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/m²) was administered with mannitol, or at a twofold larger total dosage (50 mg/m² per day for 4 days) in a 3% saline infusion. Carboplatin (300 mg/m²) was administered in combination with 5-fluorouracil, and iproplatin was administered in dosages ranging from 216 to 388 mg/m². Enzymuria and proteinuria induced by cisplatin at a total dosage of 200 mg/m² on a divided schedule did not significantly differ from that observed for the single 100 mg/m² 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/m²), and the use of 3% saline has led to the administration of high dosages (200 mg/m²) 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/m², was administered over 6 h with prehydration consisting of 10 g/m² mannitol in 500 ml/m² 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/m² cisplatin (50 mg/m² 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
each course ranged from 130 to 230 mEq/l, values similar to those reported by Corden et al. [6]. All patients had pre-treatment 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 pre-treatment 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 spectrophotometric methods [13, 16] for automated determinations on a MicroKDA 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 concentration 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 Bonferroni 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-$\beta$-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](image-url)