Cancer Chemother Pharmacol (1987) 19: 57–60

Cancer Chemotherapy and Pharmacology

Carboplatin (CBDCA), iproplatin (CHIP), and high dose cisplatin in hypertonic saline evaluated for tubular nephrotoxicity

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Summary. We compared the acute tubular nephrotoxicity of three platinum compounds in children and adults with solid tumors by monitoring the urinary excretion of alanine aminopeptidase, *N*-acetyl-β-D-glucosaminidase, and total protein. Cisplatin (100 mg/m^2) was administered with mannitol, or at a twofold larger total dosage (50 mg/m^2 per day for 4 days) in a 3% saline infusion. Carboplatin (300 mg/m^2) was administered in combination with 5-fluorouracil, and iproplatin was administered in dosages ranging from 216 to 388 mg/m^2. Enzymuria and proteinuria induced by cisplatin at a total dosage of 200 mg/m^2 on a divided schedule did not significantly differ from that observed for the single 100 mg/m^2 dose. Enzymuria and proteinuria induced by carboplatin and iproplatin were significantly less than that for cisplatin; however, one patient developed chronic tubular damage after three courses of carboplatin, and the acute tubular toxicity of iproplatin in one of 15 patients was exceptional. Our findings support the value of administering cisplatin in hypertonic saline on a divided schedule as a strategy to reduce acute tubular damage. Although carboplatin and iproplatin are less nephrotoxic than cisplatin, occasionally patients experience subclinical acute or chronic tubular damage that may lead to overt nephrotoxicity with continued therapy.

Introduction

Nephrotoxicity is the dose-limiting side-effect of cisplatin [21]. Therapeutic maneuvers to reduce nephrotoxicity include intensive parenteral hydration and mannitol-induced diuresis [14], infusion of cisplatin in a vehicle with a high chloride concentration [20, 24, 25], or the administration of uroprotective agents [27]. Hydration and diuresis reduce the incidence of clinically significant nephrotoxicity at conventional dosages (100 mg/m^2), and the use of 3% saline has led to the administration of high dosages (200 mg/m^2) that have proven clinically useful for several tumor types [10, 24, 25]. Numerous platinum analogues have been synthesized that may be equally effective at dosages that are less nephrotoxic. Carboplatin (*cis*-diamine (1, 1-cyclobutanedicarboxyatol) platinum, CBDCA, JM8) and iproplatin (*cis*-dichloro-*trans*-dihydroxy-bis-isopropylamine platinum IV, CHIP, JM9) are cisplatin analogues that have been found in phase I–II investigational trials to be less nephrotoxic than cisplatin by monitoring serum creatinine and creatinine clearance rates [3, 7]. However, creatinine determination, a reflection of glomerular filtration, is a relatively insensitive measure of drug-induced renal tubular damage.

Cisplatin-induced nephrotoxicity can be quantitated by monitoring urinary markers for tubular cell damage [1, 5, 8, 9, 15, 17]. Two widely used markers are urinary alanine aminopeptidase (AAP) and *N*-acetyl-β-D-glucosaminidase (NAG), high-molecular-mass enzymes that are localized within the microvilli and lysosomes of renal tubular cells, respectively [2, 18]. After damage to tubular cells, these enzymes are released into the urine. Cisplatin induces acute enzymuria and proteinuria in a sequence consistent with the development of acute tubular cell necrosis [12]. Total urinary protein concentrations increase because low-molecular-mass serum proteins are less efficiently reabsorbed by dysfunctional tubular cells, and the denuded tubular epithelium exudes protein [4].

We have monitored the relative magnitude of enzymuria and proteinuria associated with administration of cisplatin, carboplatin, and iproplatin. Our primary objectives were to evaluate the two cisplatin analogues for acute tubular nephrotoxicity and to compare the acute tubular damage induced by cisplatin in two clinically useful regimens.

Methods

Cisplatin, 100 mg/m^2, was administered over 6 h with prehydration consisting of 10 g/m^2 mannitol in 500 ml/m^2 5% glucose and 0.22% saline to children with solid tumors at 3–6 week intervals. These children had serum creatinine concentrations <1 mg/dl and had not received other nephrotoxic chemotherapy.

Adults with head and neck cancer received 200 mg/m^2 cisplatin (50 mg/m^2 per day for 4 days) at 4-week intervals [10]. Each dose was administered over 30–45 min in 250 ml 3% saline with saline hydration and furosemide diuresis. Urinary chloride concentrations attained during

* Supported in part by Biomedical Research Support grant RR05584 (MPG), Cancer Center Support (CORE) grant CA-21765, Childhood Solid Tumor Program Project grant CA-23099, American Lebanese Syrian Associated Charities and NCI N01-CM-07405

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each course ranged from 130 to 230 mEq/l, values similar to those reported by Corden et al. [6]. All patients had pretreatment creatinine clearances >60 ml/min.

Carboplatin, 300 mg/m^2, was administered i.–v. over 30 min to seven adults with head and neck cancer [11]. No pretreatment hydration was given. Each dose of carboplatin was followed by a 5-day continuous infusion of 5-fluorouracil, 1000 mg/m^2 per day. All patients had an initial creatinine clearance >50 ml/min and had received no prior chemotherapy.

Iproplatin was administered at 3-week intervals to 15 children with solid tumors, in dosages ranging from 216 to 388 mg/m^2 [28]. Each dose was administered in 250 ml 0.9% saline over 2 h. Although all patients had received prior therapy, none had received cisplatin, and all had serum creatinine concentrations <1.5 mg/dl. Two children had received abdominal radiation after unilateral nephrectomy. Patients were excluded from analysis if they concomitantly received aminoglycosides or amphotericin B.

Urine specimens were obtained before and daily for 1 week after administration of cisplatin, carboplatin, or iproplatin. Urinary concentrations of NAG and AAP were determined by modifications of spectrophotomeric methods [13, 16] for automated determinations on a Micro-KDA analyzer (American Monitor Corp, Indianapolis, Ind). Total urinary protein was measured with Coomassie brilliant blue (Bio-Rad Labs, Anaheim, Calif.). Enzyme and protein concentrations were expressed relative to the consentration of urinary creatinine to account for variations in urine output.

For each treatment group, a daily mean concentration was calculated for AAP, NAG, and total protein concentrations for each day beginning on the day before therapy. Also, for each course, the average marker concentrations were calculated for the 7-day period after drug administration. Increases over the pretreatment levels (average marker concentration minus the pretreatment concentration) were used for comparisons of enzyme and protein excretion. Values for courses of 100 mg/m^2 cisplatin were compared to those for each of the three other regimens by the Mann-Whitney test (two-sided), with the significance level adjusted by the Bonferonni method [22].

Results

We studied ten patients receiving their first two doses of cisplatin (100 mg/m^2). The daily mean AAP concentration increased briskly after cisplatin administration (Fig. 1) and remained elevated for 1 week. The daily mean NAG concentration increased more slowly than that of AAP,

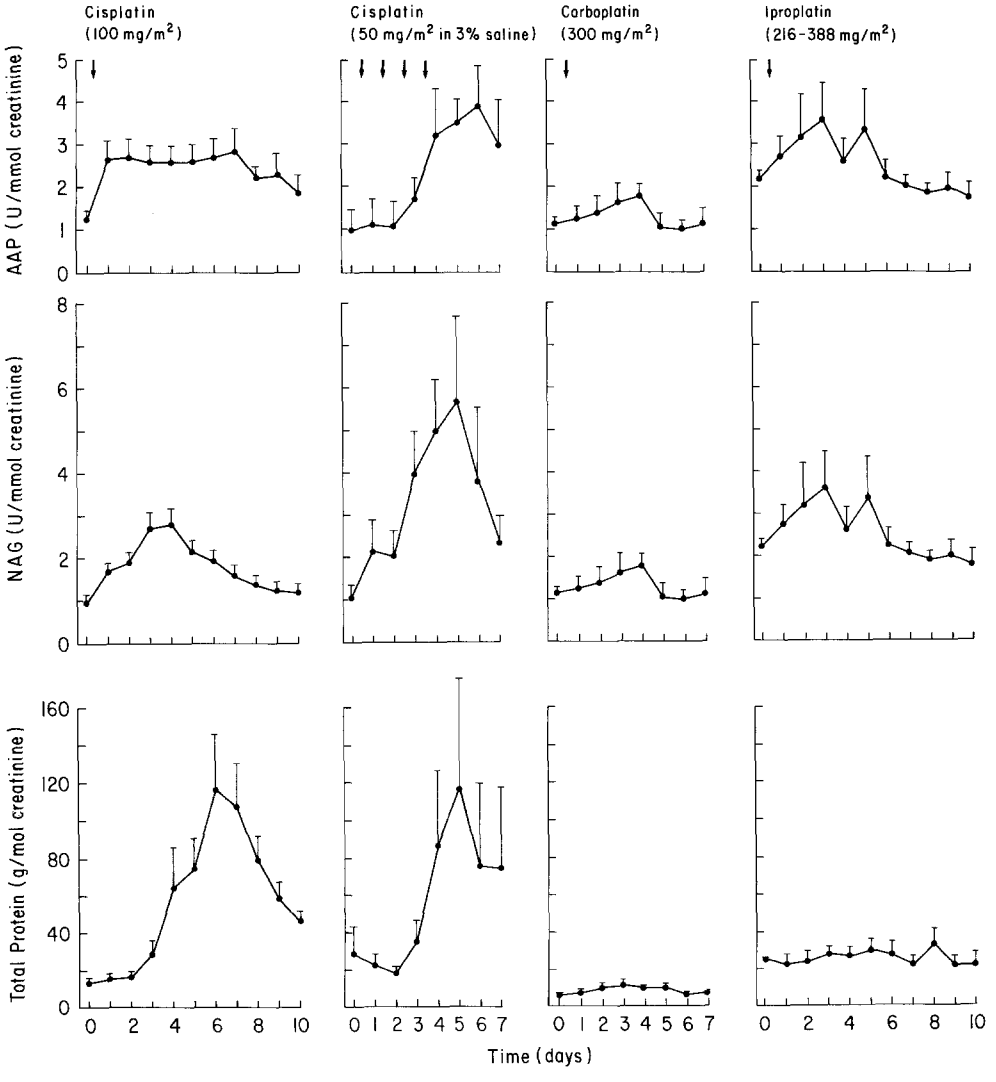

Fig. 1. Daily mean (+SEM) concentrations of urinary alanine aminopeptidase (AAP), *N*-acetyl-β-D-glucosaminidase (NAG), and total protein before and after 20 courses of cisplatin (100 mg/m^2) with mannitol, 5 courses of cisplatin (50 mg/m^2 per day for 4 days) in hypertonic saline, 10 courses of carboplatin, and 19 courses of iproplatin. The upper limits of the reference range for AAP and NAG are 3.0 and 1.1 units/mmol creatinine, and for total protein, 20 g/mol creatinine

Table 1. Average increases over baseline of urinary enzyme and protein excretion[a]

DRUG	NAG	AAP	Total protein
	Units/mmol creatinine Mean (±SD) *n*	Units/mmol creatinine Mean (±SD) *n*	g/mol creatinine Mean (±SD) *n*
Cisplatin (100 mg/m^2)	1.10 (0.60) 18	1.61 (1.14) 19	59.79 (49.30) 10
Cisplatin (200 mg/m^2)	2.39 (1.59) 5	1.40 (0.55) 5	27.42 (42.43) 5
Carboplatin	0.05* (0.38) 10	0.14* (0.44) 10	2.70* (4.13) 10
Iproplatin	0.27* (0.90) 18	0.40* (1.78) 18	2.89* (17.54) 18

[a] Values are the average marker concentrations for the 7-day period after drug administration minus the pretreatment concentration. Tests for differences of these values between cisplatin (100 mg/m^2) and each of the three other groups were done by the Mann-Whitney rank sum test (two-sided), with the significance levels adjusted by the Bonferonni method [22]; * $P<0.01$, after adjustment

achieving a peak level by the 4th day after cisplatin administration and then slowly declining towards the predose level. Total urinary protein excretion lagged behind that for NAG, achieving a peak level 1 week after cisplatin treatment. In some instances, AAP and NAG concentrations remained persistently elevated up to administration of the next cisplatin dose. However, urinary protein concentrations returned to pretreatment levels.

We evaluated high-dose cisplatin in three patients receiving their first course of 50 mg/m^2 per day for 4 days and one patient receiving his first two courses. Daily mean concentrations of AAP, NAG, and total protein increased in unison (Fig. 1), peaking on the day after the last dose of cisplatin. Increases in AAP, NAG, and total protein excretion over the pretreatment concentration did not significantly differ from those for 100 mg/m^2 cisplatin (Table 1).

In contrast to cisplatin, carboplatin did not acutely induce enzymuria or proteinuria (Fig. 1). The average marker concentrations did not significantly differ from pretreatment concentrations (Fig. 2) and were significantly ($P<0.01$) lower than those for 100 mg/m^2 cisplatin (Table 1).

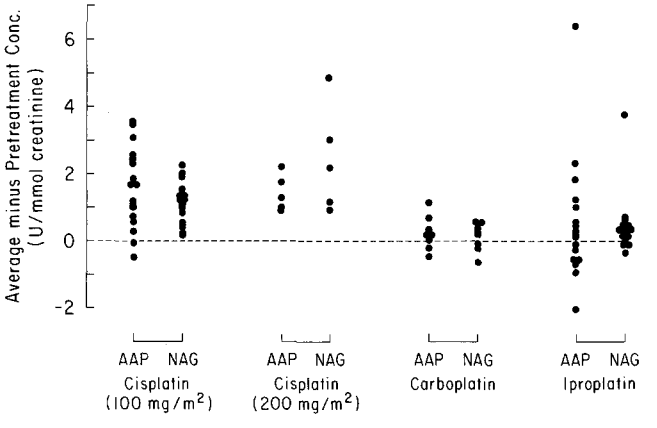

Fig. 2. Comparison of changes in AAP and NAG excretion associated with the four drug regimens. Values shown are the average enzyme concentrations for the 7-day period after drug administration minus the pretreatment concentration. *Dashed line* indicates no change from pretreatment concentration

Enzyme and protein excretion associated with iproplatin was also less than that following cisplatin (Table 1); however, one patient showed a more than threefold increase in average marker excretion over pretreatment concentrations (Fig. 2). This child and several others had high pretreatment enzyme levels, indicating preexisting renal tubular damage that could be ascribed in part to previous therapy or advanced disease. As a result of these increased pretreatment levels, total enzyme, but not protein, excretion was comparable to that for 100 mg/m^2 cisplatin (Fig. 1). However, average marker excretion did not significantly differ from pretreatment levels (Fig. 2).

Serum creatinine concentrations, measured at least 3 weeks after therapy, did not significantly differ from pretreatment concentrations for any treatment group.

Discussion

Our findings demonstrate that 200 mg/m^2 cisplatin can be administered over 4 days without a substantial increase in acute nephrotoxicity over that seen for a single 100 mg/m^2 dose of cisplatin; this supports the use of hypertonic saline as a strategy to reduce nephrotoxicity. In this study, carboplatin and iproplatin induced negligible acute tubular damage at hematologically toxic dosages. These compounds deserve further investigation to define the spectrum of their therapeutic activity and potential cumulative nephrotoxicity and ototoxicity.

Measurements of urinary markers of nephrotoxicity may be clinically useful to monitor acute [1, 5, 8, 9, 15, 17, 26] and chronic [12] tubular damage. For evaluation of acute nephrotoxicity, interpretation of these measurements depends in part upon the timing of specimen collection. For example, Pendyala et al. [26] reported that NAG excretion after iproplatin administration did not differ from that following cisplatin; however, these investigators obtained urine specimens for no more than 8 h after cisplatin administration. Figure 1 shows that obtaining specimens at 8 h is misleading, since NAG levels do not peak until several days after cisplatin administration.

The paucity of acute changes in enzymuria after carboplatin and iproplatin administration does not exclude the possibility of chronic renal damage after multiple courses. The chronic effect of retained intracellular species of platinum compounds may be more important than acute tubular nephrotoxicity [29]. The renal uptake of carboplatin and iproplatin reportedly does not differ substantially from that for cisplatin [19, 23]. Cisplatin induces chronic renal tubular damage in most patients, leading to presistent elevations of urinary NAG [12]. We have studied a patient who developed severe electrolyte abnormalities and a transient decrease in creatinine clearance after three courses of carboplatin. Of interest were chronically elevated urinary enzyme levels before the fourth course of carboplatin at a time when conventional determinations of the creatinine clearance rate and serum creatinine were in an acceptable range for retreatment. Electrolyte wasting and serum creatinine changes also followed the fourth course of carboplatin.

In addition to the total dosage administered, factors that may contribute to acute cisplatin-induced nephrotoxi-

city include the peak concentration and total duration of exposure to the drug. The increase in urinary AAP concentrations induced by cisplatin on a divided schedule in hypertonic saline was delayed in comparison to the immediate increase observed for the single high-dose cisplatin regimen (Fig. 1). This could reflect delayed sloughing of brush border microvilli, related in part to a protective effect of high urinary chloride concentrations or to lower peak cisplatin concentrations attained with the divided schedule. However, the chloride content of the vehicle for infusion and not the chloruresis itself is reported to ameliorate nephrotoxicity [20]. We are currently evaluating acute tubular nephrotoxicity in relation to the pharmacokinetics of cisplatin administered as a continuous infusion versus intermittent daily bolus.

Acknowledgements. We thank Mindy Lipson PNP and Vicki Kudla RN for clinical assistance, Susan Osborne and Barbara Blair for technical assistance. Specimens from patients receiving CHIP were from individuals who participated in Pediatric Oncology Group Study 8492.

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Received June 19, 1986/Accepted August 5, 1986