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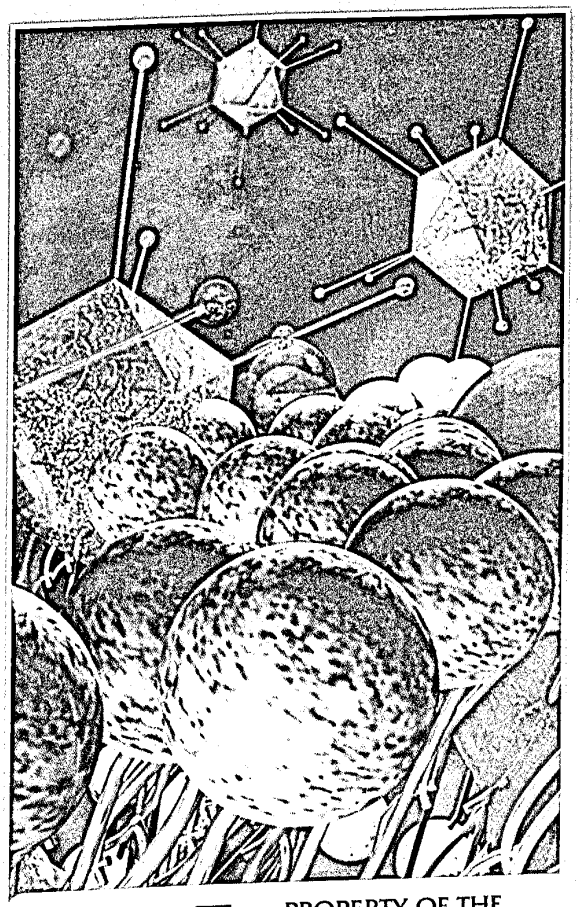

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Hepatotoxicity of antifungal agents

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Antifungal agents have been implicated in numerous cases of hepatotoxicity throughout the past few decades. Hepatotoxic reactions to antifungal agents range from slight, asymptomatic abnormalities in liver function tests to potentially fatal fulminant hepatic failure. Clinically significant hepatic injury resulting from antifungal therapy most commonly manifests as acute hepatocellular, cholestatic or mixed hepatocellular-cholestatic reactions. In general, reactions usually resolve on cessation of therapy, but some antifungal agents may induce chronic liver damage. This review will summarize the hepatotoxicity profiles of the major classes of antifungal agents and will provide recommendations for drug monitoring in order to minimize the risk of hepatotoxicity.

Keywords Adverse effect, amphotericin B, amphotericin B colloidal dispersion, amphotericin B lipid complex, antifungals, caspofungin, fluconazole, flucytosine, griseofulvin, hepatotoxicity, itraconazole, ketoconazole, liposomal amphotericin B, ravuconazole, terbinafine, toxicity, voriconazole

Introduction

During the past two decades there has been a dramatic increase in the incidence of systemic fungal infections [1]. This is due to: (i) the increasing number of bone marrow and solid organ transplantation patients receiving chemotherapy, (ii) the spread of AIDS, and (iii) advances in medical practice and technology leading to the increased utilization of invasive procedures for the treatment of critically ill patients [1]. *Candida* and *Aspergillus* species constitute the leading causes of invasive fungal infections, with *Candida albicans* accounting for the majority of all *Candida* infections [2]. However, non-albicans *Candida* spp are also increasingly reported as causes of life-threatening fungal infections. The current antifungal armamentarium available for the treatment of patients with invasive fungal infections is limited to amphotericin B and its lipid formulations, flucytosine, ketoconazole, the triazole antifungals itraconazole, fluconazole and voriconazole, and the echinocandin caspofungin [2].

Hepatic injury due to medications of all types is a concern, since it is implicated in 15 to 25% of acute liver failure cases in the US, with case fatality rates ranging from 10 to 50% [3]. With the increasing prevalence of systemic fungal infections, some requiring prolonged treatment, an awareness of the toxicity profiles of the available antifungal agents is of critical importance in the early recognition and appropriate management of adverse effects. While nephrotoxicity and other systemic effects of amphotericin B, and myelosuppression associated with flucytosine have been well documented over the past few decades, less attention has been directed towards the hepatotoxicity of antifungal agents [2].

Hepatotoxic reactions to pharmacological agents range from slight, asymptomatic abnormalities in liver function tests to potentially fatal fulminant hepatic failure. The type of hepatotoxicity can be classified with the use of liver function tests or according to liver biopsy findings [4]. Pharmacological agents may cause injury that results in degeneration or necrosis of hepatocytes (hepatocellular injury) or to arrested bile flow (cholestatic injury). Some drugs may induce a mixed pattern injury characterized by a combination of the features observed in hepatocellular and cholestatic injury. Hepatocellular injury is typically associated with predominant elevations and greater than 2-fold increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations [4]. In contrast, cholestatic injury is characterized by relatively slight elevations of aminotransferase levels, but with greater than 4-fold increases in alkaline phosphatase (ALP) concentrations (often accompanied by increased bilirubin concentrations) and an ALT/ALP ratio of less than 2 [4,5••]. Furthermore, liver biopsy findings often reveal portal inflammation in patients with cholestatic injury, but not in patients with hepatocellular injury.

This review will describe the hepatotoxicity of the major classes of antifungals (ie, polyenes, imidazole, triazoles, echinocandin, allylamine, flucytosine and griseofulvin) as summarized in Table 1. In addition, this review will provide recommendations for drug monitoring (when applicable) in order to minimize the risk of hepatotoxicity.

Polyenes

Amphotericin B deoxycholate

Amphotericin B deoxycholate, a polyene antifungal, has been in clinical use for more than 37 years and is rarely implicated in cases of acute liver failure. The incidence of acute liver failure secondary to amphotericin B deoxycholate treatment is likely to be extremely low (less than 1% incidence cited by the manufacturer) [6]. The prescribing information for this drug does not include the frequency of liver function test abnormalities. However, in a study comparing the efficacy of amphotericin B deoxycholate with liposomal amphotericin B as empirical antifungal therapy for febrile, neutropenic patients, a 20% frequency (increase in ALT or AST) was observed among patients receiving either drugs [7]. To date, despite the availability of amphotericin B deoxycholate in the US for nearly 40 years, only three cases of significant hepatotoxicity associated with amphotericin B deoxycholate have been reported in the medical literature [8•]. The pattern of liver injury observed in these cases were mixed hepatocellular-cholestatic or predominantly hepatocellular, with hepatic injury occurring

Table 1. Hepatotoxic reactions to antifungal agents.

Antifungal drug	Inreased incidence of LFTs/liver failure	Pattern of liver injury	Time of onset	Preventive strategy
Polyene				
Amphotericin B deoxycholate	Acute liver failure rarely reported	Hepatocellular and hepatocellular-cholestatic.	As early as 4 days or after total dose of approximately 5 g.	Concomitant administration of other hepatotoxic antifungals, such as itraconazole and amphotericin B, may increase the risk for hepatotoxicity due to increased leakiness of mammalian cell-membranes.
Liposomal amphotericin B	Bili = 11.1 to 18.1%; ALT = 14.6%; AST = 12.8%; ALP = 7.1 to 22.2%	Hepatocellular-cholestatic.	As early as 10 days.	-
ABLC	Not reported	Cholestatic.	Not reported.	-
ABCD	Bili = 3 to 19%; ALT/AST = 1 to 5%; ALP = 3 to 7%	Hepatocellular and hyperbilirubinemia.	Not reported.	-
Imidazole				
Ketoconazole	Transaminases = 2 to 10%	Mostly hepatocellular, cholestasis and hepatocellular-cholestatic.	7 Weeks (range of 1.5 to 24 weeks).	-
Triazoles				
Voriconazole	ALT = 10.7 to 18.9%; AST = 11.7 to 20.3%; ALP = 10.2 to 16%; Bili = 4.3 to 19.4%	Hepatocellular-cholestatic, hepatocellular and cholestatic.	Often within first 10 days of therapy.	Monitor for CYP3A4, CYP2C9 and CYP2C19-mediated drug interactions.
Fluconazole	ALT/AST = 1%	Hepatocellular, hepatic necrosis and hepatocellular-cholestatic.	4 to 34 days.	Dose adjust for renal function.
Itraconazole	ALT = 2 to 3%; AST = 1 to 2%; ALP = 1 to 2%; Bili = 4 to 6%	Hepatocellular-cholestatic and cholestatic.	5 Days to several months.	-
Echinocandin				
Caspofungin acetate	ALT = 10.8 to 13%; AST = 10.5 to 10.8%; Bili = 2.3%	Hepatocellular and hyperbilirubinemia.	Not reported.	-
Flucytosine	Transaminases = 0 to 41%	Hepatocellular, cholestatic, hyperbilirubinemia and hepatic necrosis.	Usually within 1 month.	Adjust dose for renal function; maintain peak levels of 50 to 100 µg/ml.
Allylamine				
Terbinafine	Transaminases = 4%	Hepatocellular, cholestatic and fulminant hepatic failure.	Within 4 to 6 weeks.	Monitor ALP levels in patients who develop hepatic dysfunction.
Griseofulvin	Not reported	Cholestatic.	3 Weeks to 4 months.	Avoid a second course of treatment if patient experiences facial edema/pruritis during first course.

ABCD amphotericin B colloidal dispersion, **ABLC** amphotericin B lipid complex, **ALP** alkaline phosphatase, **ALT** alanine aminotransferase, **AST** aspartate aminotransferase, **Bili** total bilirubin, **LFTs** liver function tests.

after the administration of cumulative doses ranging from 200 mg to 5 g. The exact pathophysiology of amphotericin B deoxycholate-induced hepatic injury is unknown, but interference with the hepatic cytochrome P450 enzyme system and non-selective cellular disruption have been suggested [8•,9•]. Non-selective disruption of mammalian cells increases the permeability of cells, thereby facilitating the entry of other drug entities into the intracellular compartment. The risk of hepatic injury may then possibly be increased by the administration of amphotericin B deoxycholate in combination with potentially hepatotoxic agents.

One reported case involved a 26-year-old caucasian male with pulmonary *Blastomyces dermatitidis* infection [8•]. Initial treatment employed oral itraconazole (200 mg twice daily); intravenous amphotericin B deoxycholate (25 mg on the first day, followed by 50 mg once daily) was added to the therapeutic regimen 6 days later. Asymptomatic elevations in ALT, AST and ALP concentrations were noted after the patient received four doses of amphotericin B and a cumulative dose of 3200 mg of itraconazole. Peak levels of ALT, AST and ALP occurred the next day and were 518, 294 and 205 U/l, respectively, thus prompting discontinuation of amphotericin B therapy. Within 4 days, the patient's liver

function tests normalized, despite continuation of itraconazole therapy. The patient described in this study likely experienced hepatocellular injury, as the liver damage primarily manifested as increases in ALT and AST. A possible adverse drug interaction with amphotericin B deoxycholate and itraconazole was postulated based on the enhanced entry of itraconazole into the intracellular compartment.

Two previous cases of possible amphotericin B-related hepatotoxicity occurred after considerably higher total doses: a patient receiving amphotericin B for cryptococcal meningitis developed hepatotoxicity after a cumulative dose of almost 5 g while he was also receiving chlorpromazine, a recognized hepatotoxic agent; another patient developed reversible increases in transaminases and ALP after receiving a cumulative dose of 571 mg [8•].

Liposomal amphotericin B

Liposomal amphotericin B (AmBisome), the only lipid formulation of amphotericin B that represents a liposomal drug delivery system, has been licensed for use in the US for seven years [10,11]. The incidence of elevations in bilirubin, ALT, AST and ALP levels associated with this agent in various clinical trials was 11.1 to 18.1, 14.6, 12.8 and 7.1 to 22.2%, respectively [10]. Of note, the safety data were primarily derived from clinical trials with febrile, neutropenic patients, a severely ill population in whom such abnormalities are frequently observed. At present, one case of mixed hepatocellular-cholestatic reaction secondary to liposomal amphotericin B has been reported in the medical literature [12•]. The mechanism by which liposomal amphotericin B induces hepatotoxicity is believed to be due to the lipid component of this product, as the drug is preferentially sequestered in the reticuloendothelial tissue [12•].

Mohan *et al* described a study involving a 9-year-old patient who developed hepatic dysfunction after receiving a cumulative dose of 168 mg of liposomal amphotericin B over 7 days [12•]. Liposomal amphotericin B was discontinued after 11 days when the patient's ALT, AST and ALP were found to be 364, 1112 and 1254 U/l, respectively. Within 7 days of discontinuing the drug, the patient's liver function tests normalized. The liver function test abnormalities observed in this patient indicated a mixed hepatocellular-cholestatic injury. A retrospective report on the use of liposomal amphotericin B in 133 episodes of fungal infections lends support to the mixed hepatocellular-cholestatic pattern of injury associated with this drug [13]. Mills *et al* reported that hepatotoxicity occurred in up to 17% of fungal infection episodes; two cases were severe enough to warrant discontinuation of liposomal amphotericin B. The median peak concentrations of the patients' AST, ALP and bilirubin were 103 U/l (58 to 510), 582 U/l (302 to 1362) and 55 µmol/l (15 to 310), respectively [13].

Amphotericin B lipid complex

Amphotericin B lipid complex (ABLC; Abelcet), the first lipid formulation of amphotericin B to receive approval by the US Food and Drug Administration (FDA) for use in amphotericin B deoxycholate-refractory/intolerant patients, is comprised of amphotericin B complexed with two lipids in a 1:1 drug-to-lipid molar ratio [11,14]. The Liposome Company does not specify the frequency of liver function test abnormalities (elevations in ALT, AST, ALP and bilirubin) associated with this product. However, a large analysis of open-label multicenter trials of amphotericin B deoxycholate-refractory/intolerant patients (n = 551) receiving ABLC for invasive fungal infections, showed a rise in bilirubin occurring in 33% of evaluable cases, of whom 25% had normal baseline values [15]. ABLC appears to induce cholestatic hepatic injury in some patients, as shown by the significant elevations in bilirubin and ALP levels reported in the analysis conducted by Walsh *et al*. To our knowledge, the pathogenesis of ABLC-induced cholestasis has not been elucidated. The pivotal safety and efficacy analysis included 551 patients, of whom 80% had either failed previous systemic antifungal therapy (mainly amphotericin B deoxycholate) or developed renal impairment secondary to amphotericin B deoxycholate [15]. Hematological malignancy was the most common underlying condition and was present in approximately 30% of cases. The mean serum bilirubin concentration increased by 41% from baseline at the end of therapy ($p = 0.0001$) and the mean serum ALP concentration increased by 17% from baseline at the end of therapy ($p = 0.0015$). Interestingly, the mean serum ALT level was not significantly altered at the end of treatment. Of note, patients enrolled in this study were diagnosed with numerous conditions such as sepsis, graft-versus-host disease (GVHD), veno-occlusive disease and end-organ damage due to chemotherapy that could have contributed to elevations in serum bilirubin concentrations. A similar pattern of hepatic injury was reported in a small retrospective analysis of 15 pediatric cancer patients, four (27%) of whom discontinued ABLC due to hyperbilirubinemia [16].

Amphotericin B colloidal dispersion

Amphotericin B colloidal dispersion (ABCD) is a colloidal dispersion of disc-shaped particles that received FDA approval for use in the US in December 1996 [11]. Rises in serum aminotransferases and bilirubin have occurred during ABCD therapy, but the true incidence of hepatotoxicity is confounded by the presence of competing causes for liver toxicity such as GVHD in many patients prior to treatment [1,17,18]. The incidence of elevations in bilirubin, ALT, AST and ALP levels associated with this agent in various clinical trials was 3 to 19, 1 to 5, 1 to 5 and 3 to 7, respectively [14]. Hepatocellular injury and hyperbilirubinemia represented the most commonly reported liver function test abnormalities in major clinical trials. Further research is needed to determine the mechanism responsible for its hepatotoxic effects.

A randomized, double-blind, multicenter trial in which the efficacy of ABCD was compared with amphotericin B deoxycholate for the treatment of invasive aspergillosis (n = 174) showed that hyperbilirubinemia occurred in 4.5 and 10.5% of ABCD- and amphotericin B-treated patients, respectively (p value not reported) [17]. Similarly, a phase I study of ABCD for the treatment of invasive fungal infections showed elevations in serum bilirubin concentrations in patients receiving ABCD at 2.5 to 4.0 mg/kg/day ($p = 0.002$) and ABCD at 4.5 to 6.0 mg/kg/day ($p = 0.009$). Rises in AST and ALT occurred in 9 and 13% of patients treated with ABCD, respectively, in an open-label trial that enrolled patients (n = 168) with systemic mycoses [1].

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