]. Hence, liver function test should be performed monthly. [18,13,21] studied the efficacy of maintenance ketoconazole therapy in recurrent vulvovaginal candidiasis (Table 4). 74 women with recurrent VVC were treated for an acute episode with 400mg ketoconazole per day for 14 days. They were then randomised to receive one of the three treatment regimens: placebo or oral ketoconazole 400mg for five days with onset of menses for six months or oral ketoconazole 100mg daily for six months. The study concluded that maintenance prophylactic therapy with oral ketoconazole is effective in preventing recurrent episodes of vulvovaginal candidiasis, but relapse is common after withdrawal of the drug. Because of the risk of hepatotoxicity, caution is essential in selecting patients for long term ketoconazole therapy and in following patients undergoing such treatment [21].

Itraconazole

Liver function test monitoring is needed too [18]. A study reviewed the effectiveness of one day intermittent monthly prophylaxis with 400mg itraconaozle [22]. It was a randomised study involving 57 patient and 57 controls. Results showed monthly itraconazole prophylaxis reduced the rate of recurrence, 36.4% (treatment group) vs. 64.5% (placebo group). However, its beneficial effects are lost within few months of cessation of therapy. After one year, only 38.9% of patients in the treatment group and 28.8% in the placebo group had no recurrence of symptoms. In summary, the various oral antifungal maintenance regimen yielded the same findings, that it is effective in reducing the number of episodes during the six months treatment period. However, recurrencesis almost 50% after cessation of therapy. For patients with recurrence of symptoms with cessation of maintenance therapy, this can be treated initially as for uncomplicated acute vulvovaginal candidiasis [23]. However, if infection is recurrent, the treatment process should be repeated 1, 2. In such instances,[19] recommends keeping the maintenance regimen for 12 months.

Intravaginal Antifungal maintenance therapy.

Intravaginal Clotrimazole pessary

In a prospective randomised open cross over study, looking at the value of prophylactic (monthly, perimenstrual) clotrimazole vs. empiric self treatment in recurrent vaginal candidiasis, empiric self treatment was found to be more cost effective than cyclical monthly use of pessary [24]. In this study, patients were randomised to receive one 500mg dose of clotrimazole pessary intravaginally each month just before or on the last day of menses for six months or one 500mg dose of clotrimazole intravaginally at the onset of symptoms for six months. After six months, patients were crossed over to the other regimen.

CONCLUSION

We concluded that pessaries more effective and safe than other conventional dosage forms. Pessaries prevents from first pass metabolism and other oral toxic side effect that decrease patient compliances, So the pessaries are safe and more effective for local action.

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