Pharmacokinetics and safety of itraconazole in patients with cystic fibrosis

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Objective: To assess the pharmacokinetics of itraconazole and hydroxy-itraconazole in patients with cystic fibrosis.

Methods: Patients were divided into those <16 and ≥16 years of age. All received itraconazole oral solution 2.5 mg/kg twice daily for 14 days. Serial blood samples were taken for itraconazole and hydroxy-itraconazole plasma level measurements. Safety was assessed from biochemistry and haematology data and reported adverse events.

Results: Seventeen patients entered the study. Steady-state concentrations were achieved after maximally 8 days of dosing. On day 14 average peak plasma concentrations were 404 ± 268 ng/mL (<16 years, n = 5) and 779 ± 470 ng/mL (≥16 years, n = 11 excluding one patient concurrently receiving oral clarithromycin). A high inter-subject variability in itraconazole pharmacokinetics was seen. Intra-subject variability was low. All the younger patients and 50% of the older patients failed to achieve a plasma steady-state trough concentration of >250 ng/mL. Adverse events were reported by 53% of subjects. Most were mild or moderate in intensity and not considered related to treatment. One patient withdrew from the study because of two severe adverse events. Ten significant laboratory abnormalities were reported in seven of 16 patients with paired data. Six of these were clinically relevant.

Conclusion: 2.5 mg/kg itraconazole oral solution twice daily in patients with cystic fibrosis achieves steady-state concentrations in maximally 8 days. The pharmacokinetics showed marked inter-subject variability. Plasma concentrations of >250 ng/mL were not reached in the paediatric cohort or in 50% of the adult cohort. The dosage regimen was safe and well tolerated.

Keywords: allergic bronchopulmonary aspergillosis, antifungals, itraconazole

Introduction

Aspergillus fumigatus is a ubiquitous fungal organism. Its spores are ~3 µm in diameter and can therefore penetrate the bronchial tree. Allergic bronchopulmonary aspergillosis (ABPA) describes the lung disease that may result from an immune response to A. fumigatus. A combination of types I and III hypersensitivity reactions stimulate the production of specific IgG, IgA and IgE antibodies. Chronic inflammation leads to irreversible restrictive and obstructive changes with central bronchiectasis. Patients suffer episodic wheezing, worsening lung function and typically show transient pulmonary infiltrates on chest X-ray, blood and sputum eosinophilia, circulating antibodies and a positive immediate skin test to A. fumigatus.

ABPA was first described in patients with cystic fibrosis (CF) in 1965.1 Its diagnosis in CF can be difficult as many of the features of ABPA overlap with those of the underlying disease. There is no single diagnostic test, but well-recognized diagnostic criteria.2–4 The treatment of choice has been systemic high-dose corticosteroids (45–60 mg daily in adults and 2 mg/kg/day in children),5 which are gradually reduced as the inflammatory response is controlled. However, prolonged oral corticosteroid therapy heightens the risk of diabetes mellitus, osteoporosis and impaired growth, all of which are potential complications of CF itself. The antifungal drug itraconazole is an effective steroid-sparing adjunctive treatment for ABPA.6,7 Itraconazole is metabolized by side-chain hydroxylation to hydroxy-
itraconazole. In the steady-state, hydroxy-itraconazole is found in concentrations nearly twice that of the unaltered drug. Many fungi are susceptible to both the parent drug and the hydroxylated metabolite.

The use of itraconazole oral solution formulation in patients with CF is preferred as higher itraconazole blood concentrations are achieved than with the capsule formulation. The absorption of the solution is more rapid in the fasting state. Also absorption of the oral solution, in contradistinction to the capsule preparation, is not reduced by proton-pump inhibitors.

The aim of this study was to assess the pharmacokinetics and safety of itraconazole oral solution in two groups of patients with CF, those under 16 and those 16 years of age or over.

Patients and methods

This was an open, Phase II trial which aimed to recruit 12 subjects <16 and 12 patients ≥16 years of age in whom CF had been confirmed by two positive sweat tests and/or the presence of two CF transmembrane conductance regulator gene mutations. These patient numbers were considered sufficient to allow relevant conclusions in this exploratory pharmacokinetics trial. Exclusion criteria included a concurrent febrile illness, use of concomitant therapy that may provoke adverse drug interactions, symptomatic ABPA or liver disease defined as serum transaminase values more than twice the upper normal limit or serum bilirubin >50 mmol/L. Patients were also excluded if they had received systemic antifungal therapy or prophylaxis within 2 weeks of study entry.

Each patient received an oral solution containing 10 mg/mL of itraconazole at a dose of 2.5 mg/kg twice daily for 14 days. The morning dose was taken before breakfast and the evening dose before the evening meal. The oral dose was based on the recommended adult intravenous dose of 200 mg, which equates to a dose of 2–3 mg/kg in children. Venous blood was sampled for drug analysis before and at 1, 2, 3, 4, 6, 8 and 12 h after the first dose on days 1 and 14, and before and 2 h after dosing on days 8 and 11. Plasma concentrations of itraconazole and hydroxy-itraconazole were determined by visual inspection of the data; AUC_{12} (area under the plasma concentration–time curve over a dosing interval, calculated by trapezoidal summation) and C_{max}, (average steady-state plasma concentration calculated by AUC_{12}/t). Pre-dose plasma samples taken in the morning of days 8 and 11 were used for evaluation of steady-state conditions.

At each trial visit, patients were asked whether they had experienced any adverse events with non-leading questions. At the screening visit and at the end of the study, blood was sampled for routine haematology, liver function tests and routine blood chemistry. For most haematological and biochemical tests pathological limits were set as defined by Lippert & Lehmen. For enzymes the lower pathological limit was set at zero and the upper limit at twice the upper limit of normal.

The study was approved by the hospital Ethics Committee and written informed consent obtained in all cases.

Results

Twelve patients, five male and seven female, aged ≥16 years entered the study. Only five patients, two male and three female, under 16 years agreed to enrolment because of the multiplicity of blood samples required. Median ages were, respectively, 24 years (range: 16–28) and 12 years (range: 7–15). Median body mass index and ranges were, respectively, 19.4 kg/m² (15–24.7) and 16.6 kg/m² (15–19.7). All patients were pancreatic insufficient. Apart from varied needs for pancreatic enzyme replacement therapy there were no differences between patients in the severity of any other gastrointestinal CF-related symptoms. Mean percentage predicted forced expiratory volume in the first second of expiration and mean forced vital capacity were, respectively, 39% (range 20–68) and 54% (range 26–107) in patients ≥16 years of age and 54% (range 33–74) and 75% (range 46–94) in patients <16 years of age. One subject in each age group discontinued from the trial. The reasons cited were the number of venepunctures required on day 14 (<16 years) and nausea and vomiting (>16 years). Three patients, one in the <16 year age group, used prohibited intercurrent therapy. One patient received oral itraconazole solution until day 15. Consequently the pharmacokinetic parameters were determined on day 15.

All scheduled plasma samples were available for bioanalysis except for days 11 and 14 (one patient), t = 4, 6, 8 and 12 h on day 14 (one patient), and the sample at t = 8 h on day 14 (one patient). All available data from all subjects were included in the pharmacokinetic analysis. The mean plasma concentration–time profiles of itraconazole and hydroxy-itraconazole on days 1 and 14 are shown in Figures 1 and 2. Overlay plots are shown in Figures 3–6. A summary of the pharmacokinetic parameters of itraconazole and hydroxy-itraconazole on days 1 and 14 are given in Table 1.

Mean data suggest patients achieved steady-state concentrations by 8 days of dosing and this was maintained until day 14. In the younger age group (n = 5) steady-state concentrations of >250 ng/mL were not realized in any of the patients. In patients 16 years and older plasma concentrations of >250 ng/mL were reached by 58% of the subjects on day 8, 45% on day 11 and 55% on day 14. The intra-subject variability was small. Five of six patients who reached concentrations >250 ng/mL maintained these concentrations as did four of five who achieved concentrations <250 ng/mL.

All 17 patients received co-medications which were screened for their potential effect on the pharmacokinetics of itraconazole. The highest itraconazole levels were observed in a patient who had concurrently received clarithromycin and may have resulted from a competitive inhibition of metabolism via CYP3A4. Five patients received ondansetron as co-medication. No apparent effect on itraconazole levels was observed.

Nine (53%) patients, two < 16 years of age, experienced at least one adverse event. In one patient (≥16 years), nausea and vomiting on day 8 were considered a severe adverse event and very likely related to treatment. This led to the patient’s withdrawal from the trial on the same day. Both the nausea and vomiting resolved within 24 h of withdrawal. The same patient had an episode of moderate headache and dizziness considered possibly related to treatment. Mild nausea and moderate vomiting in two other patients were considered possibly drug related. All three patients recovered from these mild or moderate symptoms. The relationships of other adverse events (nausea, dizziness, headache), to trial medication were reported as doubtful or unrelated.

Clinical laboratory data were available for all 17 patients. Paired data at baseline and at the end of the study were available for 16
subjects for the majority of the tests. Ten significant abnormal laboratory values were found in seven patients, four < 16 years old, i.e. abnormal values occurring at least twice during treatment, or once at the end of treatment, when there were non-pathological values before treatment. Only six of these were clinically relevant: peripheral blood white cell count 7.9 × 10^9 cells/L at screening rising to 11.4 × 10^9 cells/L on day 14; haemoglobin 121 g/L at screening falling to 109 g/L on day 14; serum potassium 3.9 mmol/L at screening falling to 2.9 mmol/L on day 14; serum urea 5.2 mmol/L at screening rising to 9.3 mmol/L on day 14; serum urea 5.7 mmol/L at screening rising to 10.4 mmol/L on day 14; alanine transaminase 32 U/L at screening rising to 134 U/L on day 14.

Figure 1. Mean plasma concentration–time profile of itraconazole on days 1 and 14. Dashed line, ≥ 16 years (not including patient A); solid line, < 16 years; grey line, patient A.

Figure 2. Mean plasma concentration–time profile of hydroxyitraconazole on days 1 and 14. Dashed line, ≥ 16 years (not including patient A); solid line, < 16 years; grey line, patient A.
ABPA in patients with CF is thought to have a prevalence of ∼5–15% but is probably underdiagnosed.²,⁹ It has been associated with worse lung function¹⁰,¹¹ and a more rapid decline in lung function.³ Itraconazole is a triazole antifungal agent of proven efficacy against mucosal candidiasis, dermatomycoses and deep fungal infections. Although high-dose corticosteroid therapy effectively controls the host inflammatory response that is central to the pathogenesis of ABPA-induced bronchiectasis, long-term treatment increases the risks of diabetes mellitus, impaired growth and osteoporosis. Itraconazole has been used as an effective steroid-sparing agent in ABPA.³,⁶,⁷,¹² Comparison of the bioavailability of itraconazole oral solution and capsule formulations show higher blood levels with the former.¹³ Most patients with CF have exocrine pancreatic insufficiency and despite pancreatic enzyme supplements show laboratory evidence of fat malabsorption. This may affect the absorption of lipophilic drugs such as itraconazole. Patients with CF also show an
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Increased volume of distribution and faster drug clearance often requiring higher antibiotic doses. To date there has not been a formal study of the pharmacokinetics of itraconazole oral solution in CF and therefore the requirements for achieving adequate plasma concentrations needed to be studied.

Steady-state plasma concentrations of itraconazole and its active metabolite hydroxy-itraconazole are usually attained within 2 weeks of twice-daily dosing. The manufacturer recommends a trough steady-state serum concentration for itraconazole and hydroxy-itraconazole of >250 ng/mL and >1000 ng/mL, respectively. Sermet-Gaudelus et al. found approximately one-third of patients with CF failing to achieve trough steady-state serum itraconazole concentrations > 250 ng/mL after at least 15 days oral itraconazole capsules at a dose of 10 mg/kg/day. In the older cohort in the present study steady-state itraconazole concentrations were > 250 ng/mL in ~50% of the patients. Lower concentrations were seen in the younger cohort, none of whom achieved steady-state values of

Figure 5. Overlay plot of the individual plasma concentration–time curves for hydroxy-itraconazole on day 1.

Figure 6. Overlay plot of the individual plasma concentration–time curves for hydroxy-itraconazole on day 14.
>250 ng/mL. A tendency towards lower concentrations with decreasing age has been described.16 In this study all pharmacokinetic parameters, except for $T_{\text{max}}$, were higher for the older cohort. A dose of 2.5 mg/kg oral solution twice daily is therefore likely to be inadequate in paediatric patients and will not reliably achieve effective plasma concentrations in adults with CF.

Patients with the lowest drug concentrations (180 ng/mL and <10–174 ng/mL15), show the least significant clinical and serological responses. As shown in Figures 3–6, large inter-subject variability was observed for the pharmacokinetics of itraconazole and hydroxyitraconazole in both age groups on all assessment days. Intra-subject variability was relatively small with subjects who reached concentrations > 250 ng/mL. A tendency towards lower concentrations with decreasing age has been described.16 In this study all pharmacokinetic parameters, except for $T_{\text{max}}$, were higher for the older cohort. A dose of 2.5 mg/kg oral solution twice daily is therefore likely to be inadequate in paediatric patients and will not reliably achieve effective plasma concentrations in adults with CF.

In conclusion, investigation of the pharmacokinetics of itraconazole oral solution in two age groups of patients with CF at a dose of 2.5 mg/kg twice daily over 14 days showed achievement of steady-state concentrations in maximally 8 days, and a high level of variability in the drug pharmacokinetics. In the older age group higher concentrations were generally obtained. Through plasma concentrations > 250 ng/mL were observed in about half of the patients 16 years of age or older, but in none of those <16 years of age. Over the 14 day study the incidence of adverse clinical events and clinically significant laboratory abnormalities was low, and most adverse events were categorized as mild or moderate and not considered related to treatment.

### Acknowledgements

We thank Janssen-Cilag for supplying the itraconazole oral solution and for performing the pharmacokinetic measurements.

### References


### Table 1. Pharmacokinetic parameters of itraconazole and hydroxy-itraconazole on days 1 and 14

<table>
<thead>
<tr>
<th></th>
<th>Itraconazole</th>
<th>Hydroxy-itraconazole</th>
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<tbody>
<tr>
<td></td>
<td>day 1</td>
<td>day 14</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)$^a$</td>
<td></td>
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<tr>
<td>&lt;16 years</td>
<td>&lt;16 years</td>
<td>≥16 years</td>
</tr>
<tr>
<td>patient A</td>
<td>1 (1–4)</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>≥16 years</td>
<td>2 (1–8)</td>
<td>2.5 (1–6)</td>
</tr>
<tr>
<td>patient A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;16 years</td>
<td>133 ± 135</td>
<td>404 ± 268</td>
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<tr>
<td>≥16 years</td>
<td>156 ± 108</td>
<td>779 ± 470</td>
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<tr>
<td>patient A</td>
<td>393</td>
<td>2467</td>
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<tr>
<td>$AUC_{12}$ (ng·h/mL)</td>
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<tr>
<td>&lt;16 years</td>
<td>433 ± 358</td>
<td>2298 ± 1322</td>
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<tr>
<td>≥16 years</td>
<td>717 ± 378</td>
<td>6270 ± 3688</td>
</tr>
<tr>
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<td>2309</td>
<td>21519</td>
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<tr>
<td>$C_{\text{ss,av}}$ (ng/mL)</td>
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<tr>
<td>&lt;16 years</td>
<td>119 ± 83.4</td>
<td>276 ± 161</td>
</tr>
<tr>
<td>≥16 years</td>
<td>307 ± 249</td>
<td>776 ± 429</td>
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<tr>
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<tr>
<td>$C_{\text{AUC}}$ (ng/mL)</td>
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<tr>
<td>&lt;16 years</td>
<td>191 ± 110</td>
<td>400 ± 216</td>
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<tr>
<td>≥16 years</td>
<td>523 ± 307</td>
<td>958 ± 417</td>
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</table>

Patient A in age group ≥ 16 years received clarithromycin and is shown separately. $T_{\text{max}}$ as median (range).

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