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Perspectives and Commentaries

Prevention of Cisplatin Nephrotoxicity

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CISPLATIN is a potent, dose-dependent antineoplastic agent that has earned a place in contemporary cancer chemotherapy. Nephrotoxicity is the major side effect and renal failure has been observed in a large proportion of patients treated without precautions designed to protect the kidneys. Nonspecific protection against acute renal failure and reduced tubular fluid cisplatin levels has been achieved by vigorous hydration and diuresis. A variety of strategies have been proposed for the ameliorating of the dose-limiting nephrotoxicity of cisplatin. These include the use of hypertonic chloride-containing vehicles [1, 2], varied infusion regimens [3] and the administration of selenium [4] or thiol reagents to diminish intrarenal accumulation and binding of cisplatin [5]. Intracavitary administration designed to increase drug delivery to the tumor while decreasing systemic delivery, may also reduce renal toxicity.

The use of intravenous sodium thiosulfate during intracavitary cisplatin therapy represents a novel approach to preventing nephrotoxicity which is based on the belief that thiosulfate will detoxify circulating cisplatin by forming thiosulphate-cisplatin complexes [6]. In this issue of the *European Journal of Cancer and Clinical Oncology*, Markman *et al.* provide clinical data consistent with this belief [7]. However, the absence of a control group or an assessment of the effectiveness of hydration makes this study difficult to interpret. The theoretical basis of the thiosulfate effect is, itself, uncertain since thiosulfate does not decrease circulating levels of 'active' cisplatin [6, 8]. Thiosulfate is secreted, reabsorbed and selectively accumulated in the proximal tubule [9, 10] and therefore, could form organ-specific intracellular complexes with free cytosolic platinum. On the other hand, renal protection may derive from the additional osmotic load the thiosulfate presents to the kidney. With a mol. wt of 226, the 16 g of sodium thiosulfate administered in the study of Markman *et al.* provided 70 mOsm of non-reabsorbable solute, an osmotic load approximating 12 g of mannitol.

Although up to 90% of cisplatin is excreted by the kidneys over several days, the drug is rapidly removed from the circulation by binding to tissue macromolecules resulting in a plasma half life measured in minutes [1]. The renal clearance of free platinum exceeds the glomerular filtration rate suggesting that platinum is secreted by the tubule as well as filtered [11]. Cisplatin and/or its derivates are also accumulated in the proximal tubule. Selective tubular uptake and storage appear to account for the nephrotoxicity although the form and biologic reactivity of platinum within the cell are unknown [12]. It has been proposed that replacement of chloride by hydroxyl groups in acqueous media may account for the intracellular formation of cytotoxic complexes of cisplatin [13]. In the rat, renal cortical accumulation of cisplatin is associated with necrosis of the S3 segment of the proximal tubule (pars recta) and the late development of intrarenal cysts [14].

Concentrative transport, in addition to being the major mechanism producing renal damage, provides the clinician with an opportunity to reduce cellular accumulation and hence, toxicity, by inhibition of cellular accumulation. Intrarenal accu-

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mulation can be reduced by compounds that share transport systems or intracellular binding sites with cisplatin. In the rat, competitive inhibition of the organic acid secretory system by probenecid provides protection against cisplatin nephrotoxicity [15]. Molecules that share the organic base secretory system also show protective effects [12].

The clinical importance of proximal tubular damage in cisplatin nephrotoxicity was suggested by the appearance of proximal tubular reabsorptive defects, initially recognized because of symptomatic hypomagnesemia with secundary hypocalcemia [1]. Tubular proteinuria, aminoaciduria and hypouricemia may accompany the proximal tubular damage [16]. Cisplatin-induced proximal tubule necrosis is preceded by a fall in sulfhydral enzyme activity in the cortex which indicates that the cylolytic agent or its metabolites react with SH groups. The mechanism of toxicity, however, differs from that of mercuric ions since cisplatin does not deplete the tissue of glutathione [5]. Tubular necrosis appears to be mediated by lipid peroxidation [17] and may be followed by irreversible interstitial nephritis. Potentiation of nephrotoxicity by aminoglycosides has been suggested [18]. Although persistent interstitial nephritis still occurs, irreversible renal insufficiency has been dramatically reduced in humans by sustained diuresis. Nausea, vomiting and neuropathy emerge as dose-limiting side effects when nephrotoxicity is controlled.

The contribution of individual reno-protective maneuvers following cisplatin is difficult to determine from the clinical literature because of the variety of therapeutic regimens used and the absence of rigorous controls. Although the protection afforded by different diuretics [19] suggests that increased urine flow and decreased urine cisplatin concentration *per se* reduce nephrotoxicity, other modalities of protection may play a role in the response to individual diuretics. Thus, it has been suggested that mannitol diminishes endothelial cell swelling while both mannitol and furosemide decrease protein binding and induce intrarenal vasodilatation [1]. It has also been suggested that mannitol protection may derive from its role as an hydroxyl radicle scavenger [20]. Acetazolamide has been reported to protect rats again cisplatin nephrotoxicity despite the absence of a diuretic response. This protective action may derive from transport of the carbonic anhydrase inhibitor by the organic acid transport system and/or alkalinization of the urine induced by acetazolamide [19].

Some discrepancies undoubtedly arise from the mistaken notion that administration of fluids and diuretics is equivalent in achieving a diuretic response. Unless urine output is monitored throughout the period of drug administration and for several days thereafter, the presence of sustained diuresis cannot be assured. The possibility that thiosulfate is acting as an osmotic diuretic could be tested by comparing the effects of equimolar doses of thiosulfate and mannitol on cisplatin nephrotoxicity in subjects undergoing comparable sustained diuresis. Thiosulfate might prove to be the diuretic of choice during intravenous, as well as during intracavitary cisplatin therapy, because of the additional postulated reno-protective effect, providing it does not diminish antineoplastic activity.

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