Case Report

Early onset hepatotoxicity associated with low dose fluconazole therapy in a critically ill patient: A case report

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Abstract. Hepatoxicity associated with fluconazole is less implicated than other antifungals although cases of fatalities were reported. We describe a 34-year-old kidney impaired male with Marfan syndrome manifested with elevated liver enzymes due to fluconazole therapy intravenous (IV) 200 mg stat followed by IV 100 mg daily. His baseline alanine aminotransferase (ALT) was 38 U/L, total bilirubin was 36 µmol/L and prothrombin time was 19.7 seconds. Marked elevation of ALT level (214 U/L), total bilirubin (54 µmol/L) and prothrombin time (37 seconds) were noticed starting from day 4 of fluconazole therapy. The patient subsequently developed nausea and vomiting; ALT and total bilirubin level further rose to 2394 U/L and 94 µmol/L on day 6. Discontinuation of fluconazole without rechallenged on day 8 resulted in sharp decreased in prothrombin time from 65.3 seconds to 31.9 seconds and normalization of liver enzymes in 2 weeks time. In conclusion, low dose fluconazole may induce early onset of hepatotoxicity in critically ill patient with kidney damage. Prompt discontinuation of fluconazole therapy is needed to prevent further deterioration in liver function.

Key words: Hepatotoxicity, fluconazole, antifungal agent, adverse effect

1. Introduction

Fluconazole is a triazole antifungal which has better safety profile and more favorable pharmacokinetics than older azoles such as miconazole and ketoconazole (1,2). Its longer elimination half-life (30 hours) makes daily dosing possible. The high bioavailability of oral formulation makes it more convenient for administration unless the patients are not orally tolerable. The spectrum of antifungal activities for fluconazole is slightly less than the newer triazoles such as itraconazole (3) and voriconazole (4). However, fluconazole demonstrated less extent of drug interactions than these newer triazoles (4). Visual adverse events appeared to happen more frequently in voriconazole than fluconazole recipients (5), while itraconazole has comparable tolerability profile as fluconazole (3). All these advantages of fluconazole probe it to become widely prescribed after its licensure in 1990 for candidiasis, *cryptococcal* infections and as prophylaxis for transplantations, immunosuppressed and critically ill patients (1).

In spite of relatively better safety profile, fluconazole can induced several uncommon but severe adverse effects such as Steven Johnson syndrome (6), fixed drug eruption (7), anaphylactic reaction (8) and hepatotoxicity (9). Hepatotoxicity, in particular, is reported more in immunocompromised patients such as patients having human immunodeficiency virus (9-12). Furthermore, fatalities cases associated with hepatotoxicity following fluconazole therapy were documented (9,13). However, early onset hepatotoxicity due to this drug is not well documented in critically ill patients. Here we described a case of fluconazole induced acute

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hepatotoxicity in a patient who underwent critical care.

2. Case report

A 34-year old Chinese man with Marfan syndrome and septic shock was transfered to the Cardiothoracic Intensive Care Unit (CICU) for inotrope support due to low blood pressure and unresponsive to fluid challenge. He has two years history of hypertension and hypercholesterolemia and he had underwent Bentall operation and atrial valve replacement at 7 months ago. During the course of his hospitalization, he was diagnosed with congestive cardiac failure and acute kidney injury. He does not have any history of liver impairment.

Physical examinations on admission showed a blood pressure of 60/30 mmHg, pulse rate of 81 beats per minute, respiratory rate of 20 breath per minute and body temperature of 38.5 °C. Intravenous (IV) noradrenaline and adrenaline infusion were administered as inotrope support which later raised the blood pressure to 109/46 mmHg. Slight kidney damage was noted on the first five days of his admission. His initial blood urea nitrogen (15.9 mmol/L) and serum creatinine (219 μmol/L) levels were high and calculated creatinine clearance was 41.6 mL/min. His baseline liver function test results were within normal range with an alanine aminotransferase (ALT) level of 38 U/L, an alkaline phosphatase level of 63 U/L and a prothrombin time of 19.7 seconds. However, the total bilirubin (36 μmol/L) level was slightly high.

On Day 1, IV fluconazole 200 mg stat, then 100 mg daily was initiated as an empiric therapy. Fungal infection was suspected as this patient was having an unresolved fever and sepsis secondary to hospital acquired pneumonia for the past one month, although a full course of antibiotic treatment was given previously. On day 2, IV meropenem 500 mg twice daily and spironolactone tablet 25 mg twice daily were started. IV ranitidine was initiated on day 4 for stress ulcer prophylaxis. On the same day, there was an evidence of prolonged prothrombin time (37 seconds) and rose in total bilirubin level (73 μmol/L). Besides, a marked increase in ALT level (214 U/L) was detected. Jetepar® two capsules three times daily (per capsule contained betaine glucuronate 150 mg, diethanolamine glucuronate 30 mg and nicotinamide ascorbate 20 mg) were subsequently added on day 5 to treat the liver impairment. The patient developed nausea and vomiting on the same day and was managed by IV metoclopramide 10 mg three times daily. The total bilirubin and ALT level remained high up to 94 μmol/L and 2394 U/L respectively on day 6 despite the initiation of Jetepar® therapy. Drug-induced liver injury was subsequently suspected and both ranitidine and spironolactone was discontinued on day 7. Meropenem was continued because of important empirical treatment for the nosocomial sepsis in this patient in spite of potential hepatotoxic effect. IV fluconazole was withheld on the morning of day 8. On the same day, a sharp dropped of prothrombin time from 65.3 seconds to 31.9 seconds was noted and the ALT levels decreased continuously to normal values after 2 weeks. The total bilirubin showed the same trend of dropping as well after the discontinuation of fluconazole treatment. Although both ranitidine and spironolactone regimens were restarted back on day 9 and day 10 respectively and continued for around one week, there was no sign of further liver function deterioration. The changes in the liver function of the patient and the concurrent drug treatments are demonstrated in Table 1.

3. Discussion

Fluconazole is active against cryptococcus and most of the candidias but it is resistant to *Candidia krusei* and have reduced activity towards *Candidia glabrata*. Fungistatic action of fluconazole is mediated by the inhibition of C-14, a demethylase which is required for ergosterol synthesis to build fungal cell membrane (1). Fluconazole is documented to be safer than other antifungals as Girois et al. reported that hepatotoxicity was occured in 14.1% to 18.6% of patients on amphotericin and 31.6% of patients on itraconazole as compared to only 1.9% of patients on fluconazole (14). Garcia Rodriguez et al. also concluded that ketoconazole and itraconazole were associated with marked increase risk of clinical acute liver injury as compared to griseofulvin, fluconazole and terbinafine (15). Fluconazole has been reported to cause hepatitic or cholestatic liver injury but the exact mechanism involved remains unknown (16). Guillaume et al. suggested that fluconazole-induced hepatotoxicity can be related to the inhibition of cytochrome P450 enzymes in the inner mitochondrial membrane and smooth endoplasmic reticulum which leads to hepatocyte mitochondrial disease (17). Besides, a few studies suggested that an unidentified toxic metabolite which formed during the flavin-containing mono-oxygenase (FMO) metabolism of the azole antifungal drugs in the liver, was responsible for the azole-induced hepatotoxicity (18-20).

Table 1. Serial liver and renal function test results and concurrent drugs treatment

Liver & renal function	Day of admission																	
	2	3	4*	4**	5	6	8*	8**	9	10	11	13	15	17	19	21	23	25
Alanine aminotransferase (U/L)	38	39	58	214	334	2394	1561	-	1133	760	599	349	261	154	97	80	62	60
Alkaline phosphatase (U/L)	63	79	91	96	96	157	141	-	146	126	117	112	147	112	121	111	116	127
Total bilirubin (μmoL/L)	36	37	54	73	79	94	77	-	64	59	60	68	64	73	51	63	53	57
Prothrombin time (second)	19.7	19.2	37.0	45.9	-	-	65.3	31.9	32.7	31.0	24.3	22.0	18.0	19.1	15.1	18.1	15.1	17.1
Blood urea nitrogen (mmoL/L)	15.9	12.6	13.1	8.9	12.1	15.3	10.1	-	9.7	15.2	16.7	20.7	22.0	22.6	14.5	16.4	16.0	17.4
Serum creatinine (μmoL/L)	219	150	185	110	135	97	61	-	71	93	89	99	103	133	78	110	88	106
Fluconazole	⟷	⟷	⟷	⟷	⟷	⟷	⟷											
Ranitidine		⟷	⟷	⟷	⟷	⟷			⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷
Spiranolactone	⟷	⟷	⟷	⟷	⟷	⟷	⟷			⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷
Meropenam	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷

* Morning; ** Evening

The onset of fluconazole induced hepatotoxicity was previously reported as on the day 6 to day 25 of therapy (9,12,13,21,22). However, most of the cases showed late onset at one week or more after the initiation of fluconazole treatment (12,13,21,22). Our patient exhibit significant increase of ALT, total bilirubin and PT level on Day 4 of fluconazole initiation which is considered as early onset of hepatotoxicity as compared to the above mentioned cases. The recovery period of liver functions is slow with some literatures reporting from 2 weeks to 1 months from discontinuation of therapy (10,12,21). The marked increase of ALT in our case leads to discontinuation of fluconazole and the normalization of liver enzyme was within 2 weeks, which is consistent with recovery period as reported in the literatures.

The common clinical presentations of fluconazole induced liver toxicity are mild to moderate, reversible and asymptomatic cytolysis (12,22). Nevertheless, cases of severe nausea and vomiting (9), marked jaundice (9,10), severe cholestasis (17), or fatal acute hepatic necrosis (9,13) were also reported. There was a wide variation in the reported maximum raised of ALT level which ranges from 173 U/L to 4200 U/L (9,12,13,17,21,23). The level of aspartate aminotransferase (9,12,13,17,21,23), alkaline phosphatase (9,12,13,17,21), total bilirubin (9,12,13,17,21), prothrombin time (9,13,21) and gamma glutamyl transpeptidase (17,21) were also found to be raised in the previously reported cases. In our patient, the level of ALT, total bilirubin and prothrombin time started to increase on day 4 of fluconazole treatment and declined after discontinuation of therapy on day 8. The patient remained asymptomatic since then.

Fluconazole is excreted 80% via kidney. Therefore, kidney impairment may result in an accumulation of fluconazole in the body and leads to dose dependent hepatotoxicity (13,21). A case report by Bronstein et al. showed that dose-dependent hepatotoxicity related to fluconazole was occurred within 10 days after a kidney impaired patient received 400 mg daily of oral fluconazole (13). Crerar-Gilbert et al. found another case of dose-dependent fluconazole associated hepatotoxicity in a kidney failure patient who received oral fluconazole 400 mg daily for 25 days (21). Nonetheless, our patient's liver function deteriorated in spite of reduced dose used (IV 200 mg loading dose then IV 100 mg daily). Thus, careful monitoring of liver functions on regular basis in renal impaired patient is imperative as accumulations of fluconazole might occur even in lower dose and leads to hepatotoxicity.

Concurrent potential hepatotoxic medications in our patient include spironolactone (24), meropenem (25) and ranitidine (26). Meropenem therapy was continued throughout the course of abnormal till normalized liver enzyme level and prothrombin time. Furthermore, both the ranitidine and spironolactone regimens did not demonstrated significant impact on the patient's liver enzyme level and prothrombin time. When these two drugs were discontinued initially, there was no improvement in the patient's liver function. Indeed, the subsequent re-initiation of ranitidine and spironolactone therapies did not worsen the liver function. In contrast, the discontinuation of fluconazole result in persistent

decrease in liver enzyme and prothrombin time value leading us to strongly believe that fluconazole was the offending drug. According to the American College of Cardiology Foundation/American Heart Association guideline (27), Marfan syndrome mainly involve cardiovascular, ocular and skeletal manifestations and it had not been associated with hepatotoxicity. Furthermore, analysis with the Naranjo probability scale indicated that fluconazole was the possible (score of 4) cause of our patient's hepatic toxicity.

4. Conclusion

Hepatotoxicity associated with fluconazole might occur early in critically ill patients with kidney impairment. This adverse effect may occur at low dose of fluconazole therapy as in the present case. Thus, liver function of these patients should be monitored on regular basis. Discontinuation of therapy is warranted in cases where there is a persistent unexplained raised in liver enzymes level.

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