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Trial of ketoconazole in non-invasive pulmonary aspergillosis

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ABSTRACT A one year study of the efficacy of the antifungal agent ketoconazole in non-invasive pulmonary aspergillosis was carried out. Ten patients, seven with allergic bronchopulmonary aspergillosis and three with mycetoma, were studied. They were randomly allocated to receive 400 mg daily or placebo orally in a double blind fashion. In the treated group (n = 6), concentrations of serum IgG specific for *Aspergillus fumigatus* fell significantly during treatment (mean reduction 42% (SEM 2·2%) compared with determinations preceding the study). This effect was evident by three months and continued for the 12 months of treatment. Patients receiving placebo (n = 4) showed no significant change in serum IgG concentration (mean change +10% (SEM 5·3%)). Asthmatic patients treated with ketoconazole (n = 4) had significantly lower symptom scores than those receiving placebo (n = 3) (+0·45%/month (SEM 6·9%) versus +27%/month (SEM 6·5%); $p < 0·001$). None of the patients treated with ketoconazole reported any adverse effects. Ketoconazole may cause serious liver damage but its use may be justified in bronchopulmonary aspergillosis if further experience confirms its ability to alter the course of a potentially serious disease.

Aspergillus fumigatus is associated with various respiratory disorders. Mycetoma and allergic bronchopulmonary aspergillosis are the most common non-invasive forms.

The most common symptoms caused by mycetoma are chronic small volume haemoptysis and cough. Major haemoptysis may cause death, however, in about 10% of sufferers.[1 2] The development of invasive aspergillosis in these patients may also lead to death and may be more common than was previously realised.[2] The value of chemotherapeutic treatment in this disorder is unknown and many antifungal agents have been tried with little success.[2]

Chronic uncontrolled allergic bronchopulmonary aspergillosis may lead to extensive lung destruction. Several clinical stages in the progress of the disease have been proposed.[3] An unknown proportion of patients develop irreversible airways obstruction and pulmonary fibrosis, associated with characteristic concentric proximal bronchiectasis and loss of functioning lung tissue. This has been reported to lead to cor pulmonale and death.[4] Lung damage is thought to be the result of a type III immune reaction to aspergillus antigen in the airways. Reduction of the antigen load by an effective antifungal agent might impede the destructive progress of the disease, but trials with such agents have produced disappointing results.[5–8] Repeated courses of systemic corticosteroids therefore remain the mainstay of treatment, despite their attendant complications.

In view of these problems a pilot study was undertaken to assess the efficacy of ketoconazole, an imidazole antifungal agent, in non-invasive pulmonary aspergillosis.

Methods

Ten patients with evidence of non-invasive pulmonary aspergillosis were recruited from outpatients attending a chest clinic. Their individual details are given in table 1. All the asthmatic patients with one exception were taking regular inhaled corticosteroid and bronchodilator treatment. One patient who entered the trial was taking additional oral corticosteroid and this treatment was continued throughout.

Patients were required to give informed consent after the aims, conduct, and possible risks of the trial had been explained. In the event of adverse effects all patients had direct access to an investigator (DJS).

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Table 1 *Details of the clinical state and results of pretrial investigations on patients taking part in the study*

Patient No*	Age	Sex	Diagnosis	Duration (y)	Skin tests: AF	Skin tests: Others	Radiology‡	Sputum: AF
K1	31	M	Asthma ABPA	27 4	+	+	LUL, RUL	–
K2	76	M	Asthma ABPA	+70 20	+	+	RUL, LUL, RML	–
K3	48	M	Asthma ABPA	+40 5	+	+	RUL, LUL, LLL	–
K4	61	F	Asthma ABPA	60 8	+	+	RUL, LUL	+
K5	35	M	Bronchiectasis mycetoma	31	–	+	Mycetoma, bronchiectasis	–
K6	56	F	Mycetoma	6	–	–	Mycetoma, fibrosis	–
P1	38	M	Sarcoidosis mycetoma	+5 4	–	–	Mycetoma, fibrosis	+
P2†	35	M	Asthma ABPA	35 5	+	+	LUL	–
P3	23	F	Asthma ABPA	15 3	+	+	RUL	–
P4	75	F	Asthma ABPA	4 4	+	–	RUL/RML	–

*K and P indicate patients taking ketoconazole and placebo respectively.
†Received continuous oral corticosteroid, 10–20 mg daily.
‡Areas of infiltration, consolidation, collapse, and cavitation on radiographs are referred to by side and lobes—RUL.
ABPA—allergic bronchopulmonary aspergillosis; AF—*Aspergillus fumigatus*; LLL—left lower lobe; LUL—left upper lobe; RUL—right upper lobe; RML—right middle lobe.

Patients with mycetoma were admitted to the trial if they had definite radiographic features and aspergillus precipitins. Requirements for patients with allergic bronchopulmonary aspergillosis for entry into the trial are given in table 2, they are based on those of Rosenberg *et al*[9] with the exception of bronchographic examination. We included an extra requirement that no clinical or immunological exacerbation should have occurred in the six months before the trial.

All patients entered the trial during one month, between October and November. The patients were randomly allocated to receive placebo or ketoconazole, 400 mg daily, taken as a single daily tablet of identical appearance. The trial was conducted in a double blind fashion, the key being held by Jansen Pharmaceuticals Ltd. Symptoms, signs, spirometric results and treatment of all patients were reviewed at monthly intervals. Blood for determining IgG, IgE, and ketoconazole concentrations was obtained each month and stored at −20°C and +4°C. A chest radiograph was obtained at three monthly intervals. In addition to these assessments, asthmatic subjects kept a diary of their daily symptoms and medication. Symptoms were scored on a simple 0–3 system as follows: 0—no wheeze, cough, breathlessness, or other respiratory symptoms; 1—symptoms present, but not requiring increased treatment; 2—symptoms requiring increased treatment, but not attendance of physician; 3—symptoms requiring increased treatment and attendance of physician.

Table 2 *Diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA) used in this study (all patients met all the diagnostic criteria)*

1	Asthma
2	Peripheral blood eosinophilia at some stage ($>0{\cdot}5 \times 10^9$/l)
3	Previous episode of transient infiltration or the presence of fixed changes consistent with ABPA on the chest radiograph
4	Immediate skin reactivity to *Aspergillus fumigatus* antigen
5	*A fumigatus* specific IgE
6	IgG antibodies to *A fumigatus* detected by agar gel double diffusion

The score obtained in the first month of the trial served as a baseline with which the subsequent months' scores were compared. Serum IgG to *A fumigatus* was determined by a quantitative, antibody capture, enzyme linked immunosorbent assay (ELISA). Two local strains of *A fumigatus* were used to provide antigen for the assay. The assay had intra-assay and interassay variability of less than 10% over the working range of the assay. IgG was expressed as a specific binding index (SBI) determined by comparison with precipitin positive and negative sera.[10] Total IgE was determined with the Phadenzyme PRIST assay system and specific IgE to *A fumigatus* by the Phadenzyme RAST method (Pharmacia Ltd). Serum ketoconazole concentrations were determined by high performance liquid chromatography on the monthly blood samples (Dr C Davies, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford). As blood collection was not fixed to the time of tablet ingestion the aim was to check compliance rather than to determine effective antifungal levels.

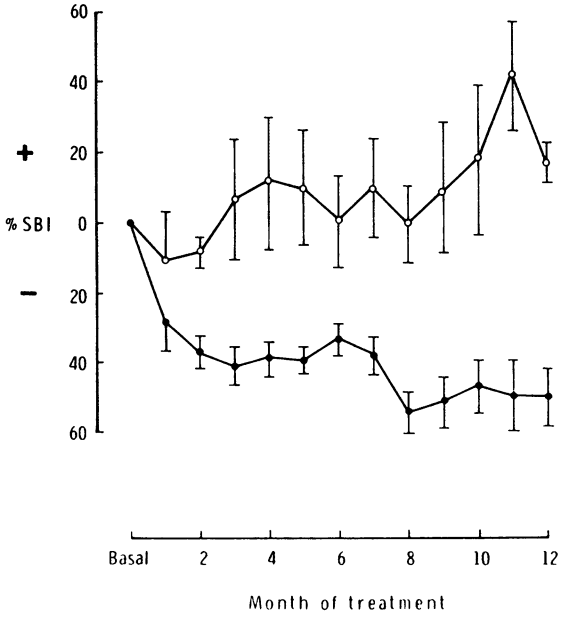

Fig 1 *Effect of ketoconazole (●) and placebo (○) on the specific binding index (SBI) for anti-Aspergillus fumigatus IgG antibody. The results are shown as the mean changes from baseline values expressed as percentages. Bars indicate SEM. In the ketoconazole group antibody levels for months 3–10 and 12 are significantly lower than the basal value for that group.*

Results were expressed as absolute measurements or as percentage changes from pretrial determinations. Data are presented throughout as means and standard errors of the mean. The significance of differences was assessed by the Students *t* test and a probability of $p < 0.05$ was considered significant. Correlations were determined from standard formulae.[11]

Results

ANTIBODIES TO A FUMIGATUS

Treatment with ketoconazole led to a reduction in specific IgG antibody to *A fumigatus*. After three months' treatment there was a 40% reduction from pretreatment levels ($p < 0.05$). This reduction was significant for all subsequent months except month 11 ($p < 0.10 > 0.05$). In the placebo treated group SBI values remained relatively stable, with an average increase of 10% compared with a mean reduction of 42% (SEM 2·2%) for the ketoconazole group over the year (fig 1).

Concentrations of total IgE and IgE specific for *A fumigatus* in the patients with allergic bronchopulmonary aspergillosis were significantly reduced after 12 months of treatment with ketoconazole (table 3) whereas no alteration was detected in the placebo group, although there were only three patients in group.

Table 3 *Total and specific serum IgE concentrations in patients with asthma before and after 12 months of treatment with ketoconazole or placebo*

	Ketoconazole (n = 4)	*Placebo (n = 3)*
Total IgE (ku × 10^{-2}/l)		
Baseline	13·5 (2·4)	5·1 (2·2)
12 months	4·9 (0·5)*	9·1 (3·4)
Specific IgE (Pru/ml)		
Baseline	7·7 (1·2)	4·2 (0·8)
12 months	5·9 (0·9)*	4·2 (1·4)

*$p < 0.05$ for comparison of 12 months and baseline results.

SYMPTOM SCORES

Ketoconazole led to a significant reduction in symptom scores. For this group the mean change was +0·45%/month (SEM 6·9%) compared with +27%/month (6·5%) for the placebo group ($p < 0.001$). There was a significant correlation between the change in IgG concentrations and symptom scores after ketoconazole ($r = 0.6$, $p < 0.05$, d f 9), but not in placebo group. The changes in symptom

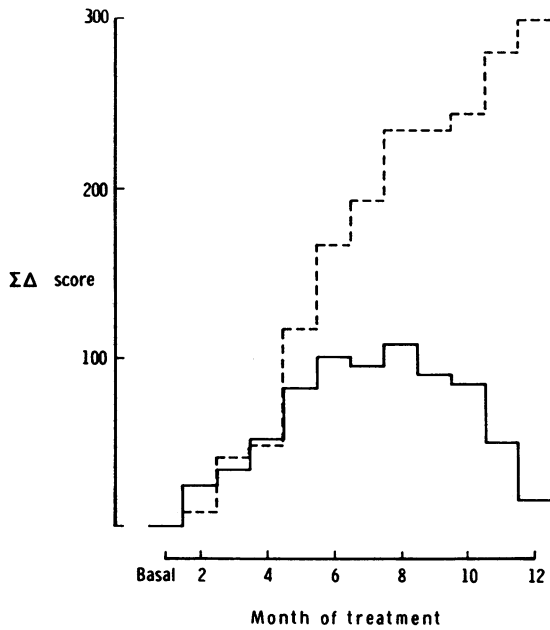

Fig 2 *Effect of ketoconazole (——) and placbeo (– – –) on asthma symptom scores. The scores are accumulated mean increments or decrements for each month by comparison with the basal period.*

scores, illustrated in figure 2, show that in the ketoconazole group scores gradually fell over the last six months of the study.

SERUM KETOCONAZOLE CONCENTRATIONS

All patients apart from one had ketoconazole detectable in their monthly serum specimens. The mean concentration for all patients receiving ketoconazole over the 12 months was 2·16 (range 0–20·5) μg/ml and confirmed good compliance in most of the patients.

RADIOLOGY

Chest radiographs in patients with allergic bronchopulmonary aspergillosis showed no new infiltrates while they were receiving ketoconazole or placebo. The established changes noted in all patients on entry to the trial showed no reversal after treatment. One patient's mycetoma resolved radiologically during treatment with ketoconazole, and this was associated with a cessation of haemoptysis. Patient P1 showed evidence of reduction in the size of the fungus ball, but he died of massive haemoptysis after nine months of placebo treatment.

SPIROMETRY

In the ketoconazole group the mean FEV_1 was 83·3% (SEM 9·6%) of the predicted value and was unchanged by the treatment period (77·5% (13·2%)). Similarly, the forced vital capcity (FVC) was unaffected by treatment (106·8% (9·8%)) of predicted normal before and 92·3% (13·6%) at the end of treatment. No significant changes occurred in the placebo group, whose initial FEV_1 and FVC were 85·5% (21%) and 83·8% (18%) of predicted normal.

Discussion

Trials of antifungal agents in non-invasive pulmonary aspergillosis, particularly in allergic bronchopulmonary aspergillosis, have been disappointing.[5-8] Other agents, such as inhaled sodium cromoglycate[12] and beclomethasone dipropionate,[13] have proved equally ineffective. Thus the only effective treatment currently available is systemic corticosteroid. This rapidly improves the radiographic features of allergic bronchopulmonary aspergillosis and reduces symptoms, serum IgE concentrations, and the frequency of sputum cultures positive for *A fumigatus*.[14] Regular treatment will maintain clinical improvement in up to 80% of patients.[12] A recent recommendation has been the administration of 0·5 mg/kg/day for 14 days during an acute exacerbation followed by the same dosage on alternate days for three to six months.[15] The drawbacks of this regimen are that a patient with repeated exacerbations[3 10] would be exposed to an unacceptable amount of corticosteroid. A study of ketoconazole was therefore thought to be reasonable.

In previous studies of antifungal treatment various markers of disease activity have been used. These have varied from clinical state, in terms of symptoms or of time lost from work, to clearance of *A fumigatus* from the sputum or radiological and immunological changes.[5-8] In mycetoma assessment of response to treatment is fairly easy, as the condition is relatively stable and there are good radiological and immunological markers. In allergic bronchopulmonary aspergillosis, where the natural history is of relapse and remission, clinical assessment alone is inadequate as significant immunological exacerbation may occur without symptoms,[13] while improvement of symptoms may reflect improvement of asthma rather than of the aspergillosis.[3] Sputum culture for *A fumigatus* is also an inadequate means of assessment since 40–50% of patients do not have positive cultures and sputum positivity is considered a minor diagnostic criterion compared with immunological markers in allergic bronchopulmonary aspergillosis.[14 16 17] Immunoglobulin E and G levels have been shown to rise during episodes of asymptomatic pulmonary eosinophilia,[13] and with the quantitative ELISA used in this study IgG concentrations have been shown to change significantly with clinical and radiological exacerbation and systemic corticosteroid treatment in individual patients.[10] Hence in the study reported here clinical, radiological, and immunological features of disease activity were followed over a 12 month treatment period.

Starting the study in the autumn allowed the pretrial clinical and immunological assessments to be made at a time when exacerbation rates are lowest. Thus the pretrial antibody levels started from remission values and would not bias the effect of the drug in favour of reduction. Furthermore, this starting point increased the chance of detecting exacerbation during the first autumn and winter period of the study.

Ketoconazole treatment led to reduction of specific IgG antibody at one and two months, but a significant reduction only occurred after three months of treatment, which may reflect the slowness of fungal eradication or the effect of higher atmospheric spore counts during the autumn, when this study started.[18-20] Edwards and La Touche,[7] when studying natamycin found that eradication of fungus from the sputum took on average six weeks, although some patients still had positive cultures after 13 weeks of treatment.

Despite the small numbers of subjects, total and specific serum IgE concentrations also showed a significant reduction after ketoconazole treatment. The reduction in the immune response to *A fumigatus*

has two possible benefits for the patient. Firstly, the reduction in IgE may lead to an improvement in asthma, as detected by the change in symptom scores of asthmatic patients in this study. Secondly, the lower IgG concentrations may lead to a reduction in the intensity of destructive type III reactions occurring in the lung.

While we accept that the changes in symptom scores may represent improvement of asthma rather than of allergic bronchopulmonary aspergillosis, unequivocal subjective benefit was gained by the ketoconazole group. This improvement in symptoms occurred without objective improvement of their asthma as both spirometric values and medication were unaffected by ketoconazole treatment. The effect on scores was not evident until the fifth month of treatment (fig 2) but continued to the end of the study. There was no increase in symptom scores with ketoconazole at the beginning of the second autumn period (months 10, 11, and 12), when exacerbation would be expected.

The use of ketoconazole is not without risks, which must be considered seriously if long term treatment is anticipated. The most serious complication, recognised before the recent publicity, is hepatitis,[21] which has been fatal. Most problems, however, are minor and hepatic damage has an incidence of about 1 in 15 000.[22] Ketoconazole therefore has to be used with discretion and long term treatment of mycetoma, usually a benign condition may be inappropriate. Allergic bronchopulmonary aspergillosis, however, is a chronic disorder, often beginning at an early age, which may lead to severe disability and death. Its incidence and prevalence are not known exactly, but it is still probably underdiagnosed.[14] The frequency of diagnosis has increased in the United Kingdom and North America when it has been looked for. Around 7–22% of those with asthma in the UK may be affected, which indicates a fairly large population at risk from long term sequelae of the disease or from corticosteroid treatment.[23–25] Hence in allergic bronchopulmonary aspergillosis the risks of ketoconazole treatment become more acceptable.

This pilot study has shown benefits from the use of ketoconazole and suggests that further studies of its use in allergic bronchopulmonary aspergillosis may be warranted.

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