Pharmacokinetics of ketoconazole and treatment evaluation in candidal infections

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SUMMARY Twenty six children with candidiasis, aged between 5 months and 14 years, were treated with different formulations and regimens of ketoconazole. Fifteen children had alimentary tract candidiasis, two had oesophagitis, one had urinary tract candidiasis, two vaginitis, two septicaemia, one endo-ophthalmitis, and three had chronic pulmonary illness with persistence of *Candida albicans* in sputum. Daily drug doses ranged from 3 to 13 mg/kg and duration of treatment from seven days to 18 months. Pharmacokinetic studies in 22 of the children are reported. A total of 3 mg/kg/day given in three divided doses did not yield sufficiently high concentrations, which were achieved with a daily dose of 8 to 10 mg/kg. The effectiveness of treatment was proved by negative mycological tests (cultures or specific antibodies, or both) in 88%, by cure in 73%, and improvement in 11%. In three patients evaluation was not possible due to an insufficiently proved diagnosis. Nausea and pyrosis in four patients were the only side effects noted and no laboratory abnormalities were found. To achieve therapeutic concentrations of ketoconazole in children we suggest a daily dosage of 7 to 10 mg/kg in two or three divided doses.

The increasing popularity of invasive procedures and of antibiotic and immunosuppressive treatments has caused an increase in candidal infections which has led to a search for new antifungal drugs, easily administered and free of side effects. New advances in systemic treatment have been reached with ketoconazole which is active against a wide range of fungi, causes no resistance, shows good absorption after oral administration and is free of serious side effects.^{1 2} Effectiveness of treatment and pharmacokinetic profiles in adults are now well documented,^{1–6} but data on children and infants are still sparse.^{7–11} We studied pharmacokinetic and clinical data in 26 children treated with ketoconazole to evaluate its efficacy and the best regimen in paediatric patients.

Materials and methods

Twenty six children, 16 boys and 10 girls whose ages ranged from 5 months to 14 years and who had candidiasis were treated with ketoconazole. Informed parental consent was obtained before treatment.

Treatment schedule. Three different treatment for-

mulations were used and these are given in Table 1. Five patients received different treatment schedules. The drug was always administered shortly before meals and the duration of treatment ranged from 7 days to 18 months. Before and during treatment, patients were monitored for renal function, haematologic parameters, hepatic enzymes, and serum concentrations of glucose, cholesterol, bilirubin, and alkaline phosphatase.

Laboratory study of ketoconazole. Minimal inhibitory concentration of ketoconazole for clinical isolates was determined by the agar dilution method on casitone medium, as previously described.¹² Ketoconazole assay was performed on the serum of 22 patients and on cerebrospinal fluid in two of these

Table 1 Different formulations and schedules of ketoconazole treatment

Formulation	No daily doses	Patients		Dose (mg/kg) Mean (range)
		No	Age range	
Suspension	3	9	5 mths–13 yrs	8.5 (3–10)
Tablets	1	8	10 mths–12 yrs	8.7 (5–13)
Tablets	2	14	11 mths–14 yrs	9.5 (8–13)

patients. Blood samples were collected in sterile tubes before administration of ketoconazole and after one, two, four, six, and eight hours; blood samples after 12 hours and 24 hours were also taken from patients being given ketoconazole on 12 hour and 24 hour schedules respectively. Serum samples were taken from the third day of treatment. Serum and cerebrospinal fluid were stored at -20°C before being examined. Concentrations of ketoconazole were determined by bioassay on casitone agar pH 7 against *Candida albicans*, strain 3153 A;⁷ each specimen was tested in triplicate.

Values for serum and cerebrospinal fluid were obtained from standard curves of ketoconazole diluted in serum and 0.9% isotonic saline, respectively. The sensitivity of the test was $0.025\text{ }\mu\text{g/ml}$ for serum samples and $0.006\text{ }\mu\text{g/ml}$ for samples of cerebrospinal fluid.

The serum half life of ketoconazole was calculated from linear regression analysis of the log serum concentration—time profile. The area under the curve was calculated by trapezoidal rule.

Results

Laboratory study on ketoconazole. Minimal inhibitory concentrations for clinical isolates ranged from 0.05 to $3.2\text{ }\mu\text{g/ml}$. Strains showed the same range of minimal inhibitory concentrations during treatment or after relapse. The pharmacokinetic data on treatment with ketoconazole suspension are reported in Table 2. The first two patients were treated with 3 mg/kg of ketoconazole and showed low blood concentrations—peak $0.5\text{ }\mu\text{g/ml}$ at two

hours and undetectable serum concentration at eight hours. Serum samples for drug determination in three patients receiving 4 to 6 mg/kg/day were taken only two hours after the dose: the ketoconazole concentrations at this time were 0.8 , 1.0 , and $1.4\text{ }\mu\text{g/ml}$. These patients are not included in Table 3. Six other patients were given higher doses of ketoconazole (8 to 12 mg/kg/day) resulting in higher blood concentrations—peak $2.04\text{ }\mu\text{g/ml}$ at two hours and detectable concentrations at eight hours.

Table 3 gives pharmacokinetic data on 11 patients treated with ketoconazole tablets given every 12 or 24 hours. One patient who was being treated with cimetidine for gastro-oesophageal reflux showed a decreased drug absorption and was, therefore, not considered. Double peaks in the serum concentration were observed in two children given 8 mg/kg or 9.9 mg/kg of ketoconazole tablets daily (Figure). These data are not included in Table 3.

Two patients whose cerebrospinal fluid was drawn for biochemical analysis were assayed for both serum and cerebrospinal fluid ketoconazole concentrations. In one patient no detectable ketoconazole concentration was observed in cerebrospinal fluid (the serum concentration was $0.15\text{ }\mu\text{g/ml}$

Figure Double peaks in ketoconazole concentrations observed in 2 patients treated with tablets.

Table 2 Ketoconazole suspension (3 doses daily): pharmacokinetic data. Values mean (SD)

No patients	Daily dose (mg/kg)	Peak (µg/ml)	Half life (minutes)	AUC 0–8 hours	Concentration at 8 hours
2	3	0.5	45	1.15	0
6	10 (1.26)	2.04 (0.56)	227 (148)	9.51 (4.71)	0.64 (0.62)

AUC=area under curve ($\mu\text{g.h/ml}^1$) from 0 to 8 hours after dose.

Table 3 Ketoconazole tablets: pharmacokinetic data. Values mean (SD).

No patients	No daily doses	Daily dose (mg/kg)	Peak (µg/ml)	Half life (minutes)	AUC 0–12 hours	AUC 0–24 hours	Serum concentration (µg/ml)		
							At 8 hours	At 12 hours	At 24 hours
7	2	9.61 (1.82)	3.46 (0.92)	154 (90)	13.64 (2.40)		0.35 (0.19)	0.10 (0.06)	
4	1	8.70 (3.46)	6.30 (1.70)	170 (58)	36.67 (7.29)	40.67 (8.72)	1.81 (0.71)	0.72 (0.32)	0.04 (0.03)

AUC=area under curve ($\mu\text{g.h/ml}^1$) from 0 to 12 hours or 24 hours after dose.

Table 4 Clinical diagnosis before treatment and results of ketoconazole treatment in 26 children with candidiasis

Clinical assessment	No	Outcome of treatment		
		Clinical and mycological cure	Clinical improvement	No response
Cutaneous and alimentary tract candidiasis in primary or secondary immunodeficiency	8	7	1	—
Recurrent alimentary tract candidiasis	7	7	—	—
Oesophageal candidiasis	2*	1	—	1
Probable respiratory tract candidiasis	3†	—	—	—
Urinary tract candidiasis	1	1	—	—
Persistent vaginitis	2	2	—	—
Candidal sepsis	2*	1	1	—
Endo-ophthalmitis	1	—	1	—
Total	26	19 (73%)	3 (11.5%)	1 (4%)

* One of these had acute lymphoblastic leukaemia.

† Therapeutic effect could not be evaluated because the diagnosis had not been proved.

concurrently). In the other patient, in spite of the absence of inflamed meninges, 0.03 µg/ml of ketoconazole were detected in cerebrospinal fluid while the serum concentration was 3.8 µg/ml.

Mycological and clinical study. After treatment, mycological cultures were either negative or specific antibodies values had decreased to normal values, or both, in 23 of 26 patients. Two of the remaining three patients were positive on culture, although with a reduced count of colonies, while one child with candidal sepsis and a high concentration of antibodies escaped monitoring, having moved to another town. As shown in Table 4, 19 of 26 children (73%) were cured and three (11.5%) improved; failure was observed in one patient with oesophagitis who was being treated with cimetidine. In spite of negative cultures the effectiveness of treatment could not be evaluated in three patients because the underlying disease did not allow determination of the extent to which candidiasis had influenced their clinical state. These three children were suffering from chronic lung diseases, their sputum was repeatedly positive, and the relation between candida and lung involvement was only suspected. In their case, cultures became negative and chest radiographs became normal in 6 to 12 months.

Studies on specific candida-related immunofunction gave a positive skin test in two children and a return to normal killing in four patients.

No laboratory abnormalities were detected but a mild transient rise in transaminases was observed in one child who was then treated with rifampicin. Side effects of nausea and pyrosis were found only in four patients.

Discussion

Our experience in paediatric patients correlates well with the previously published data on the efficacy of ketoconazole treatment of candidal infections in adults.^{1,2} From our results some points may be underlined. Ketoconazole suspension three times daily at a dosage of 3 mg/kg/day proved to be too low to obtain both therapeutic serum concentrations and stable clinical improvement (failure of one of two patients). A dosage ranging from 4 to 6 mg/kg/day yielded higher concentrations at two hours, but did not completely prevent relapses. A dose of 8 mg/kg/day or more achieved acceptable serum concentrations and definite cures.

The same dosage was also suitable for children receiving tablets, provided that an antacid drug was not given at the same time.¹³ Twice a day administration is probably to be preferred. Compared with patients given ketoconazole once a day, those receiving the drug every 12 hours showed lower peak serum concentrations; however, between each administration their drug concentration was less than 0.5 µg/ml for shorter periods of time—about five hours compared with approximately 11 hours. The wide standard deviation of the pharmacokinetic data underlines the great interpatient variability in blood ketoconazole concentrations already reported in children.¹¹ The double peaks in serum concentrations observed in two patients may be due to enterohepatic circulation or delayed absorption as suggested by Brass *et al.*⁵

The length of treatment is dependent on the site of infection, the severity of the lesions, and the immunological status of the patient. Treatment

should be maintained until mycological and clinical cures are achieved.

In our patients vaginitis was cured with a full 7 days' course of treatment, while recurrent or long lasting alimentary tract candidiasis without any detectable immunodeficiency required a longer course of three to four months, since, with treatment of one month only, relapses in three of five children occurred. In immunodeficient patients who need multiple antibiotic treatment the advisable period of treatment may be even longer—over six months at least. We have treated two such children for 14 and 18 months respectively. Even after 18 months of treatment there was no emergence of drug resistance. Ketoconazole seemed to be non-toxic and side effects were rare (no more than 15%) and mild, even after a long period of treatment.

Effectiveness of treatment of candidal infections was often accompanied by a return to normal of immune function assays (skin test, killing etc) and this could be a reliable parameter in determining when treatment should end. The need to continue long term treatment in immunosuppressed patients has not yet been proved.

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