Fluconazole-induced hepatotoxicity: Review of published case reports

Carey-Anne Lawson, James A. Karlowsky and George G. Zhanel

INTRODUCTION

Fluconazole is a bis-triazole antifungal agent which is useful in the treatment and prevention of oropharyngeal and esophageal candidiasis, serious systemic fungal infections, and cryptococcal meningitis. Fluconazole possesses excellent oral bioavailability and lacks the major toxicities associated with amphotericin B. However,azole derivatives, particularly ketoconazole but including fluconazole, have been reported to infrequently cause hepatotoxicity. Hepatotoxicity is usually detected by increases in serum hepatic aminotransferase concentrations but may also progress undetected until presentation as symptomatic hepatitis or fatal hepatic necrosis. The purpose of this paper is to review published case reports of fluconazole-induced hepatotoxicity.

Incidence

The incidence of fluconazole-induced hepatotoxicity is estimated to be very low. The most common clinical presentation of fluconazole-induced hepatotoxicity is minor transient hepatic enzyme concentration elevations that occur in less than 5% of patients. However, as depicted in Table 1, hepatic enzyme concentration elevations can sometimes be quite dramatic. More recently, isolated cases of severe jaundice and fatal acute hepatic necrosis have been associated with fluconazole therapy.

Hepatotoxicity has arisen in patients irrespective of the duration of fluconazole therapy (Table 1). Hepatic enzyme concentrations may rise in a matter of days or may occur several months following initiation of fluconazole therapy. The mean number of days of therapy prior to detected hepatotoxicity was 130 days (range 4 days–365 days). The magnitude of the increase in liver function tests in these reports ranged from 1–96X baseline; 0.4–26X baseline for AST (mean = 27X baseline); 0.4–26X baseline for ALT (mean = 10X baseline); 2–14X baseline for bilirubin (mean = 9X baseline) and 1–3.5X baseline for alkaline phosphatase (mean = 2X baseline). The mean age of patients experiencing hepatotoxicity was 35.5 years (range 24–50 years) and most had concomitant disease states such as HIV/AIDS or alcoholism. Elevated hepatic enzyme concentrations fell shortly (days to weeks) after fluconazole was discontinued in most cases. A strong cause–effect relationship existed in many cases; however, other cases were complicated by the presence of concomitant hepatotoxins and multiple medical problems, including infectious hepatitis and alcohol abuse. Other cases should be questioned whether the cause of hepatotoxicity was truly due to fluconazole.

Generally, fluconazole-induced hepatotoxicity appears to be a non-dose-dependent phenomenon, although dose-dependent hepatotoxicity has also been reported. In the single case of dose-dependent hepatotoxicity, the patient experienced enzyme elevations with fluconazole daily doses of 200mg and 400mg, but not with 100mg. This patient was re-challenged with fluconazole three times, and enzymes became elevated each time the dosage surpassed 100mg.

The mechanism of fluconazole hepatotoxicity remains enigmatic and has not been well studied. Similarly, ketoconazole hepatotoxicity arises via an idiosyncratic mechanism.

Clinical considerations and patient management

The monitoring of liver function tests in all patients receiving fluconazole is unjustified at present. Baseline and monthly hepatic enzyme concentrations should be determined with fluconazole therapy in patients with pre-existing hepatic disease, and in patients receiving concurrent hepatotoxic drugs. Patients who experience hepatic enzyme elevations following one course of fluconazole may experience enzyme elevations again upon re-challenge. In these patients, the risks and benefits of therapy must be evaluated. If fluconazole therapy is required, then baseline hepatic enzyme concentrations should be determined and monitored closely as therapy continues. Although hepatotoxicity progressing beyond increased hepatic enzyme elevations is very rare, hepatic necrosis with fluconazole has been reported. Signs and symptoms of hepatic necrosis include, but may not be

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Table I. Case reports of fluconazole-induced hepatotoxicity. Aspartate aminotransferase = AST. Alanine aminotransferase = ALT.

<table>
<thead>
<tr>
<th>Age/Sex (reference)</th>
<th>AST* (normal: 0-35 U/L)</th>
<th>ALT* (normal: 0-35 U/L)</th>
<th>Bilirubin* (normal: 2-18 µmol/L)</th>
<th>Alkaline Phosphatase* (normal: 3-120 U/L)</th>
<th>Medical conditions</th>
<th>Other drugs</th>
<th>Dose of fluconazole</th>
<th>Duration of fluconazole</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 year old female (11)</td>
<td>baseline: 269 U/L</td>
<td>baseline: 164 U/L</td>
<td>baseline: 80.4 µmol/L</td>
<td>baseline: not described</td>
<td>Alcoholism, Drug Abuse, Endocarditis, Congestive Heart Failure, Positive for hepatitis B &amp; C antibodies</td>
<td></td>
<td></td>
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<td>Day 19 &amp; 20: 200 mg daily</td>
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<tr>
<td>46 year old male (12)</td>
<td>not described</td>
<td>not described</td>
<td>baseline mid-May 1990: 10 U/L, Late June 1990: 5.5X baseline</td>
<td>baseline mid-May 1990: 160 U/L, Late June 1990: 3.3X baseline</td>
<td></td>
<td>AIDS</td>
<td></td>
<td></td>
<td>Oct 1990: 100-400 mg/day</td>
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<tr>
<td>41 year old male (15)</td>
<td>baseline June 1989: 100 U/L, November 21, 1989: 9.6X baseline, November 30, 1989: 5.9X baseline</td>
<td>not described</td>
<td>baseline June 1989: 10 U/L, November 21, 1989: 19.5X baseline, November 30, 1989: 16X baseline</td>
<td>baseline June 1989: 290 U/L, November 21, 1989: 2.5X baseline, November 30, 1989: 2.8X baseline</td>
<td>HIV positive, hemophilia, non-A, non-B hepatitis</td>
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<td>28 year old male (10)</td>
<td>baseline March 12: 70 U/L, April 2: 26.1X baseline, April 5: 11.1X baseline</td>
<td>not described</td>
<td>baseline March 12: 17 U/L, April 2: 13.5X baseline, April 5: 28.8X baseline</td>
<td>baseline March 12: 88 U/L, April 2: 2.5X baseline, April 5: 2.1X baseline</td>
<td>AIDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>28 year old female (4)</td>
<td>baseline April 26, 1993: 20 U/L, July 1993: 9.8X baseline, August 1993: 8X baseline</td>
<td>not described</td>
<td>baseline April 23, 1993: 5 µmol/L, July 1993: 14.4X baseline, August 1993: 0.6X baseline</td>
<td>baseline April 23, 1993: 1180 U/L, July 1993: 1.7X baseline, August 1993: 0.6X baseline</td>
<td>HIV positive</td>
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</table>

SUMMARY

Fluconazole is a useful antifungal agent which lacks significant toxicity in the majority of patients. Fluconazole-induced hepatotoxicity is a rare event, which, when it does occur, almost always presents as transient benign elevations in hepatic enzyme concentrations. However, clinicians must remain cognizant that rare cases of hepatic necrosis have been reported. Fluconazole-induced hepatotoxicity is generally a non-dose-dependent, idiosyncratic reaction. Clinicians should advise patients limited to, malaise, nausea, vomiting, jaundice, dark urine and abdominal pain.11,14

How should patients experiencing hepatotoxicity concurrent with fluconazole therapy be managed? Fluconazole should be discontinued if elevated hepatic enzyme concentrations (3X baseline) develop in the absence of another definable cause. If fluconazole is responsible for increases in hepatic enzyme concentrations, discontinuing the drug will allow enzyme concentrations to return to baseline in days to weeks. Patients may be re-challenged with fluconazole without hepatic enzymes rising; however, if they rise (3X baseline) the antifungal should be discontinued. In rare cases where hepatotoxicity cannot be attributed to fluconazole or infection or other medical conditions (e.g. hepatitis), liver biopsy may be required.10,15 Whether other azoles such as ketoconazole or itraconazole can be safely used in the patient suspected of developing fluconazole hepatotoxicity is unknown, but not advised by these authors.
at risk of developing fluconazole-induced hepatotoxicity to immediately report symptoms of malaise, nausea, vomiting, jaundice, dark urine and abdominal pain.

REFERENCES


