Abnormalities in liver enzymes during simultaneous therapy with itraconazole and amphotericin B in leukaemic patients

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Sir,

Systemic mycoses, such as invasive aspergillosis, are usually treated with antifungal drugs such as iv amphotericin B or itraconazole capsules.1 The plasma concentrations of itraconazole observed in patients are sometimes much higher than the minimal therapeutic level (1000 ng/mL),2 and the potential hepatic toxicity of the drug3 needs to be evaluated. A retrospective study on the effect of itraconazole on liver enzyme levels was conducted after checking bioavailability by plasma assays.

Twenty patients, hospitalized between 1 January 1993 and 1 February 1998 were studied. Fourteen had leukaemia, four chronic respiratory insufficiency and one cystic fibrosis, while one had a lung transplant, all complicated by fungal ‘infections’ (12 definitely or probably had invasive aspergillosis, seven were colonized with an Aspergillus sp. and one had Scedosporium sp. sinusitis). Inclusion criteria were: a curative treatment by itraconazole followed by at least one serum concentration (out of three to six assays) >2500 ng/mL of unchanged itraconazole and of its active metabolite (total >5000 equivalent ng/mL). Patients with known hepatic illness before the start of itraconazole therapy, and those with a history of alcohol abuse, were excluded.

Patients were treated for 44–455 days (median 143 days with itraconazole 200–600 mg/day (900 mg/day in two patients for 8 days). Twelve patients, all with leukaemia, received itraconazole and amphotericin B for 10–54 days (median 28 days). None of these patients received a bone marrow transplant.

No disorders were observed in eight patients, even during the period of high plasma itraconazole concentration. One patient with liver dysfunction presented with cholecystitis at the onset of itraconazole therapy, which was resolved by surgery, but no subsequent hepatic disorders were seen. The 11 other patients, all with leukaemia, had increases in γ-glutamyltransferase (γGT) and alkaline phosphatase (AP) (median value of 6.5 and 2.5 higher than the normal limit). In nine of these patients, ALT levels were also increased. In three patients such abnormalities were only seen during the period of high plasma itraconazole concentration, with a decrease following a decrease of itraconazole treatment.

Different co-drugs were given to these 11 patients and their possible interactions were analysed by a causality assessment.4 Amphotericin B was the only drug administered, in addition to itraconazole, to all these 11 patients with hepatic disorders. Another leukaemic patient was also treated with itraconazole and amphotericin B, with no hepatic disorders.

For the 12 patients treated with itraconazole and amphotericin B, the γGT, AP and ALT concentrations were measured at three times: (i) before the beginning of antifungal therapy (period A), during administration of amphotericin B plus itraconazole (and within 21 days after amphotericin B treatment was ended, a time corresponding to seven half-lives of the drug) (period B) and 2 months after the end of itraconazole treatment (period C) (Figure). For each patient, hepatic enzyme concentrations were greatest during period B (Friedman test: P < 0.001 for γGT and AP, P = 0.0015 for ALT). In seven patients, these abnormalities disappeared when amphotericin B was discontinued, although itraconazole therapy was continued. In three other patients, hepatic enzyme abnormalities were observed 5–19 days after the end of amphotericin B therapy. For one patient, the data for period C were not available.

A significant increase in hepatic enzyme values, in 11 (92%) out of 12 leukaemic patients was seen. This increase appeared not to be related to the period of high plasma itraconazole concentration for eight of the patients but it was observed during simultaneous treatment with itraconazole plus amphotericin B or a few days after amphotericin B treatment ended.

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These abnormalities in hepatic enzymes were probably caused by the drug treatments rather than the initial pathology since, at the start of the study, hepatic enzyme concentrations were normal. Asymptomatic increases in plasma liver enzymes have previously been reported during itraconazole therapy, but these disorders occurred in <5% of patients.\(^{3,5}\) In our study, no hepatic disorders were observed during treatment with itraconazole alone in eight patients. One patient with increased hepatic enzyme concentrations was first treated with itraconazole alone for 8 months, with no liver side effects.

Many side effects, such as renal failure, are associated with amphotericin but, to our knowledge, hepatic toxicity induced by amphotericin B has rarely been reported.\(^6\) In our study, hepatic disorders appeared during amphotericin B treatment or within a few days after it had stopped. A control group receiving amphotericin B alone was not possible.

The data reported here indicate that itraconazole alone is not toxic to the liver, even when plasma itraconazole concentrations are high. Abnormalities in hepatic enzymes only occurred when itraconazole was combined with amphotericin B, as recently suggested.\(^6\) Closer monitoring of liver enzymes during such combined therapy is strongly recommended.

**References**

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