AMPHOTERICIN NEPHROTOXICITY Jeff Kaufhold, MD Jan 2017

INCIDENCE

Incidence is variable in the clinical population depending on definition of toxicity and pretreatment condition. Significantly higher incidence in volume depleted patients or in patients who have concurrent insults to renal function (i.e. NSAIDS).

There is no correlation with length of treatment per se, although the longer the course of therapy, the greater the liklihood of exposure to concurrent insults.

This has become much less of a problem with the Liposomal preparation and the lipid complex versions.

LABORATORY MANIFESTATIONS

azotemia, decreased creatinine clearance, low urine sodium with high urinary potassium and magnesium.
May also see hematuria, pyuria, tubular cells.
Hypokalemia, hypomagnesemia.

MECHANISMS OF NEPHROTOXICITY

1) Definite vasoconstriction as shown by Cheng, et al., who identified increased renovascular resistance after either acute rapid infusion or chronic exposure. (see below for possible mechanism under TGF). Vasoconstriction is not the only mechanism, however, as nonspecific vasodilation (such as with hydralazine perfusion) does not prevent AM-B renal dysfunction.
2) Acts as ionophore in tubular cells, possibly causing :
a) Direct toxicity to tubular cells, or more likely;
b) Back leak of urea, creatinine, inulin sodium and other ions, which decreases fractional excretion of the above.

TUBULOGLOMERULAR FEEDBACK

TGF is felt to be a mechanism whereby individual nephrons regulate solute flow by altering afferent arteriolar tone, resulting in preservation of total body ion (sodium) stores necessary to survive on dry land or in fresh water. A simple example of TGF in action would begin with an elevation of blood pressure or damage to the proximal tubule, which results in increased delivery of sodium (or chloride or other ions) to the distal nephron. Somewhere in the distal nephron, possibly the juxtaglomerular apparatus, a sensor of solute flow recognizes an increase, and releases a mediator which induces vasoconstriction of the renal vascular bed. Conversely, reduced distal solute delivery would stimulate a reduction of vascular tone, which is not sufficient to counter the renovascular effects of angiotensin, but would modulate afferent vasoconstriction and maintain some urine flow.

The presumed signal is distal sodium or chloride delivery. The mediator which induces vasoconstriction is probably adenosine. As proof of this Gerkens has shown the following:

a. renal adenosine increases in volume-depleted dogs.

b. The effect of Am-B on GFR, RPF and renovascular resistance is ameliorated by treatment with aminophylline, an adenosine receptor inhibitor.

My own theory recognizes the presence of a single long cilium extending out into the lumen of the renal tubule from each proximal tubule cell. This could serve as a flag on a pole to allow measurement of flow through the tubule.

Amphotericin may alter TGF by several possible mechanisms, including proximal tubular toxicity; increased urea permeability of the distal tubule; or via direct ionophore action at the JG apparatus.

PREVENTION

Human studies have identified the negative effect of volume depletion, and suggest that volume expansion and sodium loading by a number of means is beneficial. These include normal saline, Ticarcillin sodium infusion concurrently, and combined flucytosine-ampho infusion.

A prospective study in humans, performed in West Germany, demonstrated amelioration of Amphotericin nephrotoxicity by infusion of 1 Liter of normal saline over an hour just prior to each dose of AM-B. All of their patients (leukemics with neutropenic fevers) were able to complete the full course of AM-B.

Animal studies show beneficial effects of salt loading via diet or infusion, and prevention of ampho nephrotoxicity by aminophylline infusion (see above in TGF).

This has become much less of a problem with the Liposomal preparation and the lipid complex versions.

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