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Amphotericin B – Induced Nephrotoxicity: Influence of Sodium Status

Dear Sir,

A major limitation in the use of amphotericin B is its potential to cause significant nephrotoxicity. Several studies in both animal models and human subjects suggest that sodium status may influence the onset of toxicity [1, 2]. Using purified renal tubule membranes we have examined the *vitro* effects of amphotericin B. From these findings we suggest a possible rationale for the protective effects of sodium administration on kidney toxicity. Purified renal membrane vesicles were obtained from rabbit kidney using a series of homogenation and centrifugation steps. Membrane potentials were measured by observing the fluorescence response of the potential sensitive dye 3,3-dipropylthiadicarbocyanine iodide. Individual ion permeabilities were determined from the observed membrane potential and the ion concentrations of the membrane buffers [3]. In the presence of amphotericin B the ionic permeabilities were significantly increased (1.4- to 7.5-fold) and demonstrated a selectivity for anions over cations. Estimations of renal membrane potential were made based on the observed permeabilities of the major physiologically significant anions and cations. In the absence of drug the predicted membrane potential was -50 mV while in the presence of 2.0 µg/ml amphotericin B the potential was -72 mV, a 45% change.

Recently, interest has focused on the influence of electrolytes on amphotericin B toxicity. Several studies have shown that coadministration of sodium can prevent or reverse the impaired renal function associated with amphotericin B administration [1, 2].

Amphotericin B toxicity appears to result from renal vasoconstriction modulated

through tubuloglomerular feedback, a mechanism which decreases the glomerular filtration rate in response to changes in the delivery of ions in the distal tubule [2]. Amphotericin B may initiate this mechanism through increasing both membrane permeability and membrane polarization. Increased sodium could decrease the induced hyperpolarization as well as compensate for the relatively increased ionic permeability of potassium and chloride ions, which in turn would be expected to inhibit the renal vasoconstriction associated with amphotericin B toxicity.

References

- 1 Gerkens, J.F.; Branch, R.A.: The influence of sodium status and furosemide on canine acute amphotericin B nephrotoxicity. *J. Pharmac. exp. Ther.* 214: 306-311 (1980).
- 2 Heidemann, H.T.; Gerkens, J.F.; Spickard, W.A.: Amphotericin B nephrotoxicity in humans decreased by salt repletion. *Am. J. Med.* 75: 476-481 (1983).
- 3 Schell, R.E.; Wright, E.M.: Electrophysiology of succinate transport across rabbit renal brush border membranes. *J. Physiol., Lond.* 360: 95-104 (1984).