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Cumulative renal tubular damage associated with cisplatin nephrotoxicity*

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Summary. We assessed the acute and chronic effect of multiple courses of cisplatin therapy on renal tubules by monitoring the urinary excretion of alanine aminopeptidase, *N*-acetyl-*β*-*D*-glucosaminidase, and total protein. Urine specimens were obtained before and after doses of cisplatin (90 mg/m^2) given to 12 patients. Each dose of cisplatin induced transient increases in enzyme excretion, followed by proteinuria 3–5 days later. Transient enzymuria after the last cisplatin dose was significantly greater than that after the first dose. Moreover, persistent increases in urinary *N*-acetyl-*β*-*D*-glucosaminidase and serum creatinine concentrations over pretherapy levels indicated chronic renal tubular damage. Our findings disclosed striking differences between patients in susceptibility to progressive nephrotoxicity.

Introduction

Nephrotoxicity is the principal side effect of cisplatin therapy [28]. Intensive parenteral hydration and mannitol diuresis ameliorate [17] but do not eliminate nephrotoxicity. Both acute and chronic pathological changes in the morphology of the renal tubules underlie cisplatin nephrotoxicity in animal models [4, 11, 34] and clinical studies [8, 13, 35]. Chronic reductions in glomerular filtration rates [8, 30, 39] and also renal magnesium [3, 18, 36, 37] and salt [26] wasting are related to the effects of cisplatin on renal tubules.

Whether the nephrotoxicity of cisplatin is cumulative remains controversial. Some investigators report that azotemia [35] and hypomagnesemia [3] depend upon the cumulative cisplatin dosage, whereas others have administered large cumulative dosages without appreciable nephrotoxicity [2, 7, 12, 41] or report that repeated doses of cisplatin are no more toxic than initial doses [30, 32, 41]. Differences in clinical observations have been ascribed in part to the insensitivity of measurements of serum creatinine in cachectic patients [2, 8, 31, 42]. Variation in cisplatin-induced nephrotoxicity may also be related to interactions between cisplatin and other antineoplastic agents [16], antihypertensive drugs [29], and aminoglycosides [14].

We describe a prospective investigation of cisplatin-induced nephrotoxicity in children receiving multiple doses of cisplatin. We have traced the acute and chronic effects of cisplatin on renal tubules by measurements of tubular proteinuria [6] and renal enzyme excretion [2, 9, 10, 21, 25, 41]. Changes in glomerular function have been assessed by serum creatinine determinations. We demonstrate that cisplatin is always acutely nephrotoxic, but that susceptibility to chronic and progressive toxicity varies widely among patients.

Methods

Urine specimens were obtained from 12 children with solid tumors, who received cisplatin (90 mg/m^2) at 4- to 10-week intervals. After i. v. pre-hydration consisting of 10 g/m^2 mannitol in 500 ml/m^2 5% glucose and 0.22% saline, cisplatin was administered over 6 h with 10 g/m^2 mannitol in 1000 ml/m^2 0.22% saline. The urine specimens were obtained before and for as many as 21 days after each cisplatin dose, stored at 4 °C, and centrifuged to remove amorphous salts prior to analysis. Urinary concentrations of NAG and AAP were determined by modifications of spectrophotometric methods [19, 23] for automated determinations on the Micro-KDA analyzer (American Monitor Corp, Indianapolis, Ind). Urinary total protein was measured with Coomassie brilliant blue (Bio-Rad Labs, Anaheim, Calif.). Enzyme and protein concentrations were expressed in relation to the concentration of urinary creatinine to account for variations in urine output. Paired data were compared by the Wilcoxon signed rank test (two-tailed probability).

Results

The clinical features of the children are summarized in Table 1. Patients did not receive nephrotoxins concomitantly with cisplatin therapy; however, two children received aminoglycosides within 90 days prior to therapy. The potential influence of mannitol on the urinary excretion of enzymes and protein was assessed in urine specimens obtained from three adults with isolated cerebral trauma who received mannitol to reduce cerebral edema. Results of NAG and AAP determinations obtained before and after mannitol infusion did not differ, in agreement

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Table 1. Clinical features of patients and percentage change (%) in serum creatinine and urinary NAG and AAP concentrations measured prior to the first and last doses of cisplatin

Clinical features of patients				Changes between first and last cisplatin dose[a]									
Patient no.	Age/ race/sex	Diagnosis	Other therapy[b]	Cisplatin (no of doses)	Creatinine			NAG			AAP		
					First	Last	%	First	Last	%	First	Last	%
1	13 W F	Brain tumor	G	6	0.4	1.1	175	0.5	1.5	200	1.3	2.4	85
2	13 W F	Germ cell tumor	A,B,C,VB,VC	7	0.4	1.0	150	1.4	5.0	233	1.2	12.0	900
3	13 W F	Sarcoma	D,H	5	0.5	0.9	80	0.5	2.6	420	3.9	3.4	−13
4	9 N F	Germ cell tumor	A,B,C,VB,VC	6	0.5	0.9	80	0.2	1.0	400	0.6	0.8	33
5	15 W M	PNET[c]	C,D,H	6	0.6	1.0	67	0.6	1.7	183	0.6	1.5	150
6	10 W F	Germ cell tumor	C,D	5	0.5	0.8	60	0.5	0.6	20	0.6	0.6	0
7	5 W M	Brain tumor	E	7	0.4	0.6	50	1.5	2.2	47	1.5	2.9	93
8	5 W M	Neuroblastoma	C,D,H,N,T	4	0.4	0.6	50	0.5	0.5	0	0.8	1.2	50
9	2 W M	Neuroblastoma	C,D,G,T	9	0.4	0.6	50	1.2	1.3	4	2.4	2.1	−12
10	11 W M	Brain tumor	E	2	0.4	0.5	25	1.6	3.8[d]	138	0.0	0.5	–
11	13 W F	Germ cell tumor	A,C,H,VC	3	0.5	0.6	20	0.5	0.8	60	0.7	0.9	29
12	10 W M	Brain tumor	E	2	0.6	0.7	17	0.5	0.5	0	1.2	1.4	17

[a] Patients ranked by change in serum creatinine. Units: creatinine (mg/dl); NAG and AAP (units/mmol creatinine)
[b] A, actinomycin D; B, bleomycin; C, cyclophosphamide; D, doxorubicin; E, etoposide; G, gentamicin; H, hydralazine; N, nephrectomy; T, teniposide; VB, vinblastine; VC, vincristine
[c] Primitive neuroectodermal tumor
[d] Measured after a surgical procedure

with reports of the negligible effect of mannitol infusions on NAG excretion in human volunteers [25] and in dogs [1]. Moreover, the addition to urine of cisplatin and other compounds that patients received during this study did not interfere with measurements of enzyme activity.

Cisplatin was acutely toxic to renal tubules, as evidenced by transient increases of all three urinary markers after each dose. These increases ranged from approximately 1.5- to 20-fold over the concentration measured before each dose. The temporal patterns of enzymuria and proteinuria differed (Fig. 1). AAP concentrations increased briskly after cisplatin administration, peaked most frequently within 48 h and then declined over the following week. The profile for NAG excretion was similar; however, NAG levels tended to peak 1 or 2 days later than those for AAP. In contrast to AAP and NAG, urinary total protein excretion increased more slowly, achieving peak concentrations between 4 and 8 days after cisplatin administration.

Figure 2 illustrates the progressive increases in urinary NAG concentrations observed in a patient who received six doses of cisplatin as single-agent therapy over a 160-day period (Table 1, patient 1). The increasing baseline values show cumulative renal tubular damage. The transient increases in NAG excretion after the last two doses of cisplatin are also greater than those after the first two doses, suggesting that repeated doses of cisplatin may be more nephrotoxic once the patient's tubules are damaged.

Similarly, evidence for cumulative nephrotoxicity was apparent from changes in serum creatinine concentrations and renal enzyme excretion measured prior to the first and last cisplatin doses administered (Table 1). Serum creatinine concentrations increased in all patients, albeit subclinically, from a mean value of 0.5 to 0.8 mg/dl, $P=0.003$. Mean AAP and NAG (2.50 and 1.79 units/mmol creatinine) concentrations after therapy were significantly greater ($P=0.046$ and $P=0.005$, $n=12$) than before therapy

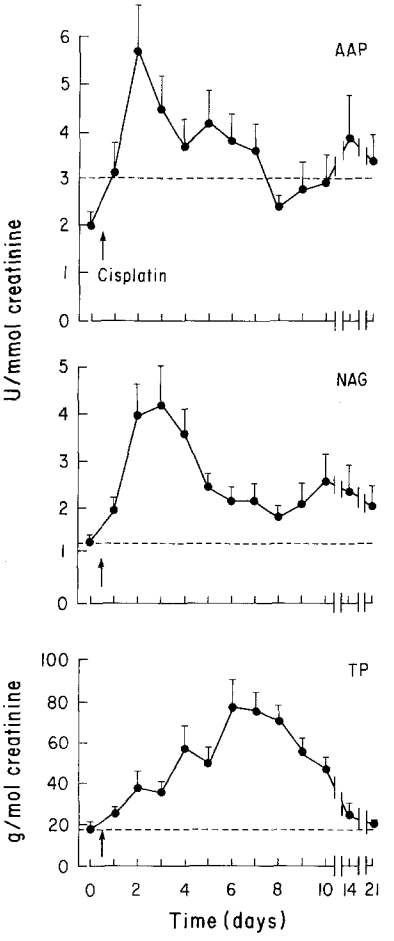

Fig. 1. Mean concentrations (±SEM) of alanine aminopeptidase (AAP), *N*-acetyl-*β*-*D*-glucosaminidase (NAG), and total protein (TP) in urine specimens obtained before and for as many as 21 days after 57 doses of cisplatin (90 mg/m^2). *Dashed line* indicates the upper limit of the normal range

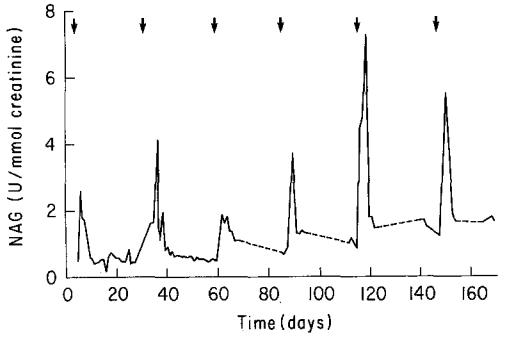

Fig. 2. Daily *N*-acetyl-*β*-*D*-glucosaminidase concentrations (NAG) in urine specimens obtained over a 6-month period from a child with a brain tumor who received six doses of cisplatin (90 mg/m^2). *Arrows* indicate days of cisplatin administration

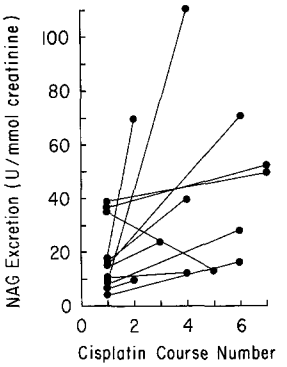

Fig. 3. Post-dose excretion of *N*-acetyl-*β*-*D*-glucosaminidase (NAG) after first and last dose of cisplatin. Post-dose excretion was estimated by integration of the area under the concentration-time curve for 10 days after each dose of cisplatin

(1.23 and 0.86 units/mmol creatinine). These changes in creatinine and enzymuria varied widely, however, and were not predictable from the cumulative cisplatin dosage. NAG excretion was a more reliable indicator of toxicity than AAP concentrations, which fluctuated near the upper limit of the normal range in most patients.

Declines in glomerular filtration were greater in patients who showed evidence for more renal tubular damage. Baseline urinary NAG levels were strikingly increased in patients 1 through 5, by an average of 277% as against 37% for the other children. Increases in serum creatinine were also largest in these five subjects, ≥ 0.4 mg/dl, leading to final concentrations ≥ 0.9 mg/dl and declines in the estimated creatinine clearance rate [38] to <95 ml/min by the end of the therapy.

We assessed the relative nephrotoxicity of the first and last doses of cisplatin by comparing the post-dose excretion of AAP, NAG, and TP. The post-dose excretion was estimated by integrating the area under the concentration-time curve for 10 days after each dose. Excretion of AAP and NAG, but not TP, was greater after the last dose of cisplatin than after the first dose (Table 2). However, the magnitude of increase varied widely between patients, as illustrated for NAG values in Fig. 3. The NAG excretion after the first dose of cisplatin in an exceptional patient who had recently received gentamicin therapy was greater than that after the last dose, suggesting a combined effect [14].

Table 2. Comparison of the post-dose excretion of urinary NAG, AAP, and TP after the first and last doses of cisplatin[a]

Marker	First dose	Last dose	*P* Value[b]
NAG	15.3 ±2.7	38.5 ±8.5	$P=0.007$ $n=12$
AAP	24.9 ±3.6	41.4 ±8.4	$P=0.025$ $n=12$
TP	407 ±52	525 ±116	$P=0.554$ $n=7$

[a] Post-dose excretion estimated by integration of the area under the concentration – time curve for 10 days after cisplatin dose. Values are means ±SEM; Units: NAG and AAP (units/mmol creatinine); TP (g/mol creatinine)

[b] Probability for paired data tested by two-sided Wilcoxon signed rank test

Discussion

By the use of urinary markers for nephrotoxicity, we have traced the acute and chronic effects of cisplatin therapy on renal tubular cells. The acute patterns of AAP, NAG, and TP excretion are consistent with reported histological descriptions of cisplatin-induced tubular cell necrosis. In rodent studies, progressive sloughing of the brush border membranes from the proximal renal tubules occurs during the first 3 days after cisplatin administration; widespread tubular necrosis is generally appreciable by the 3rd day [11, 34]. Analogously, the earliest evidence of tubular damage after cisplatin administration in our patients was the increased excretion of AAP, an enzyme localized to the microvilli of the brush border of the kidney [5]. The elevated AAP levels could originate from sloughing of these microvilli. Excretion of NAG, a high-molecular-mass lysosomal enzyme found in the proximal and distal renal tubules [27], lagged just behind the rise in AAP levels, and thus could represent a more severe derangement of tubular function. Urinary levels of NAG could increase as a result of enhanced secretion of lysosomal enzymes or extrusion of lysosomes from necrotic cells. The enzymuria cannot be ascribed to excretion of serum proteins, because proteinuria was not observed until several days later.

The proteinuria observed approximately 1 week after cisplatin treatment might be ascribed to exudation of protein from denuded tubular epithelium and less efficient reabsorption of low-molecular-mass serum proteins [6]. Urinary protein concentrations would also increase as necrotic tubular cells and casts were flushed into the urine. Obstruction of the renal tubules by necrotic epithelia could account for transient increases in serum creatinine concentrations. Although proteinuria could originate from a glomerular lesion, Sorensen et al. [39] reported only trace concentrations of urinary albumin revealed by a radial immunodiffusion technique after cisplatin administration. We previously measured urinary albumin concentrations after cisplatin administration by radial immunodiffusion and by a dye-binding method and found that the proportion of urinary protein that was albumin was generally $<50\%$ [15]. Hence, the form of proteinuria transiently

observed after cisplatin administration suggests a tubular rather than a glomerular lesion.

We assessed chronic nephrotoxicity by measuring levels of serum creatinine and urinary markers before and after cisplatin therapy. The observed increases in the serum creatinine to concentrations ≥ 0.9 mg/dl in several children reflect substantial declines in glomerular filtration rates. The increases in baseline enzymuria are consistent with observations by other investigators of persistent excretion of urinary NAG [9, 21] and AAP [2] after cisplatin administration. These chronically elevated levels could reflect increased synthesis and secretion of the enzymes or continuing tubular damage. Bulger et al. [4] reported that a single dose of cisplatin administered to rats was capable of inducing a relative increase in the numbers of proximal tubular-like cells having a brush border and numerous lysosomes. We are unaware of histological studies of human tissue designed to quantify such changes in renal tubular morphology. Nevertheless, the persistent enzymuria in our patients might be ascribed to analogous morphologic alterations that produce increased turnover of brush border and lysosomal enzymes. The greater degree of enzymuria following the last dose in comparison to the first dose was not parallelled by changes in proteinuria (Table 2), and hence suggests morphologic alterations rather than enhanced cisplatin toxicity. Regardless of the etiology, persistent enzymuria provides additional evidence of the chronic effect of cisplatin on renal tubules, also reflected by chronic and dosage-dependent induction of hypomagnesemia [3, 18, 37] and reductions in glomerular filtration rate.

Our findings agree with reports that cisplatin-induced nephrotoxicity can be progressive and dosage-dependent [3, 35, 40]. Nephrotoxicity associated with the administration of ≤ 270 mg/m^2 cisplatin is apparently subclinical, as none of the 12 children developed marked changes in renal function after three cisplatin doses. Larger cumulative dosages can be progressively nephrotoxic (Figs. 2 and 3), but we observed striking differences in cisplatin-induced nephrotoxicity in children receiving as much as 810 mg/m^2 cisplatin. This could reflect biologic variability or age differences between patients, interactions between cisplatin and other drugs, or other medical conditions. Womer et al. [42] reported great individual variation in cisplatin nephrotoxicity among children. They reported that one child tolerated 14 cisplatin doses (100 mg/m^2 per dose) with no decline in renal function, whereas the glomerular filtration rate of another child dropped to 6 ml/min per 1.73 m^2 after six doses. This led them to suggest that individual variations in renal sensitivity to cisplatin might be of far greater clinical significance than variations in technique of administration.

Age-dependent susceptibility to cisplatin nephrotoxicity has not been as thoroughly studied in children as in adults [20]. Womer et al. [42] reported that nephrotoxicity in their children was not age-dependent. The three youngest children in our study experienced minimal toxicity (Table 1). Kamalakar et al. [24] have suggested that the incidence of nephrotoxicity may be lower in children than in adults. Jongejan et al. [22] showed that cisplatin was less nephrotoxic in 3- to 4-week old rats than in >12-week old rats, and suggested that the larger relative renal mass in young rats as a proportion of total body mass might disperse the platinum, leading to less toxicity.

Although differences in tolerance to cisplatin could also be related to drug interactions or medical conditions, there were too few instances in our study for analysis. Four of our children received hydralazine; antihypertensive therapy that includes hydralazine is reportedly associated with increased cisplatin-induced nephrotoxicity [29]. Two children received bleomycin and vinblastine, a combination that has induced pathological narrowing of renal arterioles [16]. Another child had a uninephrectomy, which reportedly ameliorates cisplatin toxicity [20].

Urinary markers of nephrotoxicity have a role in clinical trials of antineoplastic chemotherapy. For example, the acute nephrotoxicity of different schedules of cisplatin administration [41] or of platinum analogues [33] has been compared by measurements of urinary markers for tubular damage. Moreover, chronic renal tubular damage can be evaluated by measurements of urinary NAG, providing information independent of that inferred from serum creatinine. Hence, combined measurements of these tubular and glomerular markers may be useful to monitor progressive nephrotoxicity in individual patients.

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