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Tubular nephrotoxicity during long-term ifosfamide and mesna therapy*

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Summary. The nephrotoxic effects of ifosfamide were assessed in 18 children and adolescents given cumulative doses of 32–112 g/m^2 (1.6 g/m^2 per day in sequential 5-day courses) with the uroprotectant mesna (1.2 g/m^2 per day). Tubular nephrotoxicity was evaluated by measuring the urinary concentrations of *N*-acetyl-β-D-glucosaminidase (NAG), alanine aminopeptidase (AAP), and total protein before and during sequential courses of therapy. Of 15 patients who had normal levels of tubular markers before ifosfamide therapy, only 1 developed a persistent increase in baseline values of the three tubular markers with the sixth course of ifosfamide. Although transient increases in the excretion of these markers were observed during each 5-day course of ifosfamide, the magnitude did not increase over sequential courses in these 15 patients. Of the remaining three patients who had increased NAG levels before ifosfamide therapy, two showed a progressive increase in enzymuria and proteinuria, and serum creatinine concentrations increased in a single patient who had obstructive uropathy. Our data suggest that children with normal renal function can be given large cumulative amounts of ifosfamide in fractionated doses with little risk of progressive clinical nephrotoxicity.

Introduction

Ifosfamide has been shown to be active against testicular carcinoma and pediatric soft-tissue sarcomas, osteosarcoma, and Ewing's sarcoma [17]. The introduction of mesna to protect the urothelial tract has eliminated hemorrhagic cystitis as a dose-limiting toxic effect of this drug [3]. Mesna also appears to reduce the incidence of severe ifosfamide-induced nephrotoxicity [5], although no controlled study has evaluated the effect of systematic variations in the dosages of either mesna or ifosfamide. The administration of high-dose ifosfamide as a bolus or by brief infusion has been associated with severe renal toxicity, despite mesna administration [5, 6, 14–16]. In contrast, the incidence of overt renal toxicity is low when ifosfamide is given in daily fractionated doses, with or without mesna [17]. However, subclinical, transient tubular proteinuria, hyperaminoaciduria, and apparent serum bicarbonate loss are observed when ifosfamide is given in fractionated doses [1, 2, 7, 9, 12]. The present study was designed to determine whether these transient tubular nephrotoxic effects lead to progressive renal impairment during long-term therapy.

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Patients and methods

We studied a subgroup of patients enrolled in a phase II trial of ifosfamide [13]. For the present study, patients were required to have received four or more courses of ifosfamide and mesna and to agree to urine collection during each course of ifosfamide therapy. None of the 18 patients received aminoglycosides or other antineoplastic agents during ifosfamide therapy, and all had two functioning kidneys. They had received previous therapy with one or more of the following agents: aminoglycosides ($n = 3$), bleomycin ($n = 1$), cisplatin ($n = 8$), cyclophosphamide ($n = 11$), dactinomycin ($n = 2$), doxorubicin ($n = 14$), etoposide ($n = 3$), high-dose methotrexate ($n = 5$), teniposide ($n = 1$), or vincristine ($n = 2$); 4 had received abdominal irradiation. Among 75 patients in the phase II investigation who did not meet the criterion of four or more treatment courses, ifosfamide therapy was discontinued due to early death ($n = 5$), withdrawal from the protocol ($n = 1$), or failure to respond to therapy ($n = 69$), but not nephrotoxicity.

Ifosfamide (1.6 g/m^2) injected intravenously over 15 min was followed by three intravenous infusions of mesna (400 mg/m^2) at 15 min, 4 h and 6 h. Each course consisted of five daily doses of ifosfamide, for a total of 8 g/m^2. Courses were given at 3- to 4-week intervals.

Before each course of ifosfamide, blood was drawn for determination of serum creatinine concentrations and urine specimens were obtained to analyze concentrations of total urinary protein as well as *N*-acetyl-β-D-glucosaminidase (NAG) and alanine aminopeptidase (AAP), enzymes localized within the lysosomes and brush border of proximal renal tubular cells, respectively. Daily urine specimens were also obtained during each course of ifosfamide to assess drug-induced tubular enzymuria and proteinuria. Concentrations of urinary markers were determined by the adaptation of spectrophotometric procedures to an automated clinical analyzer (American Monitor Perspective, Indianapolis, Ind) [7]. Enzyme and protein measurements were expressed relative to the urinary creatinine concentration to adjust for variations in urinary output.

As a measure of acute ifosfamide-induced tubular proteinuria, we calculated the average increase over the precourse value of NAG, AAP, and total protein concentrations within each 5-day treatment course. Differences between sequential, paired courses in individual patients were compared by the sign-rank test. Persistent tubular proteinuria was defined as precourse values above the normal range for NAG (>1.5 IU/mmol creatinine), AAP (>3.0 IU/mmol creatinine), or total protein (>0.18 g/g creatinine) before three sequential courses of ifosfamide. Patients who had increased urinary concentrations of any of the three markers before their initial course of treatment were considered to have preexisting renal tubular damage.

Results

Total ifosfamide dosages, initial and final NAG and serum creatinine levels, and patient characteristics are given in Table 1. A total of 15 patients had normal serum creatinine, urinary enzyme, and urinary protein concentrations before their initial course of treatment. Serum creatinine concentrations did not increase over the period of ifosfamide therapy in any of these 15 patients. Moreover, only one subject (patient 14) showed persistent increases in precourse NAG, which occurred with his final three treatment courses; this patient's urinary total protein and AAP levels were also persistently elevated (data not shown). NAG increased twofold in three other cases (patients 13, 15, and 17), but only before their final course. The range of values for NAG excretion during each course of ifosfamide treatment for these 15 patients is shown in Fig. 1. According to the sign-rank test, there was no significant trend in the magnitude of excretion of NAG, AAP, or total protein in individual patients over sequential courses.

In patients 4, 10, and 11, concentrations of urinary enzymes but not total protein were elevated before the initial course of drug treatment. Patients 4 and 10 subsequently developed proteinuria (total urinary protein 2.4 and 1.1 g/g creatinine, respectively) and further increases in NAG excretion (Table 1) by their final course of ifosfamide. Patient 4 also had an elevated preifosfamide serum creatinine concentration, due in part to 630 mg/m^2 of prior cisplatin therapy; by the fourth course of therapy, the concentration increased from 1.6 to 2.7 mg/dl in association with rapidly progressive pelvic disease and evidence of obstructive uropathy obtained by radiologic imaging studies.

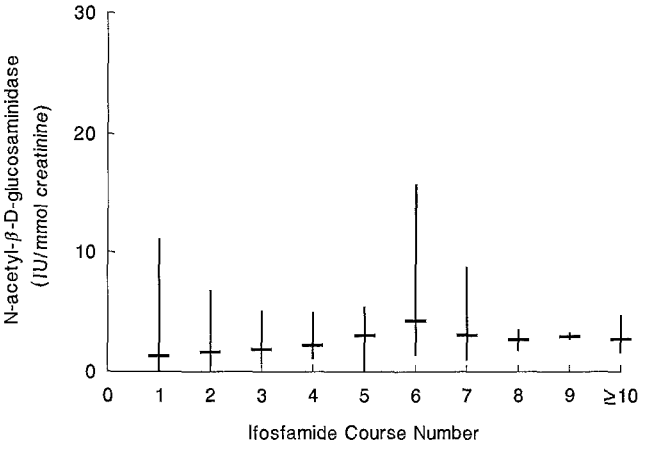

Fig. 1. Range and median (*bar*) values for NAG excretion during courses of ifosfamide for 15 patients with no preexisting tubular damage

Discussion

Reports of ifosfamide-induced renal impairment reflect differences in the duration and dosage of drug and in patient susceptibility, especially among those with compromised renal function due to tumor or recent nephrotox-

Table 1. Clinical and laboratory features

Patient number	Cumulative ifosfamide dosage (g/m^2)[a]	Diagnosis	Age (years)	NAG[b] (IU/mmol creatinine)		Serum creatinine (mg/dl)	
				Initial	Final	Initial	Final
1	32	Ewing's sarcoma	15	0.5	0.8	0.9	0.8
2	32	Osteosarcoma	16	0.8	0.5	1.3	1.1
3	32	Glioblastoma	19	1.1	0.7	0.9	0.8
4[c]	32	Neuroepithelioma	15	3.7	11.7	1.6	2.7
5	32	Neuroblastoma	5	1.3	0.6	0.8	0.8
6	32	Fibrosarcoma	3	1.4	0.9	0.7	0.7
7	32	Osteosarcoma	11	0.8	1.0	0.8	0.8
8	32	Osteosarcoma	11	0.8	1.4	0.7	0.6
9	40	Sarcoma	3	1.3	0.5	0.5	0.5
10[c]	40	Schwannoma	14	5.3	9.1	1.3	0.6
11[c]	48	Osteosarcoma	19	2.7	1.9	1.2	1.2
12	48	Osteosarcoma	10	1.2	1.3	0.7	0.6
13	64	Ewing's sarcoma	14	1.2	2.3	0.8	0.8
14	64	Osteosarcoma	5	1.2	4.6	0.9	0.8
15	64	Osteosarcoma	22	1.3	2.7	0.7	0.6
16	88	Schwannoma	16	1.1	1.3	1.0	1.0
17	96	Rhabdomyosarcoma	5	0.9	3.6	0.7	0.7
18	112	Schwannoma	16	1.0	1.6	1.1	0.9

[a] 8 g/m^2 per 5-day course
[b] Measured before the initial and final courses of ifosfamide
[c] Patients with elevated urinary levels of NAG before ifosfamide therapy

ic therapy [4, 6, 8, 10, 14, 15]. Tubular damage presenting as Fanconi's syndrome or proximal tubular acidification defect has been reported in adults after single doses of 5 g/m^2 ifosfamide without mesna [10] or multiple doses of 8 g/m^2 ifosfamide despite the coadministration of mesna [14], and, in a 2-year-old boy, 1 year after treatment with four doses of 3 g/m^2 ifosfamide with mesna [11].

Although we observed acute tubular proteinuria during sequential courses of ifosfamide, this acute nephrotoxicity was appreciable only by the use of sensitive markers of tubular damage and was reversible after as many as 14 courses of fractionated doses. None of these children required discontinuation of therapy due to nephrotoxicity. The single patient who developed increased serum creatinine concentrations had obstructive uropathy. Only one patient who did not have preexisting renal impairment developed persistent tubular proteinuria that was subclinical. The mesna dose used in this study was only 75% that of ifosfamide, and the mesna was given after completion of the ifosfamide infusion. We conclude that large cumulative doses of fractionated ifosfamide and mesna therapy can be given to children who have normal renal function with little risk of progressive nephrotoxicity. The value of more extensive mesna therapy by continuous or intermittent infusion merits further study in patients who have compromised renal function.

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