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Hyperuricemia and hypoalbuminemia predispose to cisplatin-induced nephrotoxicity*

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Summary. The usefulness of pretreatment biochemical parameters in the prediction of nephrotoxicity associated with cisplatin treatment was studied. Twenty-two patients, who received 29 cycles of cisplatin, were evaluated. Cisplatin was given every 3–4 weeks with saline and mannitol. Azotemia occurred in almost all patients and was transient, peaking 1–2 weeks after therapy. The change in serum creatinine from baseline to peak correlated inversely with pretreatment serum albumin ($r = -0.73$; $P < 0.01$) and with pretreatment uric acid ($r = 0.76$; $P < 0.01$). Ten patients with uric acid levels of < 6 mg/dl were receiving allopurinol. The competition between organic anions and cisplatin for excretion may, in part, explain the protective effects of hypouricemia. Hypoalbuminemia affects peritubular oncotic pressure and may in turn affect platinum excretion. Hypoalbuminemia also reduces the half-life of cisplatin, exposing the kidney to more of the unbound filterable drug.

Introduction

Cisplatin has a broad-spectrum antineoplastic activity and has become a major component of combination chemotherapy programs. Nephrotoxicity, however, remains a limiting side effect. In early phase I studies, when the presence of adequate hydration was not monitored, the incidence of nephrotoxicity was 50%–100% [7, 12]. The incidence of nephrotoxicity in later studies, in which adequate hydration was ensured, ranges between 6% and 13% [5, 6, 9, 15, 18]. The hydration schedules utilized include saline, diuretics, and mannitol. A variety of pharmacologic agents have also been used to reduce cisplatin-related nephrotoxicity. These include probenicid [14], diethyldiothiocarbamate [2], and sodium thiosulfate [11]. Apart from one study in which immediate post-treatment platinum levels were measured [4], we are not aware of any attempts to assess the use of biochemical parameters to predict cisplatin-induced nephrotoxicity. We therefore carried out a study to determine whether any of the routine biochemical parameters were useful in predicting nephrotoxicity associated with cisplatin.

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Patients and methods

The charts of 43 patients who had received cisplatin were reviewed. Excluded from the study were patients with abnormal renal function (creatinine clearance less than 100 ml/min or serum creatinine greater than 1.0 mg/dl) and patients in whom acute deterioration of renal function was either a terminal event or associated with sepsis or shock. After review, 22 patients, who received 29 cycles of cisplatin, were deemed eligible for the study. All these patients had advanced cancer, which included metastases to several organs (Table 1). All patients received cisplatin in combination with other cytotoxic agents. Cisplatin was given every 3–4 weeks according to a previously established protocol which included use of saline hydration and mannitol. The mean age of these patients was 52 years (range 34–75), the mean cumulative dose of cisplatin was 170 mg/m^2 (range 90–530), and the mean total duration of cisplatin medication was 3.2 months (range 0.8–17).

Serum electrolytes, urea nitrogen, creatinine, uric acid, bilirubin, albumin, liver enzymes, calcium and phosphate were measured prior to the administration of cisplatin and thereafter at 1- to 2-week intervals and prior to each subsequent cisplatin dose. The increase in serum creatinine (mg/dl) from the baseline value after giving cisplatin was correlated with each of the biochemical parameters measured prior to cisplatin administration. For those parameters where a significant correlation was obtained the effect of the total cumulative dose of cisplatin was also evaluated. Pearson's correlation coefficient, r, was used to evaluate associations. Student's t-test was used for statistical evaluation of significance.

Results

In patients where an increase in serum creatinine occurred, the azotemia was transient and peaked at 1H2 weeks after treatment. In three patients the increase in serum creatinine occurred after every dose of cisplatin. Figure 1 shows the correlation between serum levels of albumin ($r = -0.73$; $p < 0.01$) and the increase in serum creatinine (i.e., maximal baseline level). When pretreatment albumin levels of < 3.0 g/dl were considered, in six out of seven instances the serum creatinine increased by > 0.5 mg/dl. A similar increase in creatinine was seen on only one occasion when serum albumin levels of > 3.0 g/dl were considered.

Table 1. Clinical diagnosis in the 22 patients in the study

Primary site	Number
Lung	10
Brain	5
Bladder	2
Tongue	1
Testicular	2
Breast	1
Stomach	1

Figure 2 shows the correlation between serum uric acid and the increase in serum creatinine ($r=0.76$; $P<0.01$). Ten patients with uric acid levels <6 mg/dl were receiving allopurinol.

There was no significant correlation between the total cumulative dose of cisplatin and the patients' renal dysfunction.

Discussion

It is recognized that the dose-limiting nephrotoxicity of cisplatin is a major problem in the clinical management of patients receiving chemotherapy. The maneuvers studied to reduce the nephrotoxicity of cisplatin include: (a) changes in hydration or infusion rates; (b) use of other drugs; (c) methods of early detection; and (d) use of platinum analogues [17].

Our observation that hypoalbuminemia and hyperuricemia are factors in the development of cisplatin-induced nephrotoxicity has not, to the best of our knowledge, been previously reported. The mechanisms by which hyperuricemia and hypoalbuminemia contribute to renal toxicity is unknown. Ross and Gale found that when probenicid, a uricosuric agent, was administered before cisplatin to rats the peak creatinine and pathologic changes in the kidney were significantly reduced [14]. Furthermore, the use of hydration schedules utilizing mannitol and furosemide were also associated with increased urinary excretion of uric acid [10]. Other investigators have advocated that mechanisms other than hydration may be responsible for the reduced nephrotoxicity when furosemide and mannitol are utilized [1, 13]. Thus, our observation that lower serum uric acid levels may be relatively protective against cisplatin-induced nephrotoxicity may provide an additional explanation for the success fo hydration schedules.

The pars recta, a site of intracellular accumulation of platinum, is a major site of uric acid secretion [10]. Thus, competition for the same mechanism may, in part, explain our observations. On the other hand, high uric acid levels may indicate an underlying renal abnormality, i.e., the cisplatin could further affect an already "damaged" kidney. The mechanism by which hypoalbuminemia potentiates cisplatin-induced nephrotoxicity may be related to the effect of hypoalbuminemia on renal hemodynamics. Hypoalbuminemia and decreased plasma oncotic pressure favor decreased peritubular capillary resorption and thereby activate intrarenal hemodynamic changes favoring sodium resorption [3]. Such conditions are also associated with decreased secretion of organic acids such as uric acid [8]. This mechanism might be important in determining accumulation of cisplatin or its metabolites, since secretion is one way in which cisplatin is cleared by the kidney [17]. Alternatively, high albumin levels could decrease the exposure of the kidney to cisplatin by binding to the drug. Cisplatin is rapidly bound to serum proteins [8], and we have previously demonstrated that the pharmacokinetics of cisplatin following cisplatin administration vary with the serum albumin level [16]. Low serum albumin is associated with significant shortening of the half-life of cisplatin, suggesting that more of the unbound filterable drug is exposed to the kidney [16].

Our observations suggest the need for controlled studies examining the use of agents which reduce uric acid (e.g., allopurinol) and of albumin infusions for reduction of cisplatin-induced nephrotoxicity.

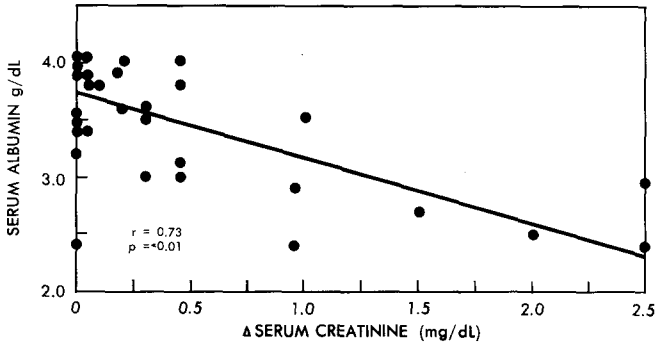

Fig. 1. Correlation between pretreatment serum albumin and change in serum creatinine after cisplatin

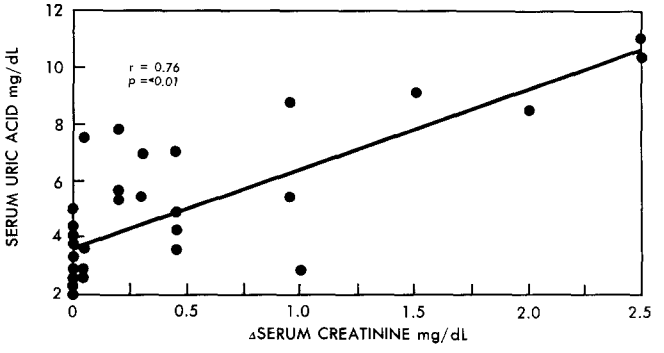

Fig. 2. Correlation between pretreatment serum uric acid and change in serum creatinine after cisplatin

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