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[1-3] which is useful in the treatment and prevention of oropharyngeal and esophageal candidiasis,[1-3] serious systemic fungal infections,[3] and cryptococcal meningitis.[1-3] 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.[4,5] Hepatotoxicity is usually detected by increases in serum hepatic aminotransferase concentrations[6] but may also progress undetected until presentation as symptomatic hepatitis[7,8] or fatal hepatic necrosis.[9] 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.[5,10] The most common clinical presentation of fluconazole-induced hepatotoxicity is minor transient hepatic enzyme concentration elevations that occur in less than 5% of patients.[6] 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.[5,9,10,11]

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 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;[5,10-12,16] however, other cases were complicated by the presence of concomitant hepatotoxins and multiple medical problems, including infectious hepatitis and alcohol abuse.[13] Other cases should be questioned whether the cause of hepatotoxicity was truly due to fluconazole.[9-10]

Generally, fluconazole-induced hepatotoxicity appears to be a non-dose-dependent phenomenon, although dose-dependent hepatotoxicity has also been reported.[13] 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.[13]

The mechanism of fluconazole hepatotoxicity remains enigmatic and has not been well studied. Similarly, ketoconazole hepatotoxicity arises via an idiosyncratic mechanism.[6,7]

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.[9,11] 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.

Age/Sex (reference)	AST* (normal: 0–35 U/L)	ALT* (normal: 0–35 U/L)	Bilirubin* (normal: 2–18 µmol/L)	Alkaline Phosphatase* (normal: 3–120 U/L)	Medical conditions	Other drugs	Dose of fluconazole	Duration of fluconazole	Result
50 year old female (11)	baseline: 269 U/L Day 22: 5.8X baseline	baseline: 164 U/L Day 22: 0.4X baseline	baseline: 80.4 µmol/L Day 22: 1.6X baseline	baseline: not described Day 22: 1.8X baseline	Alcoholism, Drug Abuse, Endocarditis, Congestive Heart Failure, Positive for Hepatitis B & C antibodies		Day 19 & 20: 200 mg daily Day 21 & 22: 100 mg daily Drug discontinued after dose on Day 22	4 days	Liver enzymes returned to baseline after fluconazole discontinued, Died of heart failure 2 months later
46 year old male (12)	not described	baseline mid-May1990:90U/L Late June 1990: 5.5X baseline October 1990: 1.1X baseline	not described	baseline mid-May 1990: 150 U/L Late June 1990: 3.3X baseline October 1990 5.9X baseline	AIDS	cotrimoxazole 120mg/kg/day from mid-May 1990 to early June 1990	100-400 mg/day	5 months October 1990:	Pre-existing cholestatic liver damage, Died
41 year old male (15)	baseline June 1989: 100 U/L November 21, 1989: 9.8X baseline November 30, 1989: 5.9X baseline	not described	baseline June 1989: 10 µmol/L November 21, 1989: 19.5X baseline November 30, 1989: 16X baseline	baseline June 1989: 200 U/L November 21, 1989: 2.5X baseline November 30, 1989: 2.3X baseline	HIV positive, hemophilia, non-A non-B hepatitis	zidovudine 1200 mg in divided doses, trimethoprim, nystatin	Dec. 1988: 50mg for 10 days; May 1989: 50mg for 10 days; Sept.14,1989-November 21, 1989: 50 mg daily	2 months	Patient experienced jaundice which resolved when fluconazole was discontinued
32 year old male (10)	baseline March 12: 34 U/L April 2: 81.5X baseline April 5: 16.9X baseline	baseline March 12: 70 U/L April 2: 26.1X baseline April 5: 11.1X baseline	baseline March 12: 17µmol/L April 2: 13.5X baseline April 5: 28.8X baseline	baseline March 12: 98 U/L April 2: 2.5X baseline April 5: 2.1X baseline	AIDS	prochlorperazone, acetaminophen/ codeine, pentamidine, acetazolamide (discontinued before April 2), cimetidine started March 17	400 mg daily	1 month	Died April 6/92 of hepatic necrosis
28 year old female (4)	baseline April 28,1993:20 U/L July 1993: 96X baseline August 1993: 60X baseline	baseline April 23, 1993:25 U/L July 1993:14.2X baseline August 1993: 8X baseline	baseline April 23,1993: 5 µmol/L July 1993: 14.4X baseline August 1993: Not described	baseline April 23 1993: 1180 U/L July 1993: 1.7X baseline August 1993: 0.6X baseline	HIV positive	Beginning January 1993 pyrimethamine 25 mg and sulfadoxine 500 mg twice a week	July 1992: 400mg daily for 2 months followed by 200mg discarded by patient after 3 months, January 1993 400mg daily x 15 days then 200mg daily. daily Discontinued April 28, 1993, mid-May-July 1993: 200mg daily	Total 11 months (Patient took for 5 months then discarded. Restarted after 1 month for 4 months then discontinued. Restarted for additional 2 months).	Second liver (August 1993) biopsy 1 month after fluconazole discontinued[1] "...showed disappearance of mitochondrial abnormalities & normalization of the aspect of the smooth endoplasmic reticulum". (4)

Table I continued on next page.

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.

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

Table I (continued from previous page). Case reports of fluconazole-induced hepatotoxicity.

Age/Sex (reference)	AST* (normal: 0–35 U/L)	ALT* (normal: 0–35 U/L)	Bilirubin* (normal: 2–18 µmol/L)	Alkaline Phosphatase* (normal: 3–120 U/L)	Medical conditions	Other drugs	Dose of fluconazole	Duration of fluconazole	Result
28 year old male (16)	baseline:11 U/L Day 14: 9.6X baseline After fluconazole discontinued: 1.2X baseline	baseline: 27 U/L Day 14: 6.4X baseline After fluconazole discontinued: 0.7X baseline	not described	baseline: 485 U/L Day 14: 1.3X baseline After fluconazole discontinued: 0.5X baseline	AIDS, disseminated tuberculosis, CNS toxoplasmosis	cotrimoxazole started on admission isoniazid, rifampin, pyrimethamine, clindamycin, phenobarbital	50 mg	14 days	Returned to baseline values after discontinuation of fluconazole
24 year old (16)	baseline:35 U/L Day 7: 21.7X baseline Day 14: 0.6X baseline	baseline: 30 U/L Day 7: 9.8X baseline Day 14: 1.4X baseline	not described Day 14: 1.5X	baseline: 417 U/L Day 7: 3X baseline tuberculosisafter baseline	HIV positive, IV drug user, oral candidiasis,	antitubercular drugs	not described	7 days	Enzyme values returned to normal after discontinuation of fluconazole
35 year old (16)	baseline:35 U/L Day 150: 12.6X baseline Day 345: 3.2X baseline	baseline: 48 U/L Day 10: 10.3X baseline	baseline: not described Day 10: 11.4X baseline	baseline: 941 U/L Day 10: 0.98X baseline	AIDS, disseminated tuberculosis, *P. carinii*, *Mycobacterium avium-intracellulare*	isoniazid and rifampin preceding 7 months	not described	10 days	Patient died 5 days after fluconazole discontinuation
27 year old male (9)	baseline:19 U/L Day 150: 12.6X baseline Day 345: 3.2X baseline	not described	baseline: 10µmol/L Day 150: 2X baseline Day 345: 1X baseline	baseline: 23 U/L Day 150: 3.5X baseline Day 345: 3X baseline	coccidioidal meningitis	not described	400 mg daily	Continued on therapy for >11 months	Biopsy on day 252 revealed mild steatosis, Fluconazole treatment continued free of hepatitis symptoms
44 year old male (9)	baseline:60 U/L Day 24: 1.3X baseline Day 360: 0.8X baseline	not described	baseline: 20µmol/L Day 24: 1.7X baseline Day 360: 1.2X baseline	baseline: 90 U/L Day 24: 2.7X baseline Day 360: 2.8X baseline	Type II Diabetes, alcoholism coccidioidal meningitis	not described	400 mg daily	Continued on therapy for >12 months	Biopsy on day 305 revealed alcoholic liver damage, patient continued on fluconazole therapy with "...no evidence of progressive hepatic damage" (9)

*All fold increases are in relation to baseline (day 1) values

at risk of developing fluconazole-induced hepatotoxicity to immediately report symptoms of malaise, nausea, vomiting, jaundice, dark urine and abdominal pain.

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