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Renal function in children and adolescents following 72 g/m² of ifosfamide

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Abstract. A detailed analysis of the renal function of 18 children and adolescents aged 7–20 years (median, 16 years) was performed at least 3 months following the completion of a non-platinum-containing chemotherapy regimen with a total dose of 72 g/m² of ifosfamide. Ifosfamide had been given as a 1-h infusion of 1.8 g/m² daily for 5 days at 5- to 6-week intervals along with mesna uroprotection. The mean glomerular filtration rate (GFR) as determined by inulin clearance was 100 ml/min/1.73 m². Although 6 of 18 patients had GFRs below normal, the lowest was only 18% less than the lower limit of normal and would not account for any clinical compromise. The renal plasma flow and filtration fraction were normal. Proximal tubular function evaluation revealed normal fractional excretion (FE) of glucose; normal mean tubular maximum phosphate reabsorption per GFR (TMP)/GFR values; high FE of urate (17%); and mild, generalized aminoaciduria in 6 of the 18 patients. Distal tubular function evaluation showed normal 24-h urinary calcium levels and FE of magnesium as well as normal urinary osmolality after water deprivation. Two patients had mild proteinuria. The findings in this study are encouraging in terms of the lack of clinically significant renal abnormalities observed in patients who had received a cumulative dose of 72 g/m² of ifosfamide.

Key words: Ifosfamide – Nephrotoxicity – Children

Introduction

Ifosfamide has now become a standard part of many combination chemotherapy regimens for pediatric patients with a wide variety of malignancies. With its increasing use, however, more reports are appearing in the literature on potentially severe ifosfamide-induced nephrotoxicity ranging from mild tubular and/or glomerular dysfunction to severe Fanconi's syndrome with osteodystrophy. These cases have recently been summarized in an extensive review by Skinner et al. [5]. Despite the anecdotal reports, there have been few systematic evaluations of the renal function of children upon completion of therapy with ifosfamide.

Suarez et al. [6] performed detailed renal testing 1 year after the completion of therapy in 74 patients who had received total cumulative doses of 36 or 60 g/m²; 6 g/m² was given over 2 days in each course. In all, 5% of the group developed major toxicity resulting in Fanconi's syndrome and a similar number developed reduced phosphate reabsorption without Fanconi's syndrome. Skinner et al. [4] performed a cross-sectional evaluation in nine patients and compared the evaluations to those performed either at the end of treatment (six patients) or 5–15 months posttreatment (three patients). They found a decrease of greater than 20% in the glomerular filtration rate (GFR, as measured by [^{51}Cr]-ethylenediaminetetraacetic acid plasma clearance) in five patients, one patient with increased proximal tubular toxicity, and one patient with renal tubular acidosis (RTA). In these patients, ifosfamide had been given at 3 g/m² daily for 2–3 days.

Goren et al. [2] evaluated 18 children given cumulative doses of 32–112 g/m² of ifosfamide before and during sequential courses of therapy (no study was done after the completion of all therapy). Tubular nephrotoxicity was evaluated by measuring the urinary concentrations of *N*-acetyl-β-D-glucosaminidase, alanine aminopeptidase, and total protein. 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. Glomerular filtration and tubular function parameters were not measured in this study.

The goal of the present study was to evaluate extensively the proximal, distal, and overall tubular function as well as the glomerular function in children and adolescents who received a total dose of 72 g/m² of ifosfamide at

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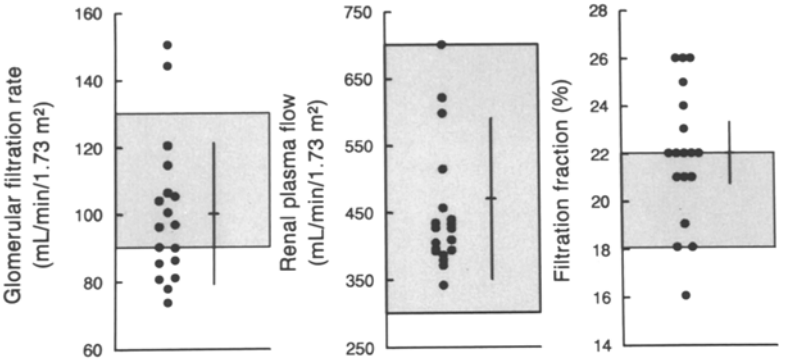

Fig. 1. Glomerular function parameters. *Dots* represent actual patient values; *shaded areas* indicate the normal range; *lines* represent mean values ± 1 SD

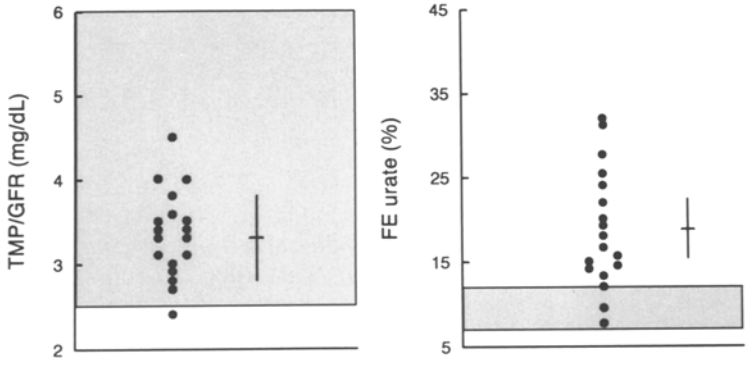

Fig. 2. Proximal tubular function parameters. *Dots* represent actual patient values; *shaded areas* indicate the normal range; *lines* represent mean values ± 1 SD

least 3 months following the completion of a non-platinum-containing chemotherapy regimen.

Patients and methods

A total of 18 patients (10 females and 8 males) were evaluated at least 3 months (range, 4–24 months; mean, 10 months) following the completion of chemotherapy with regimens that included a total dose of 72 g/m² ifosfamide. The patients ranged in age from 7 to 20 years (median, 16 years). In all, 9 patients had osteosarcoma; the others had rhabdomyosarcoma (4), Ewing's sarcoma (4), or synovial sarcoma (1). Patients with osteosarcoma had also received treatment with high-dose methotrexate (12 g/m², for a total of 8–16 courses) and Adriamycin at a dose of 75 mg/m² with each course of ifosfamide.

Patients with sarcomas other than osteosarcoma also received therapy with six courses of vincristine, Adriamycin, and cyclophosphamide given in an alternating sequence with etoposide and ifosfamide. No patient received platinum or aminoglycosides, and only one patient received a brief treatment course with amphotericin for candidal esophagitis. No radiation therapy was delivered to areas that would include the kidneys. All patients had presumably normal renal function at the onset of treatment as determined by prechemotherapy serum creatinine and/or creatinine clearance.

Ifosfamide was given as a 1-h infusion of 1.8 g/m² daily for 5 days at 5- to 6-week intervals. Mesna was given at a dose of 360 mg/m² along with ifosfamide, as a 3-h infusion immediately following ifosfamide, and then as 15-min boluses every 3 h for three (in sarcoma patients) or six (in osteosarcoma patients) additional doses. The first bolus dose was given immediately upon completion of the 3 h infusion.

Glomerular function was assessed by performing standard inulin clearance [3]. Renal blood flow was determined by *p*-aminohippuric acid (PAH) clearance [3]. Proximal tubular function was evaluated by the measurement of serum and urine concentrations of glucose, uric acid, and phosphate. Fractional excretions of glucose, phosphate [as tubular maximum phosphate reabsorption per GFR (TMP)/GFR], and uric acid were calculated. The fractional excretion of magnesium was calculated and the serum bicarbonate level was measured with investigation of urinary bicarbonate excretion only in patients who were acidotic. The 24-h excretion of calcium, amino acids, and protein was measured in all patients. Urinary osmolality following overnight water deprivation was determined so as to evaluate the concentrating ability of the nephron. Routine urinalysis was performed, as was a general physical examination with measurement of blood pressure.

Results

Glomerular function

The glomerular function analysis is detailed in Fig. 1. The mean GFR was normal at 100 ml/min/1.73 m². In all, 6 of 18 patients had GFRs lower than normal; however, the lowest value was only 18% below the lower limit of normal. The renal plasma flow and filtration fraction were also normal, with mean values being 470 ml/min/1.73 m² and 22%, respectively.

Proximal tubular function

The fractional excretion (FE) of glucose was normal in all patients, with the mean value being 0.18% (range, 0–0.3%). The mean TMP/GFR value was 3.3 mg/dl (normal). The mean FE of urate was high at 17%, with only two patients showing levels in the normal range. Figure 2 depicts the TMP/GFR values and FE of urate on a scattergram. The 24-h quantitative urinary amino acid excretion showed mild generalized aminoaciduria in 6 patients (more than twice the normal excretion of 12 or more of the 28 amino acids measured).

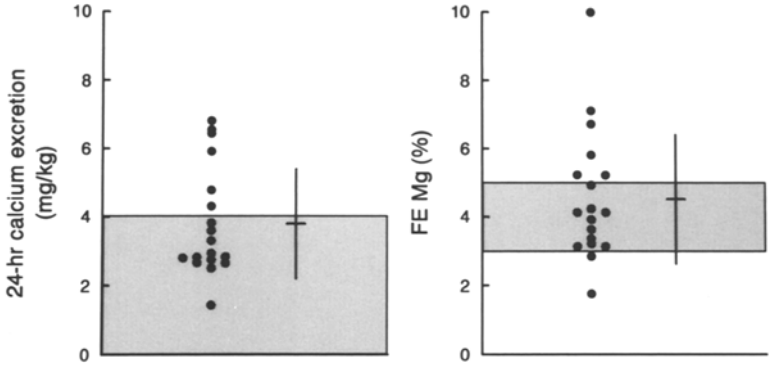

Fig. 3. Distal tubular function parameters. *Dots* represent actual patient values; *shaded areas* indicate the normal range; *lines* represent mean values ± 1 SD

Distal tubular function

The mean 24-h urinary calcium excretion and mean FE of magnesium were 3.8 mg/kg and 4.5%, respectively; the actual values are depicted in the scattergram in Fig. 3. Urinary osmolality after overnight water deprivation was >600 mosmol/kg in all but one patient. This patient had a urinary osmolality of 578 mosmol/kg and was not thought to have maintained water deprivation overnight.

Other findings

The 24-h urinary protein excretion was normal in all but two patients. Serum calcium, phosphorus, bicarbonate, and alkaline phosphatase levels were normal in all patients. There was no correlation between the various abnormal parameters noted among the patients (i.e., those patients with the lowest GFRs were not necessarily the same group who had elevated calcium or amino acid excretion). All patients had normal blood pressure.

Discussion

In this patient population, there were abnormalities suggestive of mild tubular and glomerular dysfunction, although none was clinically significant. Elevation of the FE of urate was a constant finding in all the patients. The observation that urate excretion did not correlate with calcium or sodium excretion suggests an uncoupling of these transport processes. However, urate handling is very complex, and it is difficult to localize renal damage to any particular part of the nephron on the basis of urate-handling abnormalities. The slight, generalized aminoaciduria noted in 6 of 18 patients would suggest a mild proximal tubular leak; however, the normal glucose and phosphate handling suggests that the proximal tubular dysfunction is minimal. The urinary acidification and bicarbonate reabsorption capacity was not measured utilizing bicarbonate infusion because none of the patients demonstrated a metabolic acidosis. The somewhat low GFRs are perhaps the most notable laboratory abnormality found. However, the lowest GFR observed would not cause the patient to be compromised and would not result in dose adjustment of any routinely used drugs.

The findings in the current study are encouraging in terms of the lack of significant abnormalities observed in patients who had received a cumulative dose of 72 g/m^2 of ifosfamide. Several differences between this population of children and those evaluated in other studies are worth highlighting. Reports describing significant tubular dysfunction after ifosfamide have mainly involved younger patients. The youngest patient in the present study was 7 years of age. Many ifosfamide-containing regimens involve the administration of ifosfamide every 3 weeks. The minimal ifosfamide treatment interval for the current group of patients was 5 weeks, perhaps allowing for interval recovery between treatments and, possibly, less cumulative insult to the nephron. None of the patients on the current protocol had received platinum, which is known to have an additive effect on the nephrotoxicity of ifosfamide [1].

Future cross-sectional studies of ifosfamide-induced nephrotoxicity should address the contribution of age, prior or concurrent platinum administration, treatment interval, dose per day, and method of infusion of ifosfamide (continuous versus 1-h infusion) to renal toxicity. More information is needed about the ultimate-long term (5–10 years) effect of ifosfamide on the nephron.

References

1. Goren MP, Wright RK, Pratt CB, Horowitz ME, Dodge RK, Viar MJ, Kovnar EH (1987) Potentiation of ifosfamide nephrotoxicity, hematotoxicity, and tubular nephrotoxicity by prior *cis*-di-amine-dichloro-platinum(II) therapy. Cancer Res 47: 1457–1460
2. Goren MP, Pratt CB, Viar MJ (1989) Tubular nephrotoxicity during long-term ifosfamide and mesna therapy. Cancer Chemother Pharmacol 25: 70–72
3. Liedtke RR, Duarte CG (1980) Laboratory protocols and methods for the measurement of glomerular filtration rate and renal plasma flow. In: Duarte, CG (ed) Renal function tests, clinical laboratory procedures and diagnosis. Little, Brown and Company, Boston, pp 49–63
4. Skinner R, Pearson ADJ, Price L, Coulthard MG, Craft AW (1990) A follow-up study of ifosfamide nephrotoxicity in children and adolescents (abstract 208). Med Pediatr Oncol 18: 422
5. Skinner R, Sharkey IM, Pearson ADJ, Craft AW (1993) Ifosfamide, mesna, and nephrotoxicity in children. J Clin Oncol 11: 173–190
6. Suarez A, McDowell H, Niaudet P, Comoy E, Flamant F (1991) Long-term follow-up of ifosfamide renal toxicity in children treated for malignant mesenchymal tumors: an International Society of Pediatric Oncology report. J Clin Oncol 9: 2177–2182