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Ketoconazole

Ketoconazole, one of the newer imidazole antifungal agents, is potentially the most useful derivative to date since it can be given by mouth. In vitro it has a broad spectrum of antifungal activity ranging from *Candida* species and dermatophytes to systemic pathogenic fungi such as *Histoplasma capsulatum*. Some moulds, including aspergilli, are inhibited only at high concentrations. Ketoconazole appears to act by inhibiting the conversion of lanosterol into ergosterol in the cell wall, though other mechanisms may also play some part. In man peak serum concentrations of 2-5 mg/l are found two to three hours after administration of a single 200-mg tablet.¹ Therapeutic serum concentrations do not usually persist longer than eight hours unless a high dose, over 800 mg, is given. Absorption is enhanced in the presence of acid, but whether or not concurrent administration of antacids inhibits uptake is not yet clear.² The drug is metabolised in the liver, but peak serum concentrations do not appear to be greatly altered in the presence of liver disease. Ketoconazole penetrates the cerebrospinal fluid and the peritoneal cavity in low concentrations, and less than 13% of the absorbed dose is excreted in the urine.

Ketoconazole has been used most widely in the treatment of superficial mycoses such as dermatophytosis and candidiasis. In the former there is good evidence that ketoconazole is effective; for instance, in one open study³ the investigators showed that 90% of treated patients were improved, particularly when the infection was confined to hairless skin. Three-quarters of the treated patients relapsed within five months of stopping ketoconazole, however, and the effect of the drug on nail infections was not assessed. Onychomycosis caused by dermatophytes can also be successfully treated, though toenail infections in particular are slow to respond and may be refractory to treatment. In one double-blind comparative study⁴ of ketoconazole (200 mg) and griseofulvin (250 mg ultramicrosize) clinical remissions were induced in 61% and 39% of treated cases respectively. Up till now most investigators have studied broad groups of dermatophyte infections, and it would be most helpful to substantiate these observations in specific forms of dermatophytosis such as tinea capitis.

The value of ketoconazole in chronic mucocutaneous candidiasis has been established in several studies, including one placebo-controlled trial.⁵ A substantial proportion of treated patients with chronic mucocutaneous candidiasis achieve complete mycological and clinical remission. In one study six out of 17 patients relapsed with oral infection within 8-4 months of stopping the drug but responded to retreatment.⁶ These results in an infection such as chronic mucocutaneous candidiasis are encouraging and hold out hope that similar persistent infections will respond as well. Ketoconazole is active against vaginal candidiasis and is likely to prove more acceptable to patients than topical treatment. As even short regimens of topical drugs have proved to be highly effective, however, the comparative merits of ketoconazole need to be carefully assessed.

Few reports have appeared of the use of ketoconazole in the subcutaneous mycoses, though some therapeutic effect has been described in chromomycosis.¹ Some of the systemic mycoses, however, particularly certain forms of paracoccidioidomycosis,⁷ respond dramatically to the drug. Some clinical varieties of coccidioidomycosis and histoplasmosis may also respond.¹

As yet the value of ketoconazole cannot be assessed in opportunistic fungal infections such as systemic candidiasis or

aspergillosis, since full clinical and laboratory data are available on so few patients. Ketoconazole may prove useful as a prophylactic drug in severely immunosuppressed patients. In one recent study⁸ it was more effective than topical amphotericin B and nystatin in eliminating oral fungal carriage or infection in patients with leukaemia or marrow aplasia, with the exception of those receiving allogeneic bone marrow grafts.

In clinical reports so far side effects such as nausea, headache, pruritus, and photophobia have been uncommon. Some recent reports have described probable hepatotoxicity.⁹ Liver function values become transiently abnormal in some patients and symptomatic hepatitis (cholestatic or hepatocellular) may occur in a very few patients. The incidence is probably less than one in 10 000,¹⁰ making it extremely difficult to establish a causal association; but clinicians using ketoconazole need to be aware of the possibility of liver damage with long-term treatment.

Clearly, therefore, ketoconazole is going to be a useful drug for a wide variety of fungal infections, particularly dermatophytosis, superficial candidiasis, and paracoccidioidomycosis. The response of most fungal infections to treatment varies considerably with the site of infection and the underlying condition of the patient. At present both the influence of these variables on the results of treatment with ketoconazole and the merits of the drug compared with effective alternatives are incompletely understood. The more detailed studies of keto-

conazole currently in progress will help to establish its place in antifungal chemotherapy with greater precision.

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Regular Review

Postmenopausal osteoporosis

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Osteoporosis is a diminution of skeletal mass in which bone is normally mineralised but the amount of bone tissue in a given volume of bone is reduced compared with normal. Osteoporosis may result from reduced new bone formation, increased bone resorption, or both. The most important consequence is an increase of certain fractures, which may occur either spontaneously or after minimal trauma when loss of bone has been sufficient to cause mechanical weakness. These fractures represent an end stage of the disease, and some equate osteoporosis only with the clinical syndrome of fracture due to bone loss. We consider this definition unhelpful and confusing because the diagnosis then depends on one incident which results in fracture, while the events of the previous 10 to 20 years—during which 30% of the skeletal mass may have been lost—are overlooked. In practice, therefore, we believe that the term osteoporosis should be applied when bone mass is below that expected for age and sex irrespective of whether fracture has occurred.

There are many causes of osteoporosis, the more important of which (table) must be excluded by investigation of every patient with the disorder. In adults the most common types are age-related (senile) osteoporosis and postmenopausal

osteoporosis. Aging is associated with progressive thinning of the skeleton in both sexes; this usually starts during the fifth decade in women and slightly later in men. It was established many years ago, however, that bone loss is more considerable, and consequently osteoporotic fractures more common, in women. For example, the fracture rate of the distal radius rises dramatically in women between the fifth and seventh decades but remains constant in men during this time.^{1 2}

Causes of osteoporosis in adults

Postmenopausal
Age related (senile)
Hyperparathyroidism
Hyperthyroidism
Hypercortisolism
Hypogonadism (distinct from menopause)
Myelomatosis

Metastatic carcinoma
Reticuloendothelial disorders
Connective-tissue disorders,
for example osteogenesis imperfecta
Drugs, for example corticosteroids,
heparin
Immobilisation

The concept of a second form of osteoporosis, causally related to loss of ovarian function, was first proposed by Fuller Albright *et al* to explain the increased incidence of osteoporosis and related fractures in women.³ The existence and importance of postmenopausal osteoporosis have remained controversial.