Liver failure and transplantation after itraconazole treatment for toenail onychomycosis

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ABSTRACT

Three weeks after completing a 4-pulse course of itraconazole for toenail onychomycosis, a 25-year-old woman patient developed severe liver crisis and required an emergency liver transplant. We report the case and discuss the use of itraconazole in onychomycosis and dermatomycoses.

Key words: dermatomycoses, itraconazole, liver transplantation, onychomycosis

Received: 5 June 2003, accepted 18 June 2003

Introduction

Itraconazole has been in use worldwide for some 16 years. More than 60 million patients have received the treatment, about 77% of them for skin and nail infections. Although the FDA reported 24 cases of liver necrosis, including 11 cases of death, associated with the drug, only a few reports on severe side-effects have been published in the medical literature. We present a case of a young woman who developed liver necrosis after a full course of itraconazole pulse therapy for onychomycosis.

Case report

A 25-year-old Israeli woman with a history of drug-treated hypothyroidism since the age of 12 years was seen by her family doctor because of fatigue, stomach cramps, nausea, vomiting, diarrhea and icterus. No pruritus was reported. Severe pathological values of liver chemistry tests and complete blood count (CBC) resulted in referral of the patient to hospital.

Table 1 summarises the laboratory values of the patient during hospitalisation and following liver transplantation. On admission, blood tests demonstrated severe liver dysfunction. Because of the severity of her clinical condition, including loss of consciousness, the patient was hospitalised in the intensive care unit where she underwent liver dialysis. Her condition improved temporarily and she was transferred to a medicine ward where her condition deteriorated within 24 h. She was returned to the intensive care unit and liver dialysis was repeated. Abdominal Doppler scan excluded vascular thrombosis. Liver function test values remained abnormal and she was barely conscious. Fine needle biopsy demonstrated severe liver necrosis. Tests for anti-nuclear antibody (ANA), antismooth muscle antibody, quantitative serum IgG and microsomal antibody, anti-DNA, Hepatitis A, B and C virus, Epstein–Barr virus and cytomegalovirus were negative. Coagulation function levels (prothrombin time, partial thromboplastin time, international normalized ratio) were elevated throughout her entire hospitalisation. No clinical or laboratory evidence of Wilson’s disease was found.

Table 1 Clinical and laboratory data on a woman taking itraconazole for onychomycosis, during hospitalization and after liver transplantation

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Hospitalization</th>
<th>Following transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>15.4</td>
<td>21.8</td>
</tr>
<tr>
<td>Conjugated bilirubin (mg/dL)</td>
<td>12.8</td>
<td>15.5</td>
</tr>
<tr>
<td>SGPT (ALT) (u/L)</td>
<td>2500</td>
<td>2085</td>
</tr>
<tr>
<td>SGOT (AS) (mU/mL)</td>
<td>1456</td>
<td>1300</td>
</tr>
<tr>
<td>LDH (u/L)</td>
<td>756</td>
<td>901</td>
</tr>
<tr>
<td>Alkaline phosphatase (mU/mL)</td>
<td>124</td>
<td>107</td>
</tr>
<tr>
<td>Icterus index</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>PT (s)</td>
<td>19.6</td>
<td>24.1</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>35.3</td>
<td>37.0</td>
</tr>
<tr>
<td>INR</td>
<td>1.8</td>
<td>2.42</td>
</tr>
</tbody>
</table>

NA, not available.
In view of the liver pathology, the abnormal coagulation function tests, the results of histology investigations, and her grave clinical conditions, a liver transplantation was recommended. She was sent in a hepatic coma (stage 4 hepatic encephalopathy) to Belgium where she underwent immediate liver transplantation.

The patient went back to her normal life in Tel Aviv following the liver transplantation, beginning a life-long regimen of sulphamethoxazole + trimethoprin, tacrolimus and eltroxin daily. Her liver function tests returned to normal (Table 1).

Upon her return from Belgium, the patient reported to the first author (AS) that 3 and 4 years earlier she had been twice refused systemic treatment for onychomycosis by a dermatologist because of abnormal liver function tests, which were not investigated. She also reported that 6 months prior to the present hospitalisation, she had been seen by her dermatologist regarding severe changes to her toenails. Nail culture demonstrated dermatophytes (T. rubrum), and liver function tests were normal. Four courses of pulse therapy with itraconazole (Sporanox) had been started, 400 mg/day for a week. Monthly CBC and liver function tests yielded consistently normal results. Three weeks after completing the treatment her clinical complaints began.

Discussion

An unpredictable drug reaction such as that seen in our patient depends on the particular characteristics of the patient, especially the proclivity for an immune response to an antigenic stimulus and the rate at which the host metabolises the agent. Indeed, the susceptibility to develop liver damage appears to be genetically determined. For instance, some 10% of the population have an autosomally recessive trait that involves a lack of cytochrome P450 enzyme 2D6. These individuals have impaired debrisoquin 4-hydroxylase enzyme activity, cannot metabolise several drugs, and are therefore at increased risk of hepatotoxicity. Fulminant viral hepatitis, chemicals and drugs are the usual cause of massive hepatic necrosis. The mechanism may be direct toxic damage to hepatocytes or, more often, a combination of toxicity and inflammation with immune mechanisms involving a drug or a metabolite acting as a hapten that converts a cellular protein into an immunogen.

Thus, the question arises as to whether there is a connection between itraconazole and liver necrosis.

Itraconazole is a second- and third-generation oral azole that inhibits sterol synthesis in fungal cell membranes. It has a high affinity for skin, and therapeutically active concentrations persist in the stratum corneum. It undergoes extensive hepatic metabolism and is rapidly eliminated from the systemic circulation within 7–10 days. Excretion is 35.2% in the urine and 54.2% in the faeces, mainly as inactive metabolites. Itraconazole may cause mild transient increases in hepatic enzymes in 1–7% of patients receiving continuous therapy. In more than 400 well-documented cases, asymptomatic reversible increases in liver enzymes normalised after discontinuation of therapy or spontaneously without a change in dosage.

The US Food and Drug Administration (FDA) issued two public health advisories in 2001 about Sporanox (itraconazole). It reported an association between serious hepatic toxicity including liver failure and death; some patients had predisposing liver conditions and some had no pre-existing liver disease or serious underlying medical condition. As of March 2001, the FDA had reported 24 cases of liver failure associated with itraconazole use, including 11 deaths; and recommended that healthcare providers confirm the diagnosis of onychomycosis by culture followed by blood test before prescribing the medication.

A survey of the literature from 1992 turned up few reports of liver complications in patients on itraconazole therapy. In 1992–93, a Dutch group reported three patients on itraconazole treatment who developed symptomatic hepatic injury 5–6 weeks after starting the drug, which resolved within 1–2 months after cessation of the drug. A Korean group reported a woman who developed clinical and laboratory acute hepatitis after 116 days of treatment; discontinuation of the itraconazole brought both her clinical and laboratory values to normal in 2 months. A Spanish group reported another case of hepatotoxicity after 5 days of itraconazole treatment, and disappearance all clinical and liver pathology 6 weeks from discontinuation of the drug.

According to all three reports, hepatotoxicity was a result of cholestasis rather than cytolysis, with complete resolution following discontinuation of the drug.

In a large review dealing with oral anti-fungal therapy, Hay reported side-effects with each anti-fungal drug, with emphasis on the possibility of hepatic damage. He claimed that most oral drugs used in the management of skin diseases (not only anti-fungal treatments) have been reported to cause hepatic damage. According to his review, itraconazole may cause a reaction after approximately 10 days of treatment, and liver values return to normal within 10 weeks of cessation of the drug. Hay noted the extremely low incidence of hepatic reaction, 6 in 5 million treatments, and a low frequency, 0.9%, of reversible changes in liver function tests.

In a large study of 681 patients treated with itraconazole for onychomycosis reported by Hanke et al., there were no substantial or clinically relevant changes in haematological or biochemical values and no major changes in liver function tests.

Two large reviews published in 1999 and 2001 by Nolting et al. and Gupta et al. summarized 34 million and 50 million patients under itraconazole treatment worldwide. Hepatic reaction was found in 1.5–1.7% and 1.9–3% of patients, respectively, with a return to normal values 10 weeks after discontinuation of the drug. No death or liver transplantation was reported in these two reviews.

Our patient was under the strict supervision of her dermatologist, who performed blood tests and liver function tests before
starting and during the treatment. She developed severe liver dysfunction due to liver necrosis only 3 weeks after stopping the treatment. In all the cases mentioned above, the clinical and biochemical abnormalities occurred in patients on medication, and not in those who had already stopped treatment, and there were no reports of severe liver damage. Although the FDA reported 24 liver failures including 11 deaths, no such report could be found in the literature. Fortunately, our patient had a liver transplant and now lives a normal life.

It is unusual that our case developed liver failure only after the third course of treatment. However, since 80–90% of hepatic function capacity must be eroded before hepatic failure sets in, it is possible that the first two courses of treatment eroded the capacity and the third course tipped the balance towards decompensation.

Is there a reason to stop using itraconazole for treatment of onychomycosis and dermatomycoses? The FDA does not recommend doing so. Only 24 out of 50 million patients who used the drug up to 2001 suffered liver failure, fatal in 11. Whether to prescribe itraconazole for such a problem as minor as toenail onychomycosis is the decision of the dermatologist, who must be aware of the risks involved. The fact that liver function tests proved to be no protection for our patient merits further analysis.

References


