New Drugs

New antifungal and antiviral chemotherapy

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Antifungal chemotherapy

Superficial fungal infections caused by dermatophytes and yeasts are among the commonest cutaneous diseases. Fortunately, in the United Kingdom systemic fungal infections are rare, although their incidence in recent years has been increased by opportunistic infection in immunosuppressed patients.

Despite this increase in systemic infections the development of effective antifungal drugs has lagged well behind that of antibiotics, at least in part because fewer differences in cell type exist between the eukaryotic fungal pathogen and host than between the prokaryotic bacterial pathogen and host. Until 1970 there were a few antifungal drugs, which had certain limitations including toxicity, narrow spectrum of activity, parenteral administration, and commonly a failure to cure. With the advent of the imidazole derivatives a major new class of antifungal drugs has emerged which combines low toxicity and versatility of administration with a wide spectrum of antifungal action against dermatophytes, yeasts, and dimorphic fungi.

IMIDAZOLES

The precise mechanism of action of the imidazoles is not known but one important effect may be the inhibition of the synthesis of ergosterol. This is an essential component of fungal plasma membranes which is not required by mammals. Additionally, imidazoles inhibit the transformation of candidal yeast to hyphal forms which renders the organism more susceptible to phagocytosis by host leucocytes. These diverse effects may explain the broad spectrum of the imidazoles and the rarity of drug resistant strains.

Although the antifungal properties of this group were known 40 years ago, their development for clinical use has taken place only over the past 15 years, initially with clotrimazole, miconazole, and more recently with econazole, isoconazole, and ketoconazole. These drugs are reviewed according to their route of administration.

Topical application

Clotrimazole (Canesten), econazole (Ecostatin, Gyno-Pevaryl), and miconazole (Daktarin, Dermonistat, and Monistat) are available as creams, pessaries, and vaginal tablets. Dusting powders and spray are also available for the treatment of skin

lesions. Isoconazole (Travogyn) is given as a single dose vaginal tablet. Systemic absorption of these drugs from the skin or from the vagina is minimal. Side effects are uncommon (1-4%) consisting of minor irritation, burning, or itching at the site of application.

Intravenous administration

Intravenous administration of miconazole (Daktarin) produces therapeutic drug concentrations in bone, joint, lung, and oesophageal tissue. Intrathecal administration is necessary for meningeal and cerebral infections. The drug is rapidly metabolised in the liver and its excretion is unaffected by renal insufficiency. Side effects are uncommon; intestinal disturbance is the most frequent while pruritus, rash, fever, anaemia, and thrombocytosis occur rarely. Miconazole enhances the anti-coagulant effect of warfarin.

Oral administration

Therapeutic concentrations of ketoconazole (Nizoral) are achieved one to two hours after a 200 mg oral dose. As it is a dibasic drug optimal absorption occurs in conditions of increased acidity such as exist when the drug is taken with food. Conversely, when it is taken with an antacid or the H_2 receptor antagonist cimetidine blood concentrations of ketoconazole may be appreciably reduced. It is widely distributed in the body tissues with penetration of saliva, urine, sebum, and breast milk, but intracerebral concentrations are too low to be therapeutic. In the plasma it is protein bound, primarily to albumin, and is extensively metabolised in the liver. Excretion is by biliary and faecal routes. Gastrointestinal irritation occurs in 5% of patients and less frequent side effects include nausea, headaches, pruritus, and rarely gynaecomastia. Hepatotoxicity has been reported with asymptomatic transitory increases in enzyme activity as well as symptomatic reactions of hepatocellular and cholestatic type. These reactions are rare with an incidence of less than 1/10 000 patients treated. The drug is contraindicated in pregnancy. Ketoconazole (200 mg) is given once or twice (in more severe infections) daily. Dosage does not require adjustment in renal disease. Miconazole is available in oral form but is rarely used owing to poor absorption.

IMIDAZOLES AND SUPERFICIAL FUNGAL INFECTIONS

Cutaneous infections

Superficial dermatophyte infections (tinea pedis, capitis, corporis, etc) can generally be cleared with topical treatment. In recent years imidazoles have tended to replace older cheaper remedies such as Whitfield's ointment. This is not because they have been proved to be more effective but because they are less

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messy and more convenient. For severe superficial and nail infections oral griseofulvin has been the traditional treatment. Evidence is now accumulating for the successful use of ketoconazole in cases resistant to griseofulvin.

Excessive moisture, occlusion, or altered immune state may predispose towards candidiasis (principally *Candida albicans*). The treatment of these predisposing factors should accompany drug treatment. Cutaneous candidiasis is treated topically with either the polyenes (amphotericin, nystatin) or imidazole derivatives. Both groups of drugs are highly effective in clearing skin lesions and are well tolerated.

Mucosal infections

Vaginal thrush is the commonest form of candidal infection and its incidence appears to be increasing. The polyenes and imidazoles are available in various formulations for vaginal use. Both polyenes and imidazoles have comparable cure rates (80-90%), but the imidazoles have the advantage of shorter duration of recommended treatment (three to seven days) compared with the polyenes (14 days). There is a trend towards even a shorter duration of treatment and a single application of isoconazole has recently been introduced. A five day course of oral ketoconazole is effective but expensive. It should be reserved for severe or relapsing cases in which systemic treatment may eliminate skin and gut carriage of candida; treatment of sexual partners should also be considered.

Oral candidiasis is often associated with poorly fitting dentures. Attention to these and treatment with amphotericin lozenges or nystatin solutions is usually sufficient. Patients with immune deficiencies (see below) develop severe painful deep oral and oesophageal infections. Response of these infections to nystatin solutions or amphotericin lozenges is often poor whereas rapid relief may be obtained with amphotericin 40 mg infused once a day for two to five days. While there is a negligible risk of nephrotoxicity with these short courses fever and rigors are common. Ketoconazole has been shown to be effective in open studies and a comparative trial of these two treatments is urgently required.

Chronic mucocutaneous candidiasis

Several immune and endocrine disorders may be complicated by chronic candida infection of the skin, nails, and mucous membranes. Ketoconazole is the first truly effective treatment for this condition and may benefit even longstanding cases. Full clearance of lesions may take up to a year and long term treatment is often required to prevent relapse.

Systemic infections

In the United Kingdom systemic fungal infections usually occur in patients with immune deficiency. Patients with neutropenia or qualitative neutrophil defects are particularly at risk, but other groups include patients receiving immunosuppressive drugs and diabetics. The commonest infection is systemic candidiasis; other rarer problems are pulmonary or cerebral aspergillosis, cryptococcal meningitis or endocarditis, and rhinocerebral mucormycosis. Neither intravenous miconazole nor oral ketoconazole has yet found a place as first line agent for these infections, and intravenous amphotericin or flucytosine remain the drugs of choice. Prophylactic administration of non-absorbable polyene antifungals to neutropenic patients decreases the incidence of fungal infections. Theoretically ketoconazole should be an improvement because of its systemic activity, and in general the initial reports of comparative trials confirm this. It appears, however, to be relatively ineffective in patients receiving marrow transplants because of reduced absorption for reasons which as yet are unexplained. In the United States systemic fungal infections occur in patients

with normal immunity. Cryptococcal infection is more common than in the United Kingdom and meningitis is the most frequent clinical presentation. Open clinical trials have shown that miconazole may be effective if given intrathecally or by intraventricular injections, and there are anecdotal reports of success in patients who have failed to respond to amphotericin. There have also been treatment failures, however, and in the absence of a comparative clinical trial the combination of amphotericin with flucytosine remains the initial treatment of choice with miconazole reserved for second line treatment. Ketoconazole has not been evaluated.

Blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis are the four commonest systemic fungal infections in the world; fortunately, all are rare in the United Kingdom. Ketoconazole has shown promising activity against all four organisms but, with the exception of paracoccidioidomycosis, has yet to replace intravenous amphotericin as the treatment of choice.

CONCLUSION

The topical imidazole preparations have found a place in the management of skin and mucosal fungal infections largely because they are more convenient than the older preparations. Ketoconazole is a valuable drug because it is available orally; it is useful in treating difficult dermatological and gynaecological infections but is still expensive and is being used inappropriately to treat relatively minor infections. While it has revolutionised the treatment of chronic mucocutaneous candidiasis, neither ketoconazole nor the intravenous form of miconazole has superseded amphotericin for treating most systemic fungal infections. As a group the imidazoles appear to have low toxicity, though the problem of hepatotoxicity with ketoconazole requires continued monitoring.

Antiviral chemotherapy

Viruses replicate by manipulating the reproductive mechanism of an infected cell. The requirements for antiviral chemotherapy are similar to those for cancer chemotherapy: a drug that halts the reproductive process in infected cells without inactivating or mutating the nucleic acids in normal cells. Viruses contain either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). The initial process of infection is the same for both types of virus: adsorption into the cell wall, penetration into the cell, and uncoating of the protein capsid to reveal the nucleic acids. Most DNA viruses replicate DNA within the infected cell nucleus while proteins for the capsid are synthesised within the cytoplasm. A few DNA viruses—for example, poxviruses—and all RNA viruses replicate nucleic acids and synthesise proteins in the cytoplasm. Viruses can use existing enzyme systems in the host cell, but replication of DNA and RNA viruses requires the synthesis of some virus specific enzymes. Finally the virus is assembled in the cytoplasm.

Until recently vaccination has been the main method for dealing with viral infections. Influenza and infections caused by the herpes group of viruses are unlikely to be controlled by vaccination and are the main targets for antiviral chemotherapy. The influenza viruses are capable of repeated changes in antigenicity. The herpes group includes herpes simplex virus type 1 and type 2, varicella zoster, Epstein-Barr virus, and cytomegalovirus. Two of the group (herpes virus type 2 and the Epstein-Barr virus) are possibly carcinogenic, which makes vaccination unattractive. The remainder of the group causes life threatening infections mainly in patients with immune defects. Usually these infections are due to reactivation of the virus which has been present for many years so that vaccination would have to be directed against the entire population rather than the population at risk. Primary varicella zoster infection in children with acute leukaemia is a possible exception and live virus

vaccine has been used successfully in children whose leukaemia is in complete remission after chemotherapy.

Amantadine (Symmetrel) inhibits the penetration of influenza A virus into the host cell. It has some value as a prophylactic agent in contacts but early trials suggest that it does not help symptomatic patients. Rimantadine is a derivative that has been studied in the Soviet Union; initial results show that it may be useful in treating symptomatic influenza A, and this has prompted a re-evaluation of amantadine. Neither drug is active against influenza B.

All other antiviral drugs inhibit nucleic acid synthesis. Acyclovir has recently been marketed in the United Kingdom. There are several other new drugs, however, that are either marketed abroad (Trifluridine) or have been used in clinical trials (bromovinyl deoxyuridine, ribavirin) and require brief discussion. All of the presently available agents act by inhibiting viral DNA polymerase and are active against only the herpes group of viruses (herpes simplex, varicella zoster, cytomegalovirus) and the hepatitis B virus, which is also a DNA virus. Idoxuridine (Herpid), an iodinated derivative of thymidine, is cytotoxic and mutagenic when given systemically. It is only used for the topical treatment of shingles and herpes simplex keratitis. Trifluridine, also a halogenated derivative of thymidine, is more effective than idoxuridine for the treatment of superficial herpetic keratitis and causes less local tissue reaction. Neither drug is effective against deep infections. Trifluridine is not available in the United Kingdom at present. Bromovinyl deoxyuridine is another related compound which is activated by virus specific enzymes and may be given systemically. Unfortunately, it does not cross the blood-brain barrier so it cannot be used to treat herpes encephalitis and it does not work against herpes virus type 2, the cause of genital herpes. Its clinical application is therefore likely to be limited.

ACYCLOVIR

Acyclovir (Zovirax) is inactive until phosphorylated by a herpes specific enzyme (thymidine kinase). The triphosphate that is formed inhibits DNA polymerase. In vitro it is the most active drug against herpes viruses and is far more active than vidarabine (adenine arabinoside, Vira-A), the only other systemic antiviral available. Viral activity is measured as the concentration that inactivates at least 50% of the virus (ED_{50}). Acyclovir is commercially available as a topical ointment, in tablet form, and as an intravenous injection. The ointment should be used only for ophthalmic infections. Absorption of the oral preparation is poor (about 20%). The resultant peak blood concentrations will reliably exceed the ED_{50} of herpes simplex but not of the other herpes viruses. On the other hand, the peak concentrations obtained after intravenous administration of acyclovir exceed the ED_{50} of varicella zoster, Epstein-Barr virus, and hepatitis B virus but do not exceed the ED_{50} of all cytomegalovirus strains. The usual oral dosage in the treatment of herpes simplex is 200 mg five times daily for five days. Acyclovir is not appreciably plasma protein bound and is excreted unchanged in the urine; the dose must be reduced in severe renal failure—for example, 200 mg orally every 12 hours. To date few adverse effects have been encountered. Acyclovir may have a local irritant effect—for example, transient stinging after ophthalmic use or skin inflammation if extravasation with intravenous administration occurs. There have been occasional reports of increased liver related enzymes and rashes after intravenous use but the only consistent toxic effect is a slight increase in blood urea concentration, which is probably due to drug crystals in the urine. This can usually be avoided by a slow infusion.

Acyclovir resistant strains of herpes simplex and varicella zoster already exist. The commonest mechanism of resistance is a failure of the virus to produce thymidine kinase, the enzyme that activates acyclovir. These strains may be sensitive to vidarabine but strains resistant to acyclovir because of defective DNA polymerases are usually resistant to vidarabine.

Clinical applications of acyclovir

Herpes virus infections occur in patients with normal or impaired immunity but the clinical problems of the two patient groups are entirely different. In patients with normal immunity the infections are largely self limiting and the goals of antiviral treatment are the reduction of morbidity and the prevention of reinfection. In contrast, herpes infections in immunocompromised patients are life threatening. There is no doubt that acyclovir is a major advance in antiviral treatment; it is also an expensive drug that should not be used indiscriminately because of the danger of encouraging resistant strains.

Mucocutaneous herpes simplex—In the normal host acyclovir cream merely reduces the duration of viral shedding without producing any clinical benefit or preventing reinfections. In contrast, intravenous acyclovir reduces the morbidity and mortality of mucocutaneous herpes simplex in the immunocompromised host. Infections are, however, prolonged even with treatment and this may interfere with other aspects of the patient's treatment such as cytotoxic therapy. Prophylactic oral acyclovir reduces the frequency of herpes infection in these patients, but it remains to be seen whether this will produce resistant infections.

Ophthalmic herpes simplex—Acyclovir ointment has been shown to be superior to idoxuridine and trifluridine in the rate of healing and in preventing complications. The results of comparative trials with vidarabine are conflicting but the largest trial has shown that acyclovir is superior.

Genital herpes simplex—Intravenous and oral acyclovir appreciably reduce the duration of symptoms but neither affects reinfection. The incidence of genital herpes simplex is increasing and by reducing the duration of viral shedding acyclovir may prevent the spread of infection. Many patients experience prodromal symptoms before a recurrence of infection and it is possible that patient initiated treatment may abort the infection before it becomes transmissible. These potential epidemiological benefits have yet to be confirmed in clinical trials.

Herpes simplex encephalitis—A British placebo controlled trial of acyclovir is still continuing and the results should indicate the role of acyclovir in this difficult area.

Varicella zoster infections—Chickenpox does not require treatment unless there are life threatening complications, such as pneumonitis, or immunity is impaired. Intravenous acyclovir is effective in these circumstances. Intravenous acyclovir reduces the duration of symptoms due to shingles in patients with normal immunity but does not reduce postherpetic neuralgia even in patients whose pain is relieved during the administration of the drug. There has been no trial comparing acyclovir with high dose oral prednisolone, which does reduce the incidence of postherpetic neuralgia. Intravenous acyclovir reduces morbidity and prevents the dissemination of shingles in patients with impaired immunity; prophylactic oral acyclovir is still being evaluated.

Other infections—There have been two small placebo controlled trials of intravenous acyclovir against cytomegalovirus infection: in renal transplant patients it had limited efficacy but in marrow transplant patients it was ineffective. Acyclovir does not have any place in the management of Epstein-Barr virus infections or of chronic hepatitis B infection.

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Letters to a Young Doctor

Relationships

PHILIP RHODES

The quickest way to get a bad reference for future jobs is to alienate others by inconsiderate behaviour. Your watchword must be "You judge yourself by your intentions and others by their actions." You know that you are a nice chap who never intends to hurt or harm anyone else, but often you are misunderstood. If you stop and think about it you will see that certain people seem more often to be misunderstood and resented than others. You know who they are, you do dislike their behaviour, and you know that it is their fault. Make sure that you too do not unwittingly behave badly and acquire a poor reputation.

Others judge you by your actions, which include what you do, what you say, and what you convey by your attitudes. When you move into a new job you are at first in an alien environment. You are the invader of a more or less cohesive in-group. They will be wary and watchful of you, even though they are also welcoming. They want to know whether you will fit in or not. They cannot know this except over time and seeing how you behave, so you need to be a little circumspect. Do not throw your weight about, do not criticise matters with which you are unfamiliar, and do not compare unfavourably the way things are done with those where you have come from. Your criticisms might indeed be just, but there is a time and place for voicing them, when you fully belong to the in-group. You might then be listened to, whereas previously your views will have been resented. For a while just accept what you find. After all you accepted the post with your eyes open, knowing that it must have disadvantages as well as advantages. It was you who decided that the latter outweighed the former. Those young doctors who think that everything happens for the best in the best of all possible worlds had better join Dr Pangloss in allegory and myth.

As soon as you have been appointed you will probably be handed over to one of the administrative staff who will show you round, perhaps to see the living accommodation and to arrange when you will start and at what salary. There may also be many other details to talk about. Administration is essential: do not be contemptuous of those who do it, for they are concerned to see that you are inducted as painlessly as possible into your new job. It is better for them if you are happy in their institution, so seek their cooperation. They are not your inferiors to do your bidding. They will help willingly if approached in the right way. You do not at first know where in the hierarchy this particular administrator sits, but his or her impressions of you will certainly be handed on to others and may reach the chief administrator and ultimately the consultant for whom you work. It is not a question of whether the impressions of you are correct or not. Frequently first ones are not, but they form the foundations of your reputation. Therefore be courteous.

Do not turn up for the job at the last minute. If your post begins on the 10th be there on the 9th. Unless you have made sure, the job may begin at 9 am and not the evening of the first day. A room may have to be prepared for you and a meal. Tell the administration in writing just what you intend to do, well in advance—telephoning is not enough as a call is quickly and easily forgotten unless a note is made. Too few people do this. A letter on the other hand is a constant reminder on which action must be taken, and it does not then matter if the recipient falls ill or goes on holiday or is just too busy to take much note of a phone call. Moreover, the copy of the letter which you send is a reminder to you of just what you have said you will do. You must stick to this and not vary it except for the most cogent reasons. If you do change your mind apologise to the persons you have inconvenienced, preferably before you have inconvenienced them.

A quality most revered by all, but especially chiefs, is reliability. You will appreciate it in others too. If you are asked to do something do it. If you are expected in a certain place at a certain time be there. This is especially necessary if you are to meet your chief in the operating theatre or on a ward round.

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