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Plasma Itraconazole Concentrations in Neutropenic Patients after Repeated High-dose Treatment

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Two different treatments with repeated oral high doses of itraconazole were tested for 10 days in 20 neutropenic patients, 10 receiving 400 mg per day and 10 receiving 600 mg per day. In each group 5 patients were treated for acute leukaemia and 5 patients were recipients of autologous bone-marrow transplantation (ABMT). Itraconazole plasma concentrations were assayed by high-performance liquid chromatography. Statistical analysis disclosed a significant interaction between the dispensed dose and the patient types. The difference between the two doses of itraconazole was greater in the ABMT than in the leukaemia patients. After 10 days at 600 mg per day all the ABMT patients had an itraconazole plasma concentration higher than 250 μg/l. Therefore, 600 mg per day seems more efficient to obtain a therapeutic level of itraconazole in ABMT patients but this needs to be confirmed for all the neutropenic patients.
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INTRODUCTION

NEUTROPENIC PATIENTS treated with chemotherapy are at high risk of fungal infections. These infections are most frequently caused by *Candida* spp. but also by *Aspergillus* spp. [1]. Choice of treatment to prevent or to cure these invasive fungal infections is limited by the toxicity of available agents or the efficacy of others.

Itraconazole is an orally active triazole antifungal agent. It has a wide antifungal spectrum that includes *Aspergillus* spp. [2]. It demonstrates a high degree of lipophilicity and an absence of endocrine-related side effects [3–5]. Pharmacokinetics of itraconazole in human normal volunteers are characterised by good absorption, minimal renal excretion of the parent drug and elimination half-life of about one day for a 100 mg dose [6].

This antifungal drug is thus potentially useful in the treatment or prophylaxis of aspergillosis and candidiasis in neutropenic patients. However, intensive chemotherapy used for such patients damages the intestine epithelium [7] and may reduce the intestinal absorption of antifungal drugs [8]. Consequently, the usual doses (50–400 mg per day) [3] may not be sufficient to achieve a plasma itraconazole concentration at 250 μg/l which seems necessary to protect these patients from the deep mycoses [9].

The aim of the present study was to evaluate the itraconazole plasma level after daily administration at two high doses, 400 and 600 mg per day, in neutropenic patients over 10 days, virtual steady-state [10]. Two types of neutropenic patients were studied: patients after induction chemotherapy for acute leukaemia and patients after chemotherapy followed by autologous bone-marrow transplantation (ABMT).

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PATIENTS AND METHODS

Patients' selection

20 subjects (aged 19–77) were studied. Only patients which gave their informed consent prior to starting treatment with itraconazole were included in the study. Patients were non-consecutive and were able to take oral drugs after completion of high-dose chemotherapy. Moreover, they had no treatment with antacids and those receiving amphotericin B or rifampicin were excluded.

10 patients (mean age 52.8 years) received chemotherapy for acute myeloid leukaemia with daunorubicin at 60 mg/m^2 for 3 days and cytarabine at 200 mg/m^2 for 7 days. 10 patients (mean age 36.7 years) were recipients of ABMT for malignant lymphoma after conditioning with carmustine (300 mg/m^2, one day), cyclophosphamide (1500 mg/m^2, 4 days) and etoposide (200 mg/m^2, 4 days) but without radiation. Within each chemotherapy group, 5 patients received 400 mg once per day and 5 patients 600 mg once per day.

Drug administration

The experiment started one day after the end of chemotherapy for the group of leukaemia patients and 1 day after the bone marrow transplantation for the ABMT group (3 days after the end of chemotherapy). Itraconazole was supplied by Janssen Laboratories as 100 mg capsules. Patients were administered a 400 or 600 mg oral dose of itraconazole, immediately after breakfast to assure maximal drug absorption [10]. This treatment was performed over 10 days (D1 to D10), except for 2 patients whose samples were not available for days 9 and 10.

Blood sampling

Blood samples (5 ml) were regularly collected, each day just before (minimal concentration, C_{min}) and 4 h after the administration to verify the drug intake (C_{4h}, maximal concen-

Table 1. Mean of plasma itraconazole concentration during the treatment following the given doses

	Dose			
	400 mg/day		600 mg/day	
	Plasma concentration (μg/l)*			
Days	C_{min}	C_{4h}	C_{min}	C_{4h}
1	<50 (10)	192 (194) (10)	<50 (10)	209 (96) (10)
2	84 (62) (10)	404 (214) (9)	115 (13) (9)	459 (245) (10)
3	159 (121) (10)	357 (205) (10)	162 (37) (10)	427 (157) (10)
4	160 (75) (10)	360 (179) (10)	212 (62) (9)	514 (289) (10)
5	197 (117) (10)	419 (271) (9)	256 (65) (9)	467 (224) (9)
6	208 (119) (10)	465 (245) (9)	289 (105) (10)	527 (185) (10)
7	272 (181) (9)	468 (190) (9)	313 (124) (10)	552 (335) (10)
8	276 (178) (10)	504 (316) (10)	322 (159) (9)	564 (354) (9)
9	273 (180) (9)	487 (331) (9)	305 (111) (8)	467 (263) (6)
10	274 (131) (8)	459 (181) (8)	304 (134) (7)	498 (214) (7)

* Mean (S.D.) (no. of samples).

tration after a meal) [10]. Plasma samples were separated and stored at −20°C. 371 samples were collected.

High-performance liquid chromatography assay

The chromatograph consisted of a M 45 pump, a U6K universal detector and a 441 absorbance detector (Waters Associates, Milford, Massachusetts, USA). The eluate was monitored at 254 nm and absorbance was recorded with an Omniscribe recorder (Houston Instrument, Houston, Texas, USA). The analytical column was a reverse phase Nucleosil C18 5 μ (150 × 4.6 mm, Société Française Chromato Colonne, Neuilly-Plaisance, France) equipped with a Bondapak C18/Corasil precolumn (Waters Associates). The elution system consisted of 0.5% diethylamine in acetonitrile-water (70:30) [11]. The flow-rate was constant at 0.7 ml/min. Itraconazole and internal standard were obtained from Janssen Life Sciences Products Division (Beerse, Belgium). Stock solutions of 0.1 g/l itraconazole and internal standard were prepared in methanol and stored at 4°C. Plasma specimens and standards (1 ml) were usually spiked with 10 μl of internal standard at 0.1 g/l then once extracted by a liquid–liquid method [12]. After the extraction, the samples were evaporated, the residues redissolved in 100 μl mobile phase and 40 μl was injected. Itraconazole was quantitated by comparison of the peak height ratio of the drug to the internal standard. The standard solutions contained 100, 250, 500 and 1000 μg of itraconazole per litre of plasma. The lower limit of detection was 50 μg/l. The intra-assay coefficients of variation were between 4.7 and 5.8% and the inter-assay coefficients of variation were between 3.8 and 8.2% as a function of the itraconazole concentrations.

Statistics

A three-way analysis of variance was performed to compare itraconazole titration among groups of dispensed dose, type of disease and treatment days (type I error probability = 0.05) [13].

RESULTS

The means of plasma itraconazole concentrations are given in Table 1 for the groups of patients receiving 400 and 600 mg/day for 10 days. The two groups of neutropenic patients, leukaemia and ABMT patients, were first considered as similar. There were wide intersubject variations in itraconazole concentration versus time profile. No side-effect was observed during the experiment.

An accumulation of itraconazole was observed in the plasma during the experiment. The mean values of itraconazole concentration were higher for the patients with 600 mg/day of itraconazole than for those receiving 400 mg/day. Steady-state was attained after 7 days of treatment with a value of about 273 μg/l and 311 μg/l for 400 and 600 mg/day, respectively.

For 1 patient the 4 h postdose itraconazole concentration remained low (<140 μg/l) and similar to his minimal concentration. This patient, receiving 400 mg/day, had fever and diarrhoea, and a systemic candidiasis of *Candida krusei* was detected at day 6 by several positive hemocultures. However, it was not possible to prove that this patient did not take the itraconazole treatment correctly. Three other patients of this group had low levels of minimal concentrations but more elevated 4h postdose concentrations, within a range of 200–600 μg/l.

At the end of the treatment 4 patients of the first group (400 mg/day) and 3 patients of the second group (600 mg/day) had a plasma itraconazole minimal concentration lower than 250 μg/l. One of these last patients was different from the others with a decreasing minimal concentration between days 8 and 10 from a steady-state at 280 μg/l. In half of the patients this value of 250 μg/l was reached within 7 days and 5 days with 400 and 600 mg/day, respectively.

Statistical analysis was performed on all the minimal concentrations to compare itraconazole titration among groups of dispensed dose, type of disease and treatment days. A three-way analysis of variance was used to determine whether there were differences between the two groups of neutropenic patients. It showed two sources of variation in the itraconazole concentration greater than the observed individual variations. The first significant source of variation was the day of treatment ($F = 11.6$, $P < 0.001$), this result confirming drug accumulation in plasma with repeated dosings. The other significant source of variation was the interaction between the dispensed doses and the patient types, i.e. ABMT or chemotherapy ($F = 4.1$, $P < 0.05$). In the ABMT patients there was a difference between the two doses, 400 and 600 mg/day; at 600 mg/day all these patients had a minimal itraconazole concentration higher than 250 μg/l after 10 days (Fig. 1). In the leukaemia patients the difference was less clear (Fig. 1).

DISCUSSION

We have studied the influence of large dosing regimens of itraconazole on the plasma concentration of drug in different neutropenic patients. The findings showed that a treatment of 10 days at 600 mg/day gave an adequate level of the drug in the patient plasma more surely than treatment at 400 mg/day, at least for neutropenic patients after ABMT. We observed no important side-effects for the 20 patients with this high-dose 10-day treatment. However, toxic effects have to be considered since they have been reported after longer itraconazole treatment [14].

The plasma itraconazole concentrations presented large individual variations, as previously described for normal volunteers [15], acute leukaemic patients [16] and patients with renal dysfunction [17]. The concentrations observed with two different repeated dosings cannot be predicted from initial oral dosing [15]; thus, assay of itraconazole in patient's plasma is essential.

After 10 days of treatment the concentrations in neutropenic

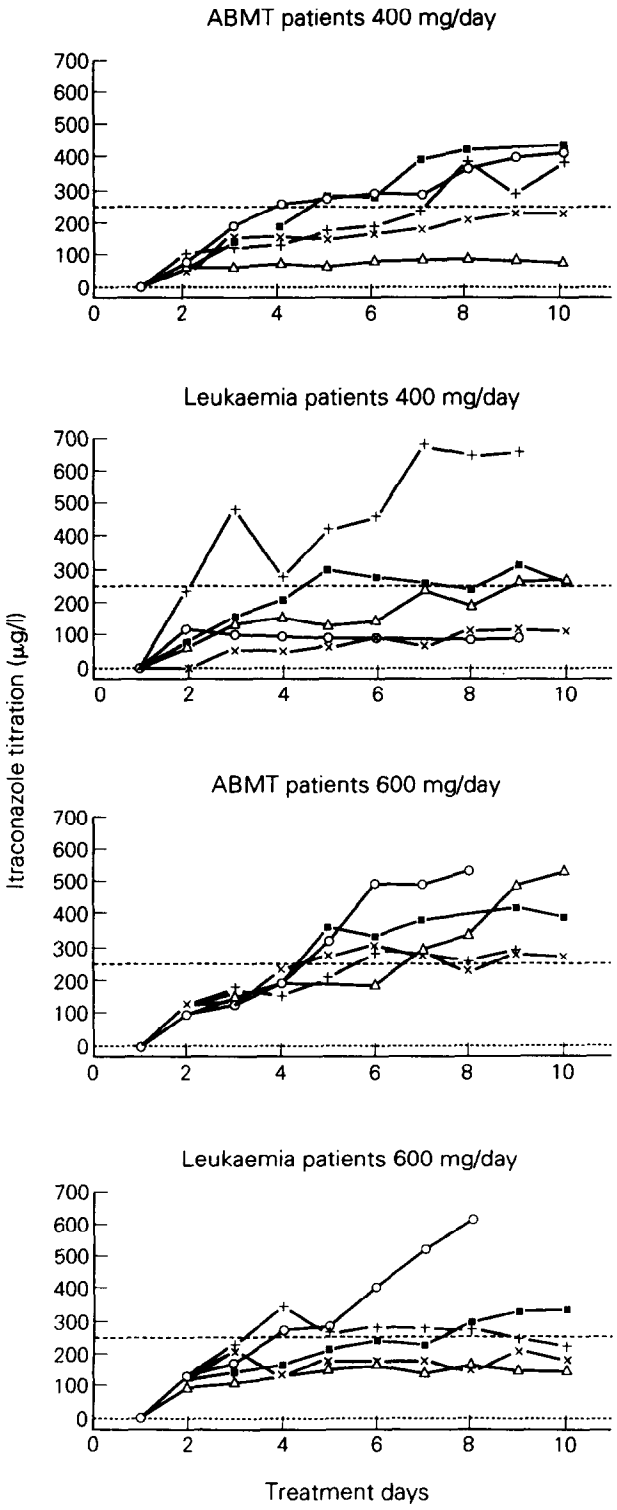

Fig. 1. Individual minimal plasma itraconazole titrations over 10-day treatments, grouped by dispensed dose and type of disease (broken lines: level of the minimal adequate concentration).

patients were inferior to concentrations reported for healthy volunteers, after a similar HPLC assay [6]. This may correspond with a decrease of intestinal absorption probably related to chemotherapy but not to poor compliance since the chosen patients were able to eat.

Not all the neutropenic patients reached the steady-state after a 10-day treatment. As Heykants *et al.* [6] have reported an experiment time within 10 and 14 days, a 14-day minimum treatment should be recommended in further studies with high dosing.

The adequate level of itraconazole in plasma is at least 250 µg/l for an efficient protection against fungal infections [9]. At the end of treatment 4 patients of the group at 400 mg/day had inadequate concentrations, this number was twice lower in the group at 600 mg/day. Moreover, the plasma drug concentrations were greater with a daily dose of 600 mg than with 400 mg/day.

Thus, a daily dose of 600 mg of itraconazole allows a greater number of patients to reach a therapeutic level more rapidly; this may be important for the protection of neutropenic patients against fungal infections. It is worth noting that the only patient with very low peak and minimal itraconazole concentrations had a candidiasis.

The higher levels observed with ABMT patients at 600 mg/day was unexpected since these patients received more intensive chemotherapy dosing with higher expected gastrointestinal toxic effect. No difference in hepatic function or in protein serum concentration was noted between the two chemotherapy groups. However, the ABMT patients were significantly younger and in better physical condition prior to the initiation of chemotherapy. Further, the condition regimen did not include total body irradiation, thereby avoiding major absorption modification [7]. The two types of neutropenic patients were therefore similar but not equivalent in our study. Differences between allogeneic bone marrow transplant patients and non-transplant patients have been reported for another antifungal drug, ketoconazole [8], but no result was available, to our knowledge, for ABMT patients.

Further studies on itraconazole will be necessary to fully determine the dosing scheme of this new antifungal agent in neutropenic patients. The repeated doses of itraconazole at 600 mg over 10 days allow all the ABMT patients to obtain an efficient level of this antifungal drug. However, the result being less obvious for the other group, it was related to the small number of patients studied and this conclusion should be considered preliminary. Moreover, this study was performed with neutropenic patients able to take oral itraconazole, thus restricting itraconazole use. Treatment was only for 10 days, therefore an adverse effect with 600 mg/day during a long-term treatment has to be considered, as recently described for patients with severe mycoses [18]. If further studies confirm our results on itraconazole plasma concentration, this will show the need of a 600 mg/day dosage for the neutropenic patients. Moreover, this study indicates that an initial high regimen should also be recommended for the treatment particularly in immunocompromised patients with documented invasive fungal infections.

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Comparison of Totally Implanted and External Catheters in Paediatric Oncology Patients

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From June 1982 until December 1989, 93 permanent central venous catheters [59 external catheters (ECs) and 34 implanted catheters (ICs)] were placed in 69 patients. The median age of these patients at placement was 5.6 years for ECs and 8.8 years for ICs ($P < 0.05$). Follow-up evaluation was possible on 86 catheters (58 ECs and 28 ICs). The median time of insertion was 236 days and 316 days for ECs and ICs, respectively ($P < 0.05$). The median number of open days was 58 for ECs and 66 for ICs (not significant). 17 catheters (6 ECs and 11 ICs) were transiently obstructed ($P < 0.005$). 30 episodes of bacteraemia were documented in 20 patients. The incidence of catheter sepsis and bacteraemia of unknown source was one in 278 and 283 open days for ECs and ICs, respectively (not significant). In this retrospective study, ECs appeared to be as safe as ICs when infection was correlated with use of the catheter, but this finding should be confirmed in a randomised design.
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INTRODUCTION

CHILDREN WITH cancer require repeated intravenous infusions and blood sampling for chemotherapy, as well as intravenous supportive care such as blood product transfusions, antibiotics and parenteral nutrition. To improve the administration of medications, and the quality of life of these children, permanent central venous catheters have been developed. Broviac *et al.* and Hickman *et al.*, in 1973 and 1979 respectively, introduced silicone rubber catheters [1, 2]. External catheters (ECs) and totally implantable catheters (ICs) are available [3].

Published series have found different rates of complications (i.e. obstruction and catheter-related sepsis) between ECs and ICs, related to the duration of insertion [4–6]. We have analysed retrospectively the complication rate in relation to the number of days the catheters were opened, with particular emphasis on infections.

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