Introduction

R.J. Hay

Department of Dermatology, Guys Hospital, London, UK

R.J. Hay, Department of Dermatology, Guys Hospital, London SE1 9RT, London, UK

The present comprehensive range of antifungal drugs used in the treatment of superficial mycoses is by no means ideal. There are, for instance, certain infections which are refractory to existing therapy such as chronic tinea pedis due to Trichophyton rubrum, which has a 60–70% relapse rate whatever the primary therapy used. Other organisms such as Scopulariopsis brevicaulis or Hendersonula torulo-idea appear to be primarily resistant to the available drugs. Secondary resistance emerging during treatment has not previously been a problem with superficial mycoses but has now been reported with oropharyngeal Candida infection in the immunocompromised patient [1]. To complicate matters further absorption of both topical and oral drugs is often variable and their penetration into sites such as nail keratin often poor. Generally the development of topically active compounds which can penetrate into nail plate has been disappointing.

Compared with the number of antibacterial drugs available, there are far fewer antifungal compounds. Even so their numbers are increasing all the time. There are three major families of drugs: the polyenes, the azoles and the allylamines. In addition there is a miscellaneous group of compounds such as flucytosine, tolnaftate, cyclopiroxol-amine and griseofulvin which do not belong to a single family of drugs. This is not a static picture and new groups of antifungals are brought forward from time to time. These include the morpholine antifungals such as amorolfine, whose activity, in part, depends on the inhibition of sterol biosynthesis [2], and the echinocandins such as cilo-fungin [3], which interfere with cell wall synthesis.

The polyenes comprise a large family of drugs which are derived from Streptomyces species [4], but only three, amphotericin B, nystatin and natamycin, are used for human disease. The activity of the polyene antifungals depends on the inhibition of the formation of the fungal cell membrane [5]. The most commonly used members of this group are amphotericin B and nystatin. Both have a broad range of antifungal activity against the main systemic fungal pathogens but in superficial infections are mainly used for candidosis. Natamycin is less frequently used but is active against dermatophytes as well as other pathogens. The azole series is another rapidly expanding family of drugs [6]. The first group to be developed, the imidazoles, contains a large number of compounds primarily aimed at topical use. These include, amongst others, clotrimazole, miconazole, econazole and sulconazole. Ketoconazole can be given both topically and orally. The principle mode of action of this series is the inhibition of cytochrome P450-dependent C14 demethylation in the formation of ergosterol in the fungal cell membrane. One of the potential disadvantages of this group is that, in many cases, there is some interference with human cytochrome P450 as well [7]. This for instance will affect human metabolic processes, the most obvious example of this being ketoconazole which is a potent inhibitor of adrenal androgen biosynthesis. The imidazole antifungals show a broad
spectrum of inhibitory activity against fungi. They affect most of the common superficial fungal pathogens as well as many systemic agents. They also inhibit some Gram-positive bacteria such as Staphylococcus aureus.

There are at present two systemically active triazole antifungals, itraconazole and fluconazole, available for clinical use. They both act by the same mechanism as the imidazoles – via inhibition of cytochrome P450. Itraconazole is active in dermatophytosis, pityriasis versicolor and candidosis whereas fluconazole is chiefly used for Candida infections and, in some countries, for dermatophytosis.

The two main allylamines, naftifine and terbinafine, are recent introductions [8]. The allylamines appear to have a similar mode of action as the tolcyclate antifungals, such as tolnaftate, on the epoxidation of squalene, an earlier stage in the formation of the fungal cell membrane than C14 methylation. While naftifine has both antifungal and anti-inflammatory activity, terbinafine is also fungicidal in vitro [9]. Although this activity covers a very wide range of fungi in vitro, in vivo it only appears to be effective against dermatophytes when given orally and against a slightly broader range of superficial pathogens including Pityrosporum yeasts when applied topically. Oral terbinafine is active in nail infections [10].

There is also a large and miscellaneous group of antifungal agents, many of which are only available for topical use. These include compounds such as tolnaftate, cyclopriroxol-amine and haloprogin, all of which are effective treatments for superficial mycoses although in the case of the first, activity is confined to the dermatophytes. Griseofulvin, an oral agent, which acts by the inhibition of intracellular microtubule formation, is widely used for dermatophytosis and is the treatment of choice for scalp and some nail infections, although the failure rate in toenail onychomycosis due to dermatophyte fungi exceeds 60%. Amongst these drugs flucytosine is the most widely used for systemic fungal infections although it has little value in superficial mycoses.

This wide range of drugs has proved of great value in the management of superficial mycoses although there are still areas where improvements are sorely needed. These include chronic dermatophytosis of the palms or soles, onychomycosis and pityriasis versicolor. In addition the reduction of relapse rates, for instance by cidal activity, or of treatment times would both be welcome improvements on existing therapy. In the light of these observations we shall be considering the role of the new morpholine antifungal, amorolfine, as a new therapeutic tool in the treatment of superficial fungal infections.

References


Hay

Introduction