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Multiple dose pharmacokinetics of an oral solution of itraconazole in autologous bone marrow transplant recipients

A. G. Prentice[a], D. W. Warnock[b]*, S. A. N. Johnson[c], M. J. Phillips[c] and D. A. Oliver[a]

[a]Department of Haematology, Derriford Hospital, Plymouth, PL6 8DH; [b]PHLS Mycology Reference Laboratory, Public Health Laboratory, Bristol, BS2 8EL; [c]Department of Haematology, Musgrove Park Hospital, Taunton, TA1 5DB, UK

The pharmacokinetics of itraconazole oral solution were measured in seven patients receiving chemotherapy followed by autologous bone marrow transplantation for leukaemia or lymphoma. Patients received 5 mg/kg/day itraconazole either as a once or twice daily dose. Drug concentrations reached steady state by day 15, in both groups. The mean pre-dose itraconazole serum concentration at hour 0, day 8 was 385 ng/mL in the od group and 394 ng/mL in the bd group, rising to 762 and 845 ng/mL by day 15, respectively. The mean AUCs for 0–24 h on day 8, 15 and 22 were 17,310 and 13,302 ng/mL/h, 24,476 and 25,154 and 22,621 and 21,423, for the od and bd groups, respectively. Thus serum concentrations of itraconazole suitable for antifungal prophylaxis can be attained in neutropenic patients, with the administration of an oral solution in a dosage of 5 mg/kg as either an od or bd schedule, following pre-autograft high-dose cytotoxic chemotherapy.

Introduction

Invasive fungal infection is a major cause of morbidity and mortality in patients receiving bone marrow transplants for leukaemia (Anaissie, 1992). This, coupled with the difficulties of diagnosing such infection, has led to the search for a prophylactic regime, active particularly against both *Aspergillus* and *Candida* species (Working Party, 1993). Amphotericin B has been used, but requires intravenous administration and has a relatively high toxicity (Gallis, Drew & Pickard, 1990). Itraconazole is an orally active triazole with a wide spectrum of antifungal activity which has been successfully used in the treatment and prevention of aspergillus infection (Tricot *et al.*, 1987; Denning *et al.*, 1990; Dupont, 1990). However, the bioavailability of the pellet capsule form is reduced in neutropenic patients (Bradford *et al.*, 1991). There may also be problems of compliance when patients have difficulties in swallowing the capsules, especially when high doses are required (Bradford *et al.*, 1991). Studies with healthy volunteers have shown that the overall bioavailability of a new formulation oral solution is 30% higher than that of the coated pellet-capsule formulation and may therefore offer advantages to patients, especially when drug bioavailability is compromised by hypoacidity, mucositis or reduced gastric function (Barone, J. &

*Corresponding author.

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Bierman, R. H., Janssen Research Foundation data on file). This study examined the pharmacokinetics of itraconazole oral solution in a group of patients who had received an autologous bone marrow transplant following high-dose chemotherapy, which is known to induce mucositis of unpredictable and variable severity.

Methods

Eight adult patients who received an elective autologous bone marrow transplant for all forms of leukaemia and lymphoma including multiple myeloma were recruited for the study. Patients were excluded from the study if they were known to be sensitive to imidazole antifungals, had severe hepatic impairment, were receiving rifampicin, had profuse diarrhoea or known ileus on presentation, were unable to give their informed consent or, in the case of women of child-bearing age, were pregnant or not taking adequate contraceptive measures. The study was approved by the ethics committees of the participating hospitals.

This was an open study, in which patients received a daily dosage of 5 mg/kg itraconazole oral solution, either as a once or twice daily dose. The oral solution consists of 10 mg/mL itraconazole in a 40% hydroxypropyl-β-cyclodextrin solution. Venous blood samples were taken from a central line at 0, 1, 2, 3, 4, 5, 6, 8 and 24 h on the first day of itraconazole administration (day 1), which was three days following reinfusion of marrow, and then again at these times on days 8, 15 and 22. Serum itraconazole concentrations were measured using reversed-phase high-performance liquid chromatography (HPLC). The method used has previously been shown to have a lower detection limit of 10 ng/mL with coefficients of variation from 2·2 to 7·8% over a range of drug concentrations from 20 to 1600 ng/mL (Warnock, Turner & Burke, 1988). The standard curve was linear from 10 to 10,000 ng/mL. The primary outcome measures were serum itraconazole concentrations expressed as daily mean maximum concentration (C_{max}), daily mean minimum concentration (C_{min}) and area under the curve (AUC) for 0–24 h calculated using the trapezoidal rule. Previous work has suggested that a level of at least 250 ng/mL itraconazole is required for effective prophylaxis (Boogaerts *et al.*, 1988) and an AUC above 1000 ng/mL/h has been proposed as a satisfactory outcome (Meunier, F., Van de Velde, V., Van Peer, A., Woestenborghs, R., De Beule, K. & Heykants, J., Janssen Research Foundation data on file).

Results

Patients

Eight patients entered the trial, but samples were only available from seven (2 od and 5 bd) (Table I). One patient (bd group) withdrew after day 8 because of an adverse event, two withdrew after day 21 because of severe vomiting, one patient was well enough to be discharged from hospital and therefore was not available for further study after day 21, and problems in obtaining blood samples occurred in one patient. The average daily dosage of oral solution itraconazole was 25·5 mL (255 mg).

Serum concentrations

The mean maximum and minimum serum itraconazole concentrations and the effects of the single or divided dose on the area under the serum concentration-time curve are shown in Table II and Table III. Average drug concentrations are plotted in the Figure.

Table I. Demographic data

	Dosage regimen	
	5·0 mg/kg od	2·5 mg/kg bd
Number	2	6
Male	2	4
Mean age (range)	50 (46–54)	33 (20–47)
Mean weight (kg)	75·8 (68·5–83·0)	82·6 (53·0–133·0)
Diagnosis	myeloma (1) non-Hodgkin's lymphoma (1) lymphoma (1)	acute myeloid leukaemia (1) Hodgkin's disease (4) non-Hodgkin's lymphoma (1)

Table II. Area under the serum concentration-time (AUC) 0–24 h), maximum (C_{max}) and minimum (C_{min}) concentrations of itraconazole for individual patients receiving 5 mg/kg od

	Mean AUC (ng/mL/h)	C_{max} (ng/mL)	C_{min} (ng/mL)
Day 1			
patient 11	2366	117	62
patient 14	3103	664	235
Day 8			
patient 11	12395	1618	123
patient 14	22225	1117	646
Day 15			
patient 11	17882	881	714
patient 14	31071	2047	810
Day 22			
patient 11	8955	438	304
patient 14	36287	2244	967
Day 29			
patient 11	38832	2547	949

Table III. Mean area under the serum concentration-time curve (AUC) (0–24 h), mean maximum (C_{max}) and mean minimum (C_{min}) concentrations of itraconazole for patients receiving 2·5 mg/kg bd

	Mean AUC (ng/mL/h)	C_{max} (ng/mL)	C_{min} (ng/mL)
Day 1	1479 (±933)	107 (±48)	19 (±33)
Day 8	13302 (±5016)	723 (±217)	394 (±110)
Day 15	25154 (±6460)	1292 (±357)	845 (±221)
Day 22	21423 (±15098)	1400 (±556)	937 (±326)

Both dosage regimens achieved satisfactory serum concentrations of itraconazole. Previous studies have suggested that a level of 250 ng/mL is the minimum required for prevention of aspergillus infection (Boogaerts *et al.*, 1988) and in most patients this level was probably exceeded within the first few days of treatment. The mean pre-dose

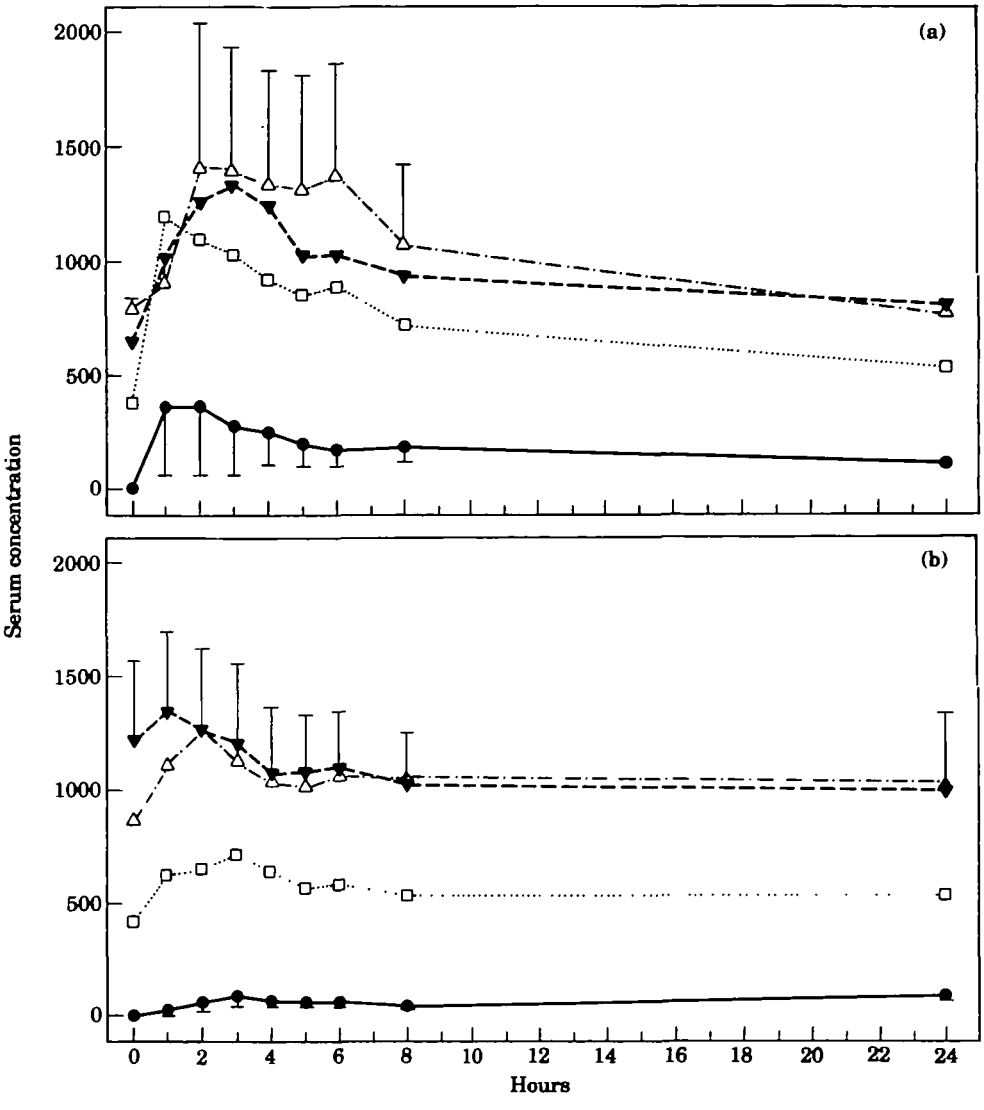

Figure. Mean serum itraconazole concentrations (ng/mL) on days 1 (●), 8 (□), 15 (△) and 22 (▼): (a) in patients receiving 5 mg/kg od itraconazole; (b) in patients receiving 2·5 mg/kg bd itraconazole. Error bars show standard deviations from top and bottom curves.

level (hour 0) on day 8 was 385 ng/mL in the od group and 394 ng/mL in the bd group. Both the once- and twice-daily dosages regimens achieved satisfactory itraconazole concentrations, with maximum AUC values of over 1000 ng/mL/h attained by day 15 in the two-patient groups.

Adverse experiences

Several patients reported adverse experiences, although it is difficult to distinguish the effects of itraconazole from those of the chemotherapy. The commonest side-effects were nausea and vomiting (eight cases) and diarrhoea (six cases), all being the

predictable presentation of the mucositis which is commonly caused by the high-dose myeloablative conditioning regimens given before the autograft is performed. Two of the cases of vomiting were severe enough to cause patients to be withdrawn from the trial. A further patient was withdrawn due to a seizure.

Discussion

This is the first multiple dose pharmacokinetics study of itaconazole oral solution in bone marrow autograft recipients. These patients have particular problems of drug absorption thought to be due to chemotherapy-induced damage to the intestinal epithelium (Shaw, Spector & Ladman, 1979). Persat *et al.* (1992) found that doses of 600 mg per day of itraconazole in the pellet capsule form were needed to achieve satisfactory levels (> 250 ng/mL) in such patients, whereas levels between 193 and 621 ng/mL have been achieved in healthy volunteers receiving just 100 mg per day (Van Peer *et al.*, 1989). The present study has shown that relatively high serum concentrations of itraconazole can be achieved in bone marrow autograft recipients receiving an average daily dose of 255 mg in the form of the oral solution, administered either as 5 mg/kg od or 2·5 mg/kg bd dosages. Patients preferred and complied better with the divided dose schedule during periods of mucositis. To avoid undue disturbances of our patients, hourly blood samples were only taken up to 12 h after the first dose. Therefore, the calculated AUC for the bd dosage schedule is probably an underestimate, since plasma itraconazole concentrations would have been rising between 12 and 24 h in these patients, who received a second dose 12 h after the first one.

Our findings agree with a previous single dose study in bone marrow transplant patients (Meunier, F., Van de Velde, V., Van Peer, A., Woestenborghs, R., De Beule, K. & Heykants, J., Janssen Research Foundation data on file). This found that 80% of patients receiving 10 mL (100 mg) of the oral solution within 10 days and again within 14 and 23 days of receiving a transplant, attained an AUC > 1000 ng/mL/h after the first dose; 75% of patients achieved this level after the second dose. Multiple dose studies in healthy volunteers receiving 200 mg itraconazole bd have suggested that a steady-state is achieved after 2 weeks (Van de Velde, V., Van Peer, A., Woestenborghs, R., Crabbe, R. & Heykants, J., Janssen Research Foundation data on file). The present study suggests that a steady-state is reached between day 8 and day 15 and that effective prophylactic levels are attained in time to coincide with the onset of neutropenia. Our study was designed to measure drug absorption under as near as possible normal clinical conditions for bone marrow autograft recipients. The use of H_2-antagonists, which may reduce the absorption of itraconazole (Stein *et al.*, 1989), was not restricted, and yet good levels were achieved with the oral solution of itraconazole despite the fact that all but one of the patients were receiving either ranitidine or cimetidine. While final conclusions cannot be drawn from this relatively small group of patients, the fact that these results were obtained under the constraints of normal clinical practice suggest that they are generally applicable. Thus the oral solution formulation of itraconazole may ensure earlier effective antifungal prophylaxis in bone marrow autograft patients who may not be able to take or to absorb the pellet formulation.

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