The host and the parasite*

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Summary

The role of the host in the management of patients with mycotic infection is considered. *In vivo* studies with ketoconazole indicate the importance of the host and the possibility of stimulating host immune mechanisms by an immune modulator.

Introduction

Considerable attention was paid during this symposium to the role of the host in mycotic infections. It becomes increasingly attractive to think that the treatment of mycotic infections might need a dual approach. On the one hand, the germ must be inhibited, on the other hand the host defences might need to be reconstituted.

Antimycotic therapy

There are excellent drugs available for the topical treatment of dermatophytoses and oral or vaginal candidiasis. There is little to improve in this field. In contrast, room is left for drugs that act systemically. The spectrum of griseofulvin is narrow. The advantages and disadvantages of amphotericin B and flucytosine have now been well described. The recently developed intravenous miconazole is safe and effective in a large variety of systemic mycoses. The intravenous route is, however, unpractical for long-term treatment. A drug that can be given orally for long periods of time, has a broad spectrum of activity, readily penetrates body fluids, is safe, and does not induce resistance would be a welcome addition to the still limited armamentarium of systemic antimycotic drugs.

Ketoconazole, which was mentioned earlier by both Borelli *et al.* (1979) and Borgers *et al.* (1979) might be a step forward. It is chemically related to miconazole and has a similar spectrum of activity. It is, however, better absorbed from the human intestinal tract. A single oral dose of 200 mg ketoconazole yields peak blood levels of approximately 5 mg/l, which is 10 times more than the level obtained after the same oral dose of miconazole, and similar to the level obtained after an i.v. dose of 600 mg miconazole. Blood levels do not decrease

after repeated treatment, because ketoconazole does not induce liver enzymes. The metabolism of ketoconazole is similar to that of miconazole. Both drugs are poorly excreted in the urine and penetrate poorly into the cerebrospinal fluid.

Like other imidazoles, ketoconazole is an inhibitor of ergosterol biosynthesis in *Candida*. A daily oral dose of 10 mg/kg induces a 80% cure rate in experimental candidiasis of the crop of turkeys, systemic candidiasis of guinea-pigs, systemic candidiasis of chickens, vaginal candidiasis of rats, skin candidiasis of guinea-pigs, dermatophytosis of guinea-pigs and pulmonary coccidioidomycosis of mice. The drug is topically effective against cutaneous mycoses of guinea-pigs caused by *C. albicans*, *Trichophyton mentagrophytes* and *Microsporum canis*.

Dr Stevens reported on the South American preliminary experience in systemic mycoses of man. European investigators reporting to Janssen Pharmaceutica have obtained promising results in dermatophytoses (34 cases), onychomycoses (76 cases), oral thrush (2 cases), *Candida* oesophagitis (1 case) and vaginal candidiasis (315 cases). The usual dose was 200 mg once daily. The longest treatment period was 7 months. The drug was well tolerated and did not induce changes in the 8 haematological and 23 biochemical parameters tested. In 18 patients treated for 7 months for onychomycosis, the drug did not affect the amounts of total lipids, total phospholipids, triglycerides, free fatty acids, free cholesterol and cholesterol esters or the lipoproteins of the sera.

It is remarkable that systemic mycotic infections can be cured with a single daily dose of oral ketoconazole or intravenous miconazole, indicating that sustained high blood levels of either drug are not needed for achieving a cure.

The available data on ketoconazole are impressive and promising. We should however not be over-optimistic. Problems usually arise in the later stages in the development of a drug. The future will tell how valuable this drug may be. Whatever the outcome, no doubt other drugs will follow because industry is highly committed in this field. Each of the newcomers should receive full attention until the gaps in present antimycotic therapy are filled.

* Part of final Panel Discussion.

Immunotherapy

One has heard about therapeutic failures in chronic dermatophytoses, chronic mucocutaneous candidiasis and chronic recurrent vaginal candidiasis. Some patients respond poorly to the antimycotic treatment, although their organisms are sensitive to the drug used. Others relapse constantly. In all probability, defects of host defences are responsible for the therapeutic failures. Such defects have, however, rarely been recognized.

Aspecific phagocytosis by polymorphonuclear neutrophils or macrophages is the first line of defence against invasion by yeasts or fungi. This defence is enhanced by cellular immune reactions. Host defences are decreased in most conditions that predispose for fungal infections (e.g. diabetes mellitus, malignant disease, corticosteroid or immunosuppressive treatment). Furthermore, selective defects may exist in patients with mycotic infections. Rutgeerts and Verhaegen (1977) studied a patient with a 2-year history of severe oesophageal candidiasis. All cellular immunological tests were normal but his polymorphonuclear cells failed to phagocytose *Candida*. The patient was cured with intravenous miconazole but, as expected, relapsed one year later. He responded to another course of antimycotic treatment.

Highly selective immune defects have also been described in viral infections such as herpes, where the lymphocyte fails to respond to the herpes antigen, all other immunological responses being normal. The detection of such a selective defect is laborious and expensive, because a complete immunological screening has to be done in each case.

Pending a better knowledge of the immunopathology of mycotic infections, it may be desirable to start empirical immunotherapy when antimycotic treatment fails and when immune defects are suspected. There are at present several immune modulators available, such as B.C.G., *Corynebacterium parvum*, transfer factor, levamisole and the thymic hormones.

Levamisole has been extensively studied in a variety of apparently unrelated diseases. It reduces the frequency, severity and duration of recurrent

bacterial or viral infections. Preliminary experience in 5 patients with chronic relapsing vaginal candidiasis suggests that it may act similarly in such patients. The 5 patients, who responded to local antimycotic therapy but relapsed after each course of treatment, remained free of infection during the 3–8 months of treatment with levamisole. These data, of course, need confirmation in controlled studies but should be considered seriously. Many fields of immunotherapy have been discovered through a succession of hypotheses, pilot studies and controlled studies. The more rational way, i.e. the correction by immunotherapy of a pre-established immune defect has been much less rewarding.

The tremendous successes of antibiotics and corticosteroids during the last decades have diverted interest from Metchnikoff's teaching on host defences and from pre-war 'unspecific stimulation therapy'. However, the failures of antimicrobial, immunosuppressive and antiphlogistic treatments have revived interest in the reconstitution of host defences and are leading to modern immunotherapy. A similar evolution might happen in the treatment of mycotic infections. Many of them are opportunistic and occur only in hosts whose defences are impaired.

Immunotherapy may be a useful adjunct to antimycotic treatment in such patients. It may also be a useful tool to unravel the mechanisms that are responsible for the recurrent or persistent character of certain mycotic infections.

References

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