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Late Reversibility of Chronic Ifosfamide-Associated Nephrotoxicity in a Child

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Although reversibility of acute ifosfamide-induced nephrotoxicity is well documented, there is a paucity of data concerning the long-term outcome of chronic renal toxicity, and full recovery from established damage has not been reported. A 4-year-old boy presented with hypophosphatemic rickets 9 months after completion of combination chemotherapy (including ifosfamide) for prostatic rhabdomyosarcoma. Further investigation confirmed glomerular and generalised tubular dysfunction with a Fanconi syndrome. However, serial investigation over the next 4 years revealed complete and sustained recovery of this chronic nephrotoxicity.

Key words: renal toxicity, tubular dysfunction, recovery of renal function

INTRODUCTION

Partial or complete recovery from acute ifosfamide nephrotoxicity is well documented in both adults and children [1,2]. However, despite several reports of the occurrence of chronic nephrotoxicity after treatment with ifosfamide in children [3–7], there are few published data concerning the degree of reversibility of such damage [6]. Partial recovery from chronic nephrotoxicity has been reported [8,9], but complete recovery has not yet been clearly documented. Therefore the long-term consequences of chronic ifosfamide-induced nephrotoxicity in children remain uncertain. A child is reported in whom severe chronic ifosfamide-induced nephrotoxicity was followed by complete and sustained recovery of renal function over a 4-year period.

CASE REPORT

A 23-month-old boy presented with acute urinary retention due to a prostatic rhabdomyosarcoma. He was treated with chemotherapy for a total of 18 months, including cisplatin (total 359 mg/m^2) during the first 6 months and ifosfamide (total dose 177 g/m^2; 9 g/m^2/course as 72-hour continuous infusion) during the next 12 months (see Fig. 1). Serum phosphate, bicarbonate, and creatinine concentrations and alkaline phosphatase activity were normal when ifosfamide was commenced; glomerular filtration rate (GFR) was not measured at this time. Vincristine, cyclophosphamide, doxorubicin, actinomycin D, and etoposide were also given. In addition, he received radiotherapy to the prostate area, but his kidneys were not included in the treatment field.

At 4 years of age, 10 months after completing treatment, he was noted to have difficulty in walking due to bilateral genu valgum. An X-ray of his knees showed signs of rickets and secondary hyperparathyroidism. Renal function studies (see Table I) showed a reduced GFR and widespread renal tubular damage leading to a Fanconi syndrome comprising glycosuria, phosphaturia, hypophosphatemia, hypokalemia, acidosis, and low urine osmolality. Serum alkaline phosphatase activity was raised. In retrospect, he had been hypophosphatemic since the completion of his ifosfamide.

He was started on oral phosphate supplements. His serum phosphate concentration slowly improved despite poor compliance with treatment, and the serum alkaline phosphatase activity fell. Treatment with oral phosphate supplements was discontinued 10 months after diagnosis of rickets. However, difficulty in walking and genu valgum persisted, eventually necessitating corrective bilateral tibial osteotomies.

Subsequent investigations showed progressive improvement of renal function (see Table I and Fig. 1). GFR, serum phosphate, potassium, and bicarbonate concentrations, alkaline phosphatase activity, and the renal tubular threshold for phosphate all returned to normal by 34 months after the completion of ifosfamide treatment, and by 57 months the fractional excretion of glucose was only minimally elevated. Radiological examination of his knees 2 years after diagnosis of rickets was normal.

DISCUSSION

Details of this patient have been published previously after he presented with ifosfamide-induced hypophos-

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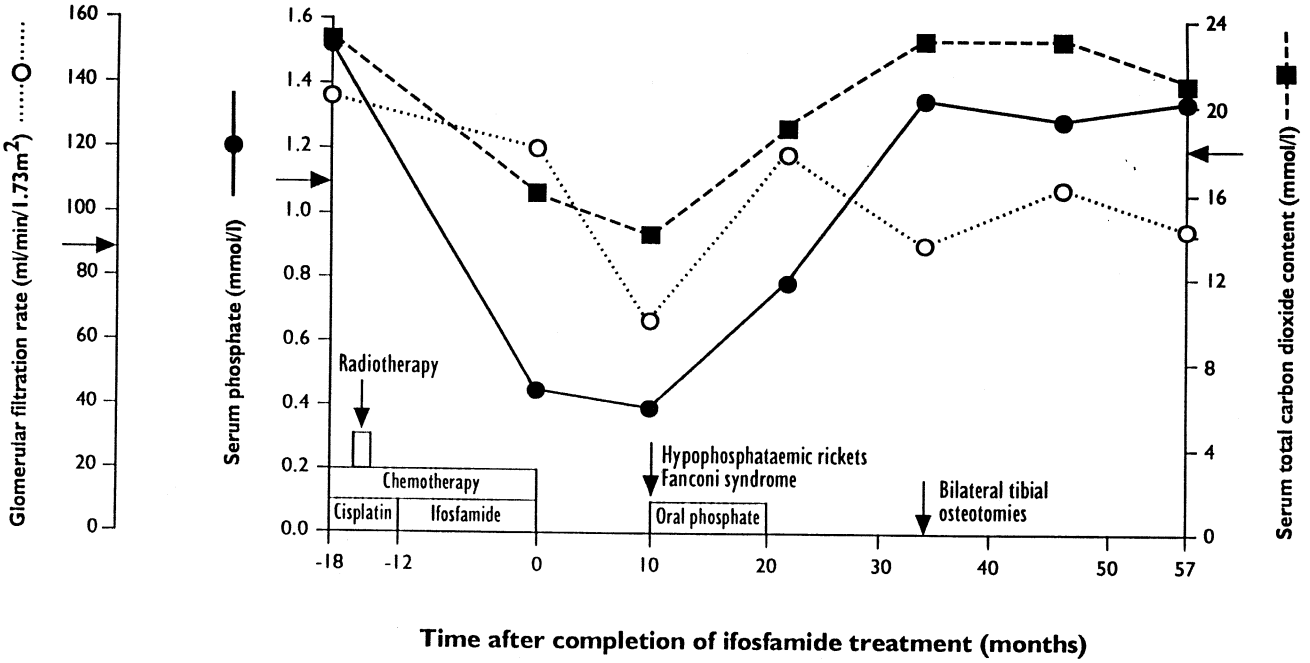

Fig. 1. Time course of onset and resolution of nephrotoxicity, in relation to ifosfamide chemotherapy. The GFR, serum phosphate, and serum bicarbonate (total carbon dioxide) concentrations are shown.

TABLE I. Results of Serial Renal Function Studies*

	Months after completing ifosfamide treatment				
	10	22	34	46	57
GFR (ml/min/1.73 m^2)[a]	66	118	90	108	95
Serum concentrations of					
Phosphate (mmol/litre)	0.39	0.78	1.35	1.29	1.34
Bicarbonate (mmol/litre)	14	19	23	23	21
ALP (U/I)	475	498	297	266	279
Urine					
FE glucose (%)	41.6	4.2	1.2	0.5	0.2
Tm_p/GFR (mmol/litre)	0.04	0.68	1.31	1.18	1.15
Early morning osmolality (mOsm/kg)	329	654	647	642	751
Normal values					
GFR (ml/min/1.73m^2)			>87		
Serum concentrations of					
Phosphate (mmol/litre)			1.10–1.85		
Bicarbonate (mmol/litre)			20–26		
ALP (U/I)			<350		
Urine					
FE glucose (%)			<0.1		
Tm_p/GFR (mmol/litre)			1.00–1.65		
Early morning osmolality (mOsm/kg)			>600		

*ALP, alkaline phosphatase activity; FE, fractional excretion; Tm_p/GFR, renal tubular threshold for phosphate. For FE and Tm_p/GFR see reference [12] for details of calculation. The above normal values are obtained from reference [12] except for FEglucose (English MW, Skinner R, unpublished observations) and Tm_p/GFR [13].
[a]GFR measured from plasma clearance of ^{51}Chromium-labelled EDTA.

phatemic rickets [3]. He had also received treatment with cisplatin. However, the pattern of renal toxicity with a Fanconi syndrome, the absence of hypomagnesemia, and the timing of onset suggested that ifosfamide was the principal cause of nephrotoxicity. The initial severity of toxicity may have been related to the use of a high cumulative ifosfamide dose at a relatively young age [6]. Improvement in ifosfamide-induced hypophosphatemia,

with healing of rickets without specific treatment, has been reported previously [9]. Furthermore, amelioration of the biochemical manifestations of the Fanconi syndrome within a few months of onset in some children has been described [8]. However, *complete* recovery from severe chronic glomerular and tubular impairment in children has not been documented clearly in the literature. This child has been followed for 5 years since his presentation with symptomatic hypophosphatemic rickets accompanied by evidence of glomerular and generalised tubular dysfunction. During this period, full recovery of renal function has occurred, with radiological evidence of complete healing of rickets. Several studies have suggested that previous or concurrent treatment with cisplatin increases the incidence and severity of ifosfamide-induced nephrotoxicity [10,11], and there is no obvious reason to expect a greater degree of reversibility of ifosfamide nephrotoxicity in children who have also received cisplatin.

However, follow-up investigations in our pediatric oncology unit have shown that this degree of reversibility of chronic ifosfamide-induced nephrotoxicity is rare, and that most children demonstrate no improvement in renal damage over the first 2 years after completion of ifosfamide treatment (Skinner R, unpublished observations). Furthermore, a recent study has suggested that a progressive deterioration in glomerular function may occur in some children during follow-up of several years (Lewis IJ, personal communication).

Over the last three decades, major advances in the treatment of children with cancer have led to a considerable increase in the number of children surviving into adulthood cured of their malignant disease. Therefore, the avoidance of chronic treatment-related toxicity has assumed increasing importance. Despite a great deal of information about the manifestations of chronic ifosfamide-induced nephrotoxicity in children, the frequency and extent of reversibility or deterioration, and therefore the importance and long-term consequences of this adverse effect, remain uncertain. There is an urgent need for careful long-term studies of renal function in children treated with ifosfamide, with follow-up for several years, in order to clarify these uncertainties.

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