

Leading articles

The azole antifungal drugs

The azole drugs constitute a large group of synthetic compounds whose members show a range of therapeutic activity encompassing fungal, protozoal and anaerobic bacterial infections, as well as immunostimulation. However, it is the antifungal potential of many of these drugs which has attracted much attention (Odds, 1980) and developmental research. Before their appearance, choice amongst antifungal drugs was limited. For the systemic mycoses, for instance, amphotericin B and flucytosine were the only alternatives and for some fungal infections, such as onychomycosis due to candida, there was no effective treatment. The availability of a range of antifungal imidazoles and, more recently triazoles, for both topical and systemic use has now widened the choice.

The number of topical imidazoles for use in superficial fungal infections is large—some would say excessive—and there are more in development. Those currently available in Britain include clotrimazole, miconazole, econazole, ketoconazole, sulconazole, and isoconazole. The importance of these compounds lies mainly in their efficacy, confirmed by numerous studies, against the main superficial mycoses (dermatophytosis, candidosis and pityriasis versicolor). However, it has generally proved impossible to establish therapeutic differences between them which would be of use in making a choice of drug (Roberts, 1980). Recent attempts to simplify the use of topical antifungal therapy have shown that bifonazole, for instance, when used once daily in dermatophytosis, is as effective as the more usual twice daily regimen (Doring & Stettendorf, 1982). While this may reflect an inherent difference in the pharmacological properties of the drug, it is likely that other azoles will be found to behave similarly; indeed isoconazole shows sufficient skin surface retention to justify once daily use (Dykes, Marks & Tauber, 1986). Single dose treatments with clotrimazole, isoconazole and tioconazole are available for vaginal candidosis and produce satisfactory cure rates, although the chief benefit from simplification of topical regimens probably lies in increased patient compliance.

Only a few members of this group can be given systemically but the imidazoles, keto-

conazole (oral) and miconazole (intravenous), and the triazoles, itraconazole (oral) and fluconazole (oral), produce therapeutic blood levels. Of these only ketoconazole has been widely used in superficial infections and is effective in dermatophytosis, chronic mucocutaneous candidosis (for which it has become the treatment of choice) and pityriasis versicolor. Comparative studies of ketoconazole versus griseofulvin have highlighted some differences such as a more rapid response of tinea corporis to the former (Hay *et al.*, 1985). But recovery rates of nail infections are similar. Early studies of itraconazole show that it is similarly active in some of these infections (Delescluse, Cauwenbergh & Degreef, 1986). In subcutaneous mycoses the azoles have made a small but significant impact. For instance, ketoconazole has been found to be effective in mycetomas caused by *Madurella mycetomatis* (Mahgoub & Gumaa, 1984) and itraconazole was shown to be curative in sporotrichosis (Restrepo *et al.*, 1986) although in the latter study only 35.3% of patients were cleared of the infection within 90 days of the start of therapy. In the case of the systemic mycoses objective clinical assessments have proved more difficult. However, in a few infections the effectiveness of some azoles has been established by small open studies. For instance in paracoccidioidomycosis oral miconazole, which is poorly absorbed, was effective in some cases (Lima *et al.*, 1977), but ketoconazole produced much better results and has since become the main treatment for this disease (Restrepo *et al.*, 1980). The latter drug has also been found to be useful in some forms of histoplasmosis, blastomycosis and coccidioidomycosis (Dismukes *et al.*, 1983), particularly for infections affecting soft tissues.

The value of azole antifungals as treatment or prophylaxis for infections caused by systemic opportunists such as candida or aspergillus is less clear. Most of the data come from single case reports or, at the best, small series. With ketoconazole these indicate activity in some candida infections in non-neutropenic patients, such as candida endophthalmitis (Drouhet & Dupont, 1983), but, in accordance with the in-vitro sensitivity, little effect in aspergillosis. In the latter infection it is possible that itraconazole may prove helpful if its in-vitro activity (Van Cutsem *et al.*, 1985)

is mirrored by subsequent clinical experience (see, for example, Tricot *et al.*, 1987). However, there are still insufficient numbers of critically assessed patients to establish clear guidelines for the use of these compounds in opportunistic infections even though attempts have been made to improve the flow of information by monitored release, in the case of intravenous miconazole (Barton, Fox & Waldron, 1981). A multicentre study of ketoconazole in the U.S.A. has also provided useful data on the treatment of systemic infections (NIAID Mycoses Study Group, 1985).

Azole antifungals are not without disadvantages. For instance poor cover of aspergillus and zygomycete infections limits the use of miconazole or ketoconazole as empirical therapy in febrile neutropenic patients. Absorption of ketoconazole in some patients, particularly after bone marrow grafts, is poor (Hann *et al.*, 1983) and it is not clear at present whether this extends to the new oral triazoles. In rare cases azole cross resistance has been reported following continuous long-term use of ketoconazole in patients with chronic mucocutaneous candidosis (Ryley, Wilson & Barrett-Bee, 1984) or AIDS (Tavitian *et al.*, 1986). When ketoconazole has been used as a prophylactic agent continued faecal carriage of less sensitive, but potentially pathogenic, organisms such as *Torulopsis (Candida) glabrata* has posed clinical problems. It has also been reported that amphotericin B is less effective in mice with experimental aspergillosis if the animals are pretreated with ketoconazole (Schaffner & Frick, 1985); a similar phenomenon has not been recorded in human infections.

The incidence of drug toxicity caused by antifungal azoles has generally been low. Nevertheless, miconazole, for instance, can cause ventricular tachycardia and anaphylaxis (Fainstein & Bodey, 1980) on rare occasions. With the wider use of ketoconazole cases of drug related hepatitis were reported (Lewis *et al.*, 1984; Lake-Bakaar, Scheuer & Sherlock, 1987). At present the estimated incidence of the latter is approximately 1 in 10,000 patients and while the risk factors are not completely understood, a history of liver disease and the use of the drug for the treatment of onychomycosis are both associated with an increased risk of hepatitis. Unfortunately the mechanism appears to be idiosyncratic and unpredictable. Inhibition of pathways of steroid biosynthesis dependent on cytochrome P450 is thought to be responsible for the

androgen blocking activity of ketoconazole at high dosage (Pont *et al.*, 1984) and the development of azoles without affinity for the human enzyme is regarded as an important objective since toxicity of this nature necessarily limits the use of drugs for non life-threatening conditions.

The oral triazoles currently in development, itraconazole (Van Cutsem *et al.*, 1985) and fluconazole (Richardson *et al.*, 1985), have shown promise in superficial fungal infections. Itraconazole is absorbed in low concentrations, and is avidly tissue bound. In contrast fluconazole is well absorbed and penetrates urine and cerebrospinal fluid, and only a small proportion is protein bound. Both drugs appear to have potential in deep mycoses including some infections such as aspergillosis (itraconazole) and urinary candidosis (fluconazole) that are not well covered by existing antifungals. It will be a challenge to devise suitable methods of establishing their therapeutic roles in systemic fungal disease.

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Penicillin-induced hypersensitivity vasculitides

Hypersensitivity to penicillin gives rise to a wide variety of clinical syndromes including maculopapular rashes, urticaria, angioedema, haemolytic anaemia, anaphylactic shock, and acute interstitial nephritis. Very uncommon manifestations of penicillin hypersensitivity are necrotizing angitis, polyarteritis nodosa (Spring, 1951; Peters *et al.*, 1960; Schrier, Bulger & Vam Arsdel, 1966; Vahanian *et al.*, 1977) and, most frequently within this group of rare reactions, hypersensitivity vasculitis (McCoombs, 1965; Mullick *et al.*, 1979).

Necrotizing angitides constitute a heterogeneous group of diseases whose histological common denominators are fibrinoid necrosis and inflammation of the vessel walls with a pleomorphic cellular infiltrate with predominant polymorphonuclear leucocytes. According to Alarcon-Segovia (1980), hypersensitivity vasculitides are defined as necrotizing but not granulomatous vasculitides involving cutaneous or systemic small vessels. Hypersensitivity vasculitides may be associated with various diseases such as lupus erythematosus, mixed cryoglobulinaemia, neoplasia, leukaemia and rheumatic or intestinal inflammatory diseases.