Reversible hepatotoxicity related to amphotericin B

Mark A. Miller, MD

Hepatotoxicity is regarded as a rare side effect of amphotericin B therapy. A patient with acute myelogenous leukemia who had normal liver function was treated with amphotericin B for fungal pneumonia. While he was receiving the drug at high dosages asymptomatic elevation of the levels of alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase and bilirubin was noted. The levels returned to normal when the drug was discontinued. Rechallenge with a lower dosage prompted a rapid rise in the levels, with subsequent return to normal when the medication was withdrawn.

L'hépatotoxicité de l'amphotéricine B est tenue pour rare. Pendant l'emploi de ce médicament à hautes doses dans le traitement d'une aspergillose pulmonaire probable chez un malade souffrant de leucémie myéloïde aiguë, dont la fonction hépatique a été normale jusque-là, on observe une augmentation asymptomatique des taux de phosphatase alcaline, de transaminase glutamique oxaloacétique et de transaminase glutamique pyruvique sériques, de lactico-déshydrogénase sérique et de bilirubine. Retour des taux à la normale dès cessation du médicament. Une contre-épreuve à une dose plus faible provoque une prompte remontée des taux, qui se normalisent encore une fois à l'arrêt du traitement.

An ever-increasing role in modern medicine is played by fungal infections, both those due to primary pathogens (e.g., *Coccidioides immitis* and *Histoplasma capsulatum*) and those caused by the growing number of opportunistic pathogens (e.g., *Cryptococcus neoformans* and *Candida* sp.) in patients with impaired defence mechanisms.[1] Amphotericin B has been shown to be one of the most effective antimicrobial agents for systemic and other serious fungal infections and is the only parenterally administered antifungal agent available at present.

The main limiting factor in administering amphotericin B is its toxicity. Common side effects include flushing, chills, fever, phlebitis, headache and anorexia, some of which diminish even with continued administration of the agent at the same dosage.[2] Renal toxicity is by far the most serious and dose-limiting problem. It has been claimed that 80% of patients receiving amphotericin B suffer some renal impairment.[3] Other long-term effects include hypokalemia, presumably of renal origin,[4] and normochromic normocytic anemia of undetermined origin but associated with low circulating erythropoietin levels.[4,5] As well, there have been rare cases of anaphylaxis, thrombocytopenia and convulsions, presumably secondary to infusion of the drug.

Adverse effects of amphotericin B on the liver have been reported to be rare.[1,6] Up to now there has been only one documented case of amphotericin B-induced hepatotoxicity: in a 32-year-old man with cryptococcal meningoencephalitis treated with amphotericin B intermittently over 1 year (total dose, 4.82 g) acute toxic hepatic degeneration (demonstrated at autopsy) developed 4 days prior to death while the patient was receiving chlorpromazine and amphotericin B.[7] The dosage of the latter had recently been increased.

The present report describes a patient in whom transient liver dysfunction that was reproducible with rechallenge developed while he was being treated with amphotericin B.

Case report

A 51-year-old man with no significant past medical history was admitted to hospital with a diagnosis of acute myelogenous leukemia. He complained of fever, chills, headache, rhinorrhea, weakness, anorexia and a nonproductive cough but was afebrile. He drank alcohol only rarely. His soft, nontender liver spanned 10 cm; no splenomegaly was noted. The results of laboratory investigations and chest roentgenography were normal except for the diagnostic bone marrow findings. He was found to be anergic in skin testing.

Induction chemotherapy was begun on the fourth hospital day with daunorubicin (45 mg/m^2 of body surface per day for 3 days) and cytarabine (200 mg/m^2 per day for 7 days). Two days after therapy was begun, while the patient was neutropenic, he became febrile, with no evidence of a source of infection. A chest roentgenogram was normal. Therapy with ticarcillin, 4 g given intravenously every 4 hours, and amikacin sulfate, 500 mg given intravenously every 12 hours, was begun, and the fever resolved.

While receiving this therapy the patient again became febrile, with hemoptysis, on the 22nd hospital day. A chest roentgenogram showed a pneumonic process in the superior segment of the left lower lobe. All cultures of blood, sputum and urine were sterile. Therapy with cloxacillin, 1.5 g given intravenously every 6 hours, was added. The fever continued, and therapy with amphotericin B was begun on the 25th hospital day. Initial doses of 1 mg and then 10 mg produced no adverse reactions, and the patient was then given 20 mg daily via a central catheter, with complete defervescence the following day. The ticarcillin, amikacin and cloxacillin were discontinued.

The patient continued to do well, although cavitation appeared in the pneumonic area. A sample of the

From the Department of Medicine, Montreal General Hospital and McGill University, Montreal

Reprint requests to: Dr. Mark A. Miller, Montreal General Hospital, 1650 Cedar Ave., Montreal, PQ H3G 1A4

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fluid in the cavity, obtained by transthoracic needle aspiration, showed no evidence of microorganisms when stained and cultured. Therapy with amphotericin B, 30 mg per day, was continued for treatment of suspected *Aspergillus* pneumonia. The lack of a significant toxic response to the drug and the desire to continue antileukemic therapy prompted an increase in the daily dose to 50 mg, with subsequent clearing of the pneumonia and the central cavity. The only detectable side effects of the drug thus far were nephrogenic hypokalemia and a mild decrease in the creatinine clearance.

After a cumulative dose of amphotericin B of 571 mg over 18 days the results of liver function tests were noted to be abnormal for the first time (Fig. 1). The patient was receiving no other medication at the time, and a physical examination gave completely normal results, including absence of liver tenderness and fever. Three days later, because of a further rise in the levels of alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH) and bilirubin, amphotericin B was discontinued. There was an immediate fall in most of the levels, and near-normal levels were noted 6 days later. Because the total amount of amphotericin B received by the patient was small (721 mg), therapy with the drug was restarted, at 20 mg per day; there was a prompt worsening of liver function the next day. After 2 more days of liver function impairment amphotericin B therapy was again stopped, and over the next 14 days the results of liver function tests returned to normal. Titres of antibody to hepatitis B surface antigen and the results of a liver/spleen scan at this time were normal. The patient received no further amphotericin B. The pneumonia and the cavity continued to clear, without recrudescence of fever.

The patient had a leukemic relapse on the 70th hospital day. Remission was reinduced with 6-thioguanine and cytarabine, and he was discharged home on the 73rd hospital day. Close follow-up for 1 year following the initial diagnosis disclosed persistently normal results of chest roentgenography and liver function tests and no relapse of the leukemia.

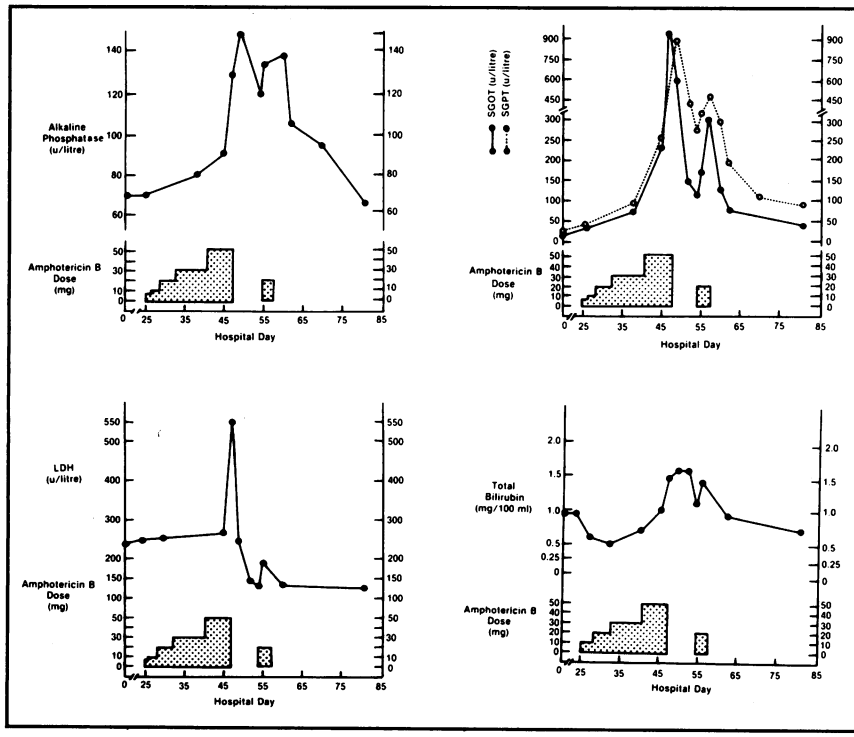

Fig. 1—Relations of levels of alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH) and bilirubin with amphotericin B therapy in patient with acute myelogenous leukemia.

Discussion

This case documents a rare adverse effect of therapy with amphotericin B. Although the drug is metabolized mainly in the liver, no clear case of amphotericin B-related hepatotoxic effects has ever been shown.

To evaluate an adverse drug reaction one needs certain information:[8]

- The known characteristics of the main clinical state.
- The known patterns of response to the drug(s) being used.
- An evaluation of the concentration(s) of the drug(s) in the patient.
- The time relations between the adverse effect and the drug(s).
- The results of cessation of or rechallenge with the drug(s).

Even with this information there is often a marked discrepancy between the findings of trained observers simultaneously evaluating the adverse effect of a given drug.[9]

There was no apparent reason why this patient's clinical state produced transient liver dysfunction. Although he had received a total of 8 units of packed red blood cells and 46 units of platelets between the 11th and 24th hospital days, the abnormalities were inconsistent with transfusion-related hepatitis: they were short-lived and were clearly provoked after amphotericin B was given. The patient was receiving no other medication at the time, and the temporal sequence supports the conclusion that the effects were related to amphotericin B alone. Finally, rechallenge with the drug resulted in reproduction of liver dysfunction, with resolution after the drug was discontinued. It should be noted that amphotericin B has a long half-life (approximately 15 days).[10]

The cause of the toxicity is unknown. It may be secondary to amphotericin B itself or to sodium desoxycholate (41 mg per 50 mg of amphotericin B), a normal constituent of bile that is used to effect colloidal dispersion of insoluble amphotericin B. Whatever the cause, the toxicity appears to involve the entire hepatobiliary system, with transient rises in the levels of alkaline phosphatase, SGOT, SGPT, LDH and bilirubin.

Conclusion

Hepatotoxicity has been cited for many years, without any documented proof, to be a rare adverse effect of amphotericin B. Certainly, transient liver dysfunction has never been shown to be among the side effects of amphotericin B therapy. The present case documents such dysfunction, reproducible with rechallenge, in a patient receiving the drug.

Abnormal results of liver function tests in patients who are receiving amphotericin B should be investigated completely with respect to both common and uncommon causes related to the primary and associated illnesses. However, as shown, liver dysfunction can be a result of amphotericin B therapy alone.

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