



# Calcium-channel blocking agents as therapy for amphotericin B nephrotoxicity

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■ Amphotericin B is a broad-spectrum antifungal agent shown to be effective in the treatment of systemic fungal infections. Unfortunately, therapeutic doses are often associated with a variety of adverse effects, including nephrotoxicity. Studies of the deleterious effects of amphotericin B on the renal microvasculature are yielding clues to sparing kidney function. In selected patients, concomitant use of a calcium-channel blocker may prevent the nephrotoxic effects of amphotericin B and allow full therapeutic doses to be used.

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**A**MPHOTERICIN B is used extensively to treat systemic fungal infections. Data reviewed by Branch<sup>1</sup> indicate that fungal organisms are isolated in increasing numbers of hospitalized patients and in 1988 accounted for approximately 25% of all cases of primary septicemia. Amphotericin B remains the broad-spectrum antifungal drug of choice for the treatment of such infections.

This article will discuss adverse effects of amphotericin treatment and the effects of salt loading and salt depletion on amphotericin toxicity, as well as the use of calcium-channel blockers to minimize the effects of amphotericin B on glomerular function.

## ADVERSE REACTIONS TO AMPHOTERICIN B

Although it is the drug of choice for the treatment of systemic fungal infections, amphotericin B causes a multitude of adverse reactions, including fever, chills, nausea, vomiting, hypokalemia, anemia, and phlebitis. The most significant complication of amphotericin B is nephrotoxicity.<sup>2-5</sup> Although the adverse reactions are generally manageable, such toxicity can necessitate

reductions in total dosage of the drug—which is counterproductive, since it is the total dosage of amphotericin which is important for eradication of disseminated fungal disease.

In addition to decreases in the glomerular filtration rate (GFR) with rises in the serum creatinine concentration and blood urea nitrogen concentration, other renal effects have also been noted, including decreased urinary concentrating ability and renal tubular acidosis. Furthermore, symptomatic hypokalemia due to urinary potassium wasting and urinary magnesium wasting may also be present. The frequency of these renal abnormalities is variable and dependent upon how one defines nephrotoxicity. Medoff and Kobayashi<sup>6</sup> have reported that the GFR falls approximately 40% in most patients within 2 weeks after starting amphotericin B therapy, and stabilizes at 20% to 60% of normal for the remainder of the treatment period.

## USE OF SALT LOADING

Branch<sup>1</sup> has speculated that glomerulotubular feedback may be the mechanism of nephrotoxicity caused by amphotericin B. With this background, studies were initiated to evaluate the effect of salt loading or salt depletion on amphotericin B toxicity.<sup>7-9</sup> Such experiments have demonstrated that salt loading prevented

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nephrotoxicity of amphotericin. Clinical case reports and retrospective studies also support the use of 0.9% saline as therapy or to prevent the nephrotoxic effects of amphotericin B.<sup>10</sup> Branch<sup>1</sup> has proposed an algorithm for the management of amphotericin B nephrotoxicity. He emphasizes that salt depletion must be avoided and that concomitant antibiotics be mixed with sodium salts, with the additional caveat that the underlying disease be assessed carefully to determine if sodium loading will exacerbate the condition. If so, the risk-benefit ratio must be considered.<sup>11</sup>

#### USE OF CALCIUM-CHANNEL BLOCKERS

A recent article by Sawaya et al<sup>12</sup> from the University of Michigan at Ann Arbor has shed new light on potential mechanisms for changes in renal function that can occur with systemic administration of amphotericin B.

The authors tested the hypothesis that amphotericin B decreases the GFR by activating the glomerulotubular feedback mechanism present within the nephron. They hypothesized that amphotericin B damages tubular epithelium to allow an increase in delivery of sodium and chloride to the distal tubule, which would initiate a vasoconstrictor response in the afferent arteriole to that individual nephron (ie, glomerulotubular feedback). This increase in afferent arteriolar tone would subsequently reduce glomerular blood flow and GFR, which would reduce the rate of formation of filtrate and, therefore, the rate of delivery of solute to the distal nephron, thus completing the glomerulotubular feedback loop.

The authors infused 1 mg/kg of amphotericin B in anesthetized rats over 50 minutes, which produced a

significant decrease in the GFR, with an increase in the urinary flow rate and urinary chloride excretion. Single-nephron GFR measured in proximal or distal tubules decreased to a similar degree, thus eliminating the mechanism of glomerulotubular feedback for alterations noted in GFR. In addition, the authors examined isolated perfused afferent arterioles from rabbit kidneys and showed that amphotericin B produced constriction of these vessels. Such constriction did not occur in a calcium-free medium or in the presence of a calcium-channel blocker. The authors concluded that amphotericin B induced reduction in the GFR, not by any mechanism of glomerulotubular feedback, but by direct vasoconstriction that is probably initiated by the opening of calcium channels induced by depolarization. More recent data from Tolins and Raij<sup>13</sup> have supported this concept in rat studies which indicated that the calcium-channel blocker diltiazem protects the kidney from decreases in GFR when the rats were treated with amphotericin B.

Thus, the recent studies by Sawaya et al<sup>12</sup> and Tolins and Raij<sup>13</sup> become extremely important. Although salt loading may in fact prevent the vasoconstriction caused by amphotericin B, the use of calcium-channel blockers may also be therapeutic. Thus, calcium-channel blockers such as nifedipine and verapamil may be of use in patients with decreases in GFR due to amphotericin B. The dose of such drugs that will protect GFR is not known, and the effect this dose will have on GFR is also not known. However, for those patients who are not able to tolerate salt loading, the use of a calcium-channel blocker may be of great usefulness in sparing kidney function and in allowing therapeutic doses of amphotericin B to be provided.

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