Nephrotoxicity after ifosfamide

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Abstract

Eleven children and adolescents with previously normal renal function who received ifosfamide for the treatment of extrarenal solid tumours underwent detailed investigation of glomerular and renal tubular function to assess the incidence and extent of renal damage. None had received cisplatin. Glomerular filtration rate (measured by plasma clearance of ⁵¹Cr labelled edetic acid) was reduced in six children. All 11 patients had evidence of proximal, and six of distal, tubular damage. Proximal tubular toxicity was indicated by phosphaturia and hypophosphataemia (n=4), glycosuria (n=5), increased urine β₂ microglobulin excretion (n=11), and generalised aminoaciduria (n=10); distal tubular damage caused a reduction of the osmolality of the urine in an early morning sample. Two children developed clinical hypophosphataemic rickets, and one of these also had severe nephrogenic diabetes insipidus. Glomerular and tubular nephrotoxicity are common and potentially serious complications of ifosfamide treatment in children.

Ifosfamide, a structural isomer of cyclophosphamide, was introduced into early clinical trials in 1972. Its use has gradually become more widespread because of its apparent efficacy in the treatment of some cyclophosphamide resistant tumours, and its lower bone marrow toxicity which has enabled the use of higher doses.¹ Recent trials have shown it to be a useful drug in the management of several tumours including Ewing's sarcoma, rhabdomyosarcoma, and soft tissue sarcomas.¹⁻⁴ Ifosfamide is now part of the first line management of some of these malignancies.

Although nephrotoxicity is a common side effect in adults, appreciable renal damage has

seldom been reported after ifosfamide in children, and its incidence is unknown.

We describe a detailed cross-sectional assessment of glomerular and renal tubular function in 11 patients, which was undertaken to determine the incidence of nephrotoxicity in children treated with ifosfamide.

Patients and methods

PATIENTS

Fourteen children and adolescents with cancer who started treatment at the paediatric oncology unit of the Royal Victoria Infirmary, Newcastle upon Tyne between August 1986 and March 1988 received more than one course of ifosfamide. The 11 surviving patients were studied—six during the course of treatment, and the other five between two and 15 months after their last course of ifosfamide (table 1). Their median age at diagnosis was 6.0 years (range 3.1-16.3), and at the time of study 6.7 years (range 4.0-17.5). At the time of diagnosis all the children had normal renal function, as indicated by normal plasma concentrations of electrolytes, creatinine, calcium, and phosphate, normal alkaline phosphatase activity, and normal analysis of the urine. None had any evidence of renal involvement or urinary tract obstruction by tumour, or a family history of renal disease.

The total dose of ifosfamide received ranged from 55.5 to 124.4 g/m² (mean 89.4), given over six to 17 courses (median 11.3). This was given as a continuous infusion at a dose of 3 g/m²/day, for either two or three days, depending on the treatment protocol. The infusion always contained mesna at the same dose of 3 g/m²/day, and was accompanied by 3 l/m²/day of fluid given intravenously; the mesna and the hydration were continued for 12 hours after completion of the ifosfamide infusion.

Table 1 Details of patients

Case No	Sex	Age at diagnosis (years)	Diagnosis	Total dose of ifosfamide (g/m ²)	Time since last course of treatment (months)	Duration of other potentially nephrotoxic treatment (days)*
1	Female	3.1	Soft tissue sarcoma	124.4	2	38
2	Male	3.8	Rhabdomyosarcoma	105.7	15	9
3	Female	4.0	Rhabdomyosarcoma	60.0	1	11
4	Male	4.2	Rhabdomyosarcoma	75.0	0	6
5	Female	4.3	Rhabdomyosarcoma	108.0	0	63
6	Male	6.0	Soft tissue sarcoma	96.6	0	4
7	Male	10.5	Rhabdomyosarcoma	89.3	5	41
8	Female	10.9	Soft tissue sarcoma	71.3	2	11
9	Female	13.0	Ewing's sarcoma	100.8	0	24
10	Male	13.7	Ewing's sarcoma	55.5	0	26
11	Male	16.3	Ewing's sarcoma	97.1	3	8

*Aminoglycosides, acyclovir, and amphotericin B (all given intravenously).

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Other chemotherapy received by the children included actinomycin-D (n=7), adriamycin (n=8), cyclophosphamide (n=3), etoposide (n=7), melphalan (n=1), and vincristine (n=11). No child received cisplatin. Nine children also received radiotherapy; in one patient (case 4) the field included the medial borders of both kidneys, and in another (case 10) it included the medial lower quarter of the left kidney, although shielding was attempted. All the children received potentially nephrotoxic supportive treatment (intravenous aminoglycosides, acyclovir, and amphotericin B) for between four and 63 days (median 11).

INVESTIGATIONS

Glomerular, proximal, and distal renal tubular function were all assessed on the same day with a standardised investigation protocol. Blood pressure was also measured.

Glomerular filtration rate was measured from the rate of clearance of ⁵¹Cr labelled edetic acid from plasma. Proximal tubular function was assessed by measurement of electrolytes, creatinine, glucose, calcium, magnesium, phosphate, urate, and amino acids in blood and urine samples taken at the same time (blood—Technicon SMAC Auto-Analyser, Technicon Auto-Analyser II (glucose, urate), Perkin Elmer 2380 AAS (magnesium), Hilger Chromaspec Auto-Analyser (amino acids); urine—Beckman Astra (creatinine), Yellow Springs Analyser (glucose), Perkin Elmer AAS (calcium, magnesium), Technicon RA 1000 (phosphate), and urate and amino acids as for blood samples). In addition, ionised calcium (Radiometer ICA 1 Ionised Calcium Monitor) and red blood cell magnesium (Perkin Elmer 2380 AAS, to reflect tissue concentrations) were measured in the blood samples, and protein and albumin were measured in both the blood and urine samples (blood—Technicon SMAC Auto-Analyser; urine—Du Pont ACA (protein—turbidometric method), Behring Laser Nephelometer (albumin)). Urinary β_2 -microglobulin was measured (RIA kit, Pharmacia Diagnostics AB), to reflect proximal tubular reabsorption, and the concentrations of the renal tubular enzymes (alanine aminopeptidase, alkaline phosphatase, lactate dehydrogenase, and N-acetylglucosaminidase) in urine were determined as previously described,^{5 6} to give a more general indication of renal tubular damage.

Distal tubular function was assessed by measurement of osmolality (Camlab Osmometer Automatik) and pH (PTI 15 Digital pH Meter) in the first urine specimen passed by the child on the morning of the study. Urinalysis was performed using BM Test 7 urine testing reagent strips (Boehringer Mannheim) for glucose and protein, and Albustix (Ames) for albumin. Urine microscopy was carried out with a Nikon Labophot phase contrast micro-

scope. Plasma alkaline phosphatase activity (Technicon SMAC Auto-Analyser) and intact parathyroid hormone concentration (AllegroTM Intact PTH Immunoassay, Nichols Institute Diagnostics) were determined to assess the

effects of changes in calcium, magnesium, or phosphate homeostasis on bone metabolism.

CALCULATIONS

The urinary concentrations of protein, albumin, β_2 -microglobulin, and the renal tubular enzymes were divided by the creatinine concentration of the same sample, and the ratio used for subsequent analysis.

The renal fractional excretions (the proportion of the filtered load at the glomerulus that is subsequently excreted in the urine) of glucose, calcium, magnesium, and phosphate were calculated for each patient using the blood and urine samples, and applying the formula: fractional excretion of 'a' = $Ua/Pa \times Pcr/Ucr \times 100\%$, where P=plasma concentration, U=urine concentration, and cr=creatinine. The tubular reabsorption of any substance is equal to (100–fractional excretion)%.

The plasma ionised calcium concentration was taken to reflect the quantity of calcium filtered at the glomerulus. Similarly, 80% of the plasma magnesium, and all the plasma glucose and plasma phosphate were assumed to be ultra-filterable at the glomerulus.⁷ Appropriate adjustment was therefore made in the case of magnesium.

The renal threshold for phosphate, as quantified by the maximal rate of tubular phosphate reabsorption divided by the glomerular filtration rate (Tm_p/GFR), was calculated for each child using the formula proposed by Brodehl⁸: $Tm_p/GFR = Pp - [(Up \times Pcr)/Ucr]$, where P=plasma concentration, p=phosphate, U=urine concentration and cr=creatinine. This gives an estimate of tubular phosphate reabsorption that is independent of phosphate load, unlike the fractional excretion of phosphate, which is directly related to the plasma phosphate concentration.

REFERENCE RANGES

The normal ranges (as shown in tables 2, and 3, and fig 1) were those used in the department of clinical biochemistry, or in the paediatric

Table 2 Normal ranges of results of renal function tests

Test	Normal range
Glomerular filtration rate (ml/min/1.73m ²)	87–174
Plasma creatinine concentration (μmol/l):	
3–6 Years	30–75
7–14 Years	45–90
14–18 Years	50–105
Plasma phosphate concentration (mmol/l):	
2–5 Years	1.10–1.85
6–12 Years	1.00–1.80
13–16 Years	0.90–1.75
Plasma alkaline phosphatase activity (U/l):	
2–9 Years	90–350
10–15 Years	70–450
16–18 Years (boys)	50–300
Fractional excretion of phosphate (%)	<20 ^{*7}
Fractional excretion of glucose (%)	<1
Fractional excretion of calcium (%)	<2 ⁷
Fractional excretion of magnesium (%)	about 3 ⁷
Early morning urine osmolality (mmol/kg)	>600
Urinary β_2 -microglobulin concentration (mg/mmol creatinine)	<0.01 ⁹
Urinary protein concentration (mg/mmol creatinine)	<20
Urinary albumin concentration (mg/mmol creatinine)	<10

*Approaches zero in hypophosphataemia.

Table 3 Urinary excretion of renal tubular enzymes

Enzyme	No of patients	No with increased excretion	Median value (range) (U/mmol creatinine)	Normal range (U/mmol creatinine)
Lactate dehydrogenase	4*	3	5.4 (2.5-26.8)	<2.6
Alanine aminopeptidase	4*	4	2.5 (1.9-4.0)	<1.0
Alkaline phosphatase	9†	1	0.06 (0.01-1.06)	<0.41
N-acetylglucosaminidase	9†	8	0.8 (0.5-1.8)	<0.6

*Measured in cases 3, 5, 6, and 8; †measured in cases 3-11.

Figure 1 Renal tubular threshold for phosphate (maximum tubular reabsorptive capacity/glomerular filtration rate) in 11 patients after treatment with ifosfamide (□) with upper and lower limits of normal.¹⁰ The four patients with hypophosphataemia all have low thresholds.

nephrology unit, except where indicated in the tables. Variations in the normal ranges of biochemical values due to age are indicated in table 2 and fig 1.

No clear guidance is available about the 'normal' range for the fractional excretion of glucose, and little about the 'normal' urine β_2 -microglobulin:creatinine ratio.

Glycosuria detectable by urine testing strips (usually greater than 13.9 mmol/l) is regarded as abnormal, but as the threshold for glucose reabsorption varies from tubule to tubule and from person to person, a mild degree of glycosuria may be detectable by more sensitive assays in healthy subjects. For the purpose of this study a fractional excretion of glucose of more than 1% was regarded as abnormal.

The only study to have measured the urine β_2 -microglobulin:creatinine ratio in a large number of children described a mean value of 0.008 mg/mmol creatinine in daytime samples

with a narrow spread, so values above 0.01 mg/mmol creatinine were regarded as abnormal.⁹

STATISTICAL ANALYSIS

Clinical variables were correlated with glomerular filtration rate and biochemical values using the Spearman rank correlation coefficient, and the plasma alkaline phosphatase activities before and after treatment were compared by the paired *t* test.

Results

Table 4 summarises the results of those investigations for which the results were abnormal in several patients.

GLOMERULAR FILTRATION RATE

Six children had glomerular filtration rates below the normal range, ranging from 61 to 85 ml/min/1.73m². Only the two children with the lowest values, however, had plasma creatinine concentrations above the standard age related normal values.

PROXIMAL TUBULAR FUNCTION

Four children had plasma phosphate concentrations below their age related normal ranges, and of these three had severe hypophosphataemia. Three of these four children showed fractional excretion of phosphate of greater than 20%, and in the fourth it was 12.2% despite profound hypophosphataemia. Figure 1 shows that the same four children had abnormally low renal tubular thresholds for phosphate.

Five patients showed fractional excretion of glucose of greater than 1%; all of these had at least two pluses on urinalysis strip testing, and of the other six patients, two showed one plus, and four were negative. All the children were normoglycaemic.

Table 4 Renal function in 11 children treated with ifosfamide. Abnormal results are shown in bold type

Case No	Glomerular filtration rate (ml/min/1.73m ²)	Plasma			Fractional excretion of phosphate (%)	Fractional excretion of glucose (%)	Amino aciduria	Early morning urine osmolality (mmol/kg)	Urinary concentration (mg/mmol creatinine)		
		Creatinine concentration (μmol/l)	Phosphate concentration (mmol/l)	Alkaline phosphatase activity (U/l)					β_2 -microglobulin	Protein	Albumin
1*	76	57	0.34	439	32.6	50.3	Yes	275	52.30	722	135
2†	71	89	0.96	365	39.6	7.8	Yes	356	>7.80	163	27
3	135	40	1.41	162	10.2	0	No	887	0.79	500	269
4	104	48	1.41	307	17.0	1.1	Yes	322	0.94	105	18
5‡	162	27	0.49	536	12.2	16.1	Yes	577	21.40	455	59
6	84	56	1.47	259	12.6	0.5	Yes	417	12.70	120	19
7§	84	72	1.41	371	9.0	0.6	Yes	711	1.90	42	6
8	85	49	1.22	238	10.0	0.2	Yes	393	0.51	0	<3
9	189	49	1.11	171	7.8	0	Yes	633	0.19	29	<3
10	141	36	1.41	294	2.9	0	Yes	1028	0.04	19	<1
11	61	172	0.59	446	47.0	11.8	Yes	675	>4.27	107	17

*Plasma potassium concentration 2.4 mmol/l; †fractional excretion of calcium 6.6% and fractional excretion of magnesium 10.8%; ‡serum urate <0.05 mmol/l; §fractional excretion of calcium 3.3%; and ||fractional excretion of calcium 3.9% and fractional excretion of magnesium 8.4%.

All 11 children had increased urine β_2 -microglobulin:creatinine ratios. Plasma amino acid concentrations were normal in all the children, but 10 had generalised amino aciduria.

One child was hypokalaemic, and one had a low serum urate concentration. Plasma calcium, serum magnesium, ionised calcium, and red blood cell magnesium concentrations were normal in all the patients. Three showed slightly increased fractional excretion of calcium, and two mildly increased fractional excretion of magnesium (these increases were less than those seen in fractional excretion of phosphate or glucose).

DISTAL TUBULAR FUNCTION

Six patients failed to concentrate their urine to greater than 600 mmol/kg in early morning samples. Only one child was able to acidify an early morning sample of urine to a pH of less than 5.4. As the plasma carbon dioxide content and anion gap were normal in all the children, however, further investigation of urinary acidification was not carried out, and the relevance of these results is uncertain.

RENAL TUBULAR ENZYMES

Because of difficulties with processing samples, these were not measured in all children. Alanine aminopeptidase excretion was raised in all four children in whom it was measured, alkaline phosphatase in one out of nine, lactate dehydrogenase in three out of four, and N-acetylglucosaminidase in eight out of nine (table 3).

PROTEINURIA AND ALBUMINURIA

Ten children showed abnormal proteinuria (of whom eight were positive on strip testing), and seven abnormal albuminuria (all of whom were positive on strip testing). No child, however, had low plasma protein or albumin concentrations.

BONE CHEMISTRY

At the start of treatment all the patients had normal plasma phosphate concentration and alkaline phosphatase activity (unpublished observations). By the time of study, the alkaline phosphatase activity was increased in the four children with hypophosphataemia, but it remained normal in the other seven. Compared with values before treatment, however, all patients showed increased alkaline phosphatase activity (fig 2) and this was significant in the group as a whole ($t=4.14$, $p=0.002$). Parathyroid hormone was normal in the six in whom it was measured (cases 1, 3, 5, 6, 9, and 10; unpublished observations).

RESULTS OF OTHER TESTS

All the children had normal blood pressure. Analysis of urine showed the results described above as well as small amounts of haemolysed blood in two children, and microscopic haematuria in one child who was recovering from an

Figure 2 Plasma alkaline phosphatase activity before and after treatment with ifosfamide, showing rise after treatment in all 11 patients. The four patients with hypophosphataemia (●) all have values above the age related normal range after treatment.

episode of haemorrhagic cystitis. Microscopy of the urine showed hyaline and granular casts in two children.

CLINICAL PROBLEMS

Two children (cases 1 and 5) had appreciable clinical problems as a result of renal damage. Both developed hypophosphataemic rickets, which caused a painful limp in both cases; they also showed radiological changes of rickets. Case 1 also developed severe nephrogenic diabetes insipidus (she showed no response to exogenous vasopressin (DDAVP)), and this necessitated prolonged and intensive hospital treatment and discontinuation of her ifosfamide treatment. She still had severe impairment of urinary concentration one year later.

The two children with overt rickets were treated with oral phosphate, but vitamin D was not given because of the risk of hypercalcaemia and subsequent nephrocalcinosis. Both received 3 mmol/kg/day of phosphate in divided doses, with improvement in plasma phosphate concentration and alkaline phosphatase activity, and in their gait.

CORRELATIONS

Younger age correlated significantly with higher concentrations of urinary protein ($r_s=-0.708$, $p=0.015$) and urinary albumin ($r_s=-0.739$, $p=0.009$), and with lower osmolality of the early morning specimen of urine ($r_s=0.628$, $p=0.039$). Patients receiving a larger total dose of ifosfamide had lower plasma phosphate concentrations ($r_s=-0.716$, $p=0.013$) and osmolality of early morning specimens of urine ($r_s=-0.670$, $p=0.024$), and higher fractional excretion of glucose ($r_s=0.795$, $p=0.004$) and β_2 -microglobulin ($r_s=0.816$, $p=0.002$). The length of time since the last course of ifosfamide

correlated significantly with a lower glomerular filtration rate ($r_s = -0.732$, $p = 0.011$).

Discussion

The known adverse effects of ifosfamide include haemorrhagic cystitis, encephalopathy, myelosuppression, alopecia, nausea, and vomiting. Nephrotoxicity has been described in adults on several occasions, and ranges from impairment of glomerular function,^{11 12} to renal tubular damage,¹³ which may be widespread and lead to an adult Fanconi syndrome.^{14 15}

Studies describing the use of ifosfamide in children have generally reported either no nephrotoxicity,¹ or only mild and reversible renal damage, with signs such as reduced glomerular function,⁴ proteinuria,¹⁶ metabolic acidosis, aminoaciduria, and glycosuria,^{17 18} or increased urinary excretion of renal tubular enzymes.^{4 19} In one study, nephrotoxicity was found only in children who had previously received cisplatin.³

Recently, severe nephrotoxicity leading to glomerular impairment and a Fanconi syndrome has been described in a young child (who had also received cisplatin),²⁰ and to widespread tubular damage in five children (three of whom had reduced glomerular filtration rates).²¹⁻²³ Severe phosphaturia and hypophosphataemia leading to rickets has also been reported in four children.^{20 24}

We are not aware of any previously published studies of the incidence of nephrotoxicity in children receiving ifosfamide. In this study, six of 11 children and adolescents treated with ifosfamide developed glomerular impairment, all 11 had evidence of proximal tubular damage, and six of distal tubular toxicity. Proximal tubular impairment was indicated by phosphaturia and hypophosphataemia in four patients, glycosuria in five, raised urinary excretion of β_2 -microglobulin in all 11, and generalised aminoaciduria in 10. The distal damage was reflected in impairment of urinary concentration. Ten children had abnormal proteinuria, and seven had abnormal albuminuria. One young child developed severe nephrogenic diabetes insipidus and hypophosphataemic rickets, and another suffered rickets alone.

The implications of glomerular impairment occurring after ifosfamide treatment include the need for great care (including measurement of the glomerular filtration rate) when a treatment regimen incorporates both cisplatin and ifosfamide. This is emphasised by a report of two children with pre-existing severe renal impairment caused by cisplatin who developed terminal renal failure after subsequently receiving ifosfamide.²⁵ Furthermore, care is needed in prescribing drugs with renal excretion (such as aminoglycosides) in children who may have glomerular impairment as a result of ifosfamide treatment.

The phosphaturia (indicated by increased fractional excretion of phosphate) in four children seems to have been caused by proximal tubular damage, which in turn led to a reduced tubular threshold for phosphate reabsorption (fig 1). The resulting hypophosphataemia may

lead to myopathy in the short term, and rickets over a longer period. Rickets is a serious problem in any young child, and even more so in one whose mobility and general well being are already compromised by malignancy and its treatment. Of the four hypophosphataemic children in this study, two developed clinical rickets and have been treated with oral phosphate.

In the presence of normal plasma concentrations, increased urinary excretion of β_2 -microglobulin and of amino acids reflects impairment of proximal tubular reabsorption. Plasma β_2 -microglobulin concentrations are increased in several B cell lymphoproliferative disorders, and in certain solid malignancies in adults, but there is little information about childhood solid tumours.²⁶ Although plasma concentrations were not measured in this study, it is likely that the increased β_2 -microglobulin excretion in urine is a genuine indication of proximal tubular damage in view of the high concentrations seen (particularly in those children who had other evidence of severe proximal toxicity, such as phosphaturia), and the presence of aminoaciduria in 10 of the patients. Increased urinary excretion of β_2 -microglobulin is a sensitive marker of proximal tubular impairment.²⁷

The degree of glycosuria and amino aciduria seen in the children studied, although severe, is unlikely to compromise growth if attention is paid to nutrition. The patients, parents and other medical staff caring for the child should, however, be informed of the glycosuria to avoid diagnostic confusion.

Proximal tubular damage and impairment of urinary concentration may lead to serious problems with fluid and electrolyte balance. These may be particularly severe during chemotherapy, operation, and intercurrent infections.

Proteinuria and albuminuria seem to be common signs of ifosfamide nephrotoxicity in children without necessarily being predictive of severe damage. Those children with severe and more generalised nephrotoxicity did, however, tend to have more severe proteinuria and albuminuria.

Table 5 shows the widespread distribution of nephrotoxicity seen in the patients, and shows that four had damage affecting glomerular, proximal, and distal tubular function. This was particularly severe in the two youngest children. Although many children were either symptom free or had only aminoaciduria or raised urinary β_2 -microglobulin excretion, they all had some evidence of renal damage. This corresponds with the experience of another group using ifos-

Table 5 Subdivision of renal damage by site

Case No	Glomerular	Proximal tubular	Distal tubular
1	Yes	Yes	Yes
2	Yes	Yes	Yes
3	No	Yes	No
4	No	Yes	Yes
5	No	Yes	Yes
6	Yes	Yes	Yes
7	Yes	Yes	No
8	Yes	Yes	Yes
9	No	Yes	No
10	No	Yes	No
11	Yes	Yes	No

famide in children (RJJ Lippens, personal communication).

Because each child was only studied once, no detailed information is yet available on the reversibility or otherwise of the changes in renal function seen. The severity of the glomerular and tubular damage seen in some cases, however, raises the worrying possibility of progression to end stage renal failure in a proportion of the children. No reversibility has been described in previous reports of appreciable nephrotoxicity after ifosfamide in children.²⁰⁻²⁴ There is an urgent need for detailed prospective follow up studies of nephrotoxicity in children receiving different regimens of ifosfamide.

We believe that the nephrotoxicity seen in these children is caused by the ifosfamide, as the pattern of damage is similar to previous descriptions in adults of ifosfamide nephrotoxicity including one report when ifosfamide was used as a single agent,¹⁴ but it is dissimilar to that seen with aminoglycosides,²⁸ amphotericin B,²⁹ or acyclovir.³⁰ There was no evidence of abnormal renal function before treatment in any of the children, and none received cisplatin. Nephrotoxicity has rarely been reported as an adverse effect of the other cytotoxic agents received by these children.³¹ The pattern of nephrotoxicity seen in this study has not been observed in the absence of ifosfamide in children who have been given otherwise similar chemotherapy and supportive treatment.³² Tumour rickets is unlikely, as this improves with successful treatment of the tumour.³³

Although cisplatin also causes nephrotoxicity, with a reduction in glomerular filtration rate and hypomagnesaemia as a result of magnesuria,³² the pattern of tubular damage is clearly different to that seen with ifosfamide. In this study the plasma magnesium concentration was normal and the fractional excretion of magnesium was normal or only slightly increased in all the children. Ifosfamide and cisplatin induced tubular nephrotoxicity seem to be synergistic,^{34 35} however, perhaps because the damage caused by cisplatin leads to reduced availability of urinary mesna and hence to potentiation of ifosfamide toxicity.³⁶

Two previous reports have described renal damage in children after relatively small cumulative doses of ifosfamide,^{20 23} and the authors suggested that these may have represented idiosyncratic reactions to the drug. The findings of this study, however, argue strongly against nephrotoxicity being an idiosyncratic adverse effect of ifosfamide in most cases.

It is not clear why some children developed such severe renal damage while others did not. The small number of children studied makes interpretation difficult, but some interesting correlations were noted between possible risk factors and measures of renal damage.

There seemed to be a tendency for younger children to suffer greater toxicity, but this was only significant in the cases of proteinuria, albuminuria, and impairment of urinary concentration. The total dose of ifosfamide received correlated with the severity of hypophosphataemia, glycosuria, impairment of urinary concentration, and urine β_2 -microglobulin

excretion. The oldest patient in the study suffered severe nephrotoxicity, however, and although the most severely affected children had over 100 g/m² of ifosfamide, another patient received this amount with little damage. It is possible that both younger age and higher dose are important risk factors for nephrotoxicity, and larger prospective studies may clarify this. These may allow safer guidelines to be issued for the administration of ifosfamide, and permit continued use of this effective cytotoxic agent.

Haemorrhagic cystitis after treatment with ifosfamide (or cyclophosphamide) is mainly caused by the toxic metabolite acrolein, which is a product of the conversion of 4-aldoifosfamide (or aldophosphamide) to isophosphoramidate (or phosphoramidate) mustard. We are not aware of any evidence that nephrotoxicity is caused by acrolein or any other product of ifosfamide metabolism, but this might be a possible cause. If this is the case, then it would be reasonable to expect mesna (or a similar agent) to have a protective effect, provided that the regimen allows adequate concentrations of mesna to reach the renal tubules.³⁷

A recent publication has described decreased excretion in urine (and hence presumably reduced production) of carboxyphosphamide (an inactivated metabolite) in a number of patients receiving cyclophosphamide, and corresponding findings in a similar proportion of patients receiving ifosfamide, and has suggested that this might be caused by a specific aldehyde dehydrogenase genotype.³⁸ The authors termed these patients 'low carboxylators'. As a result of their impaired carboxylation these patients produced increased amounts of phosphoramidate mustard and acrolein (which arise from the alternative metabolic pathway). It is therefore possible that this subgroup of patients is at greater risk of haemorrhagic cystitis, and possibly of nephrotoxicity. Detection of such a 'low carboxylator' phenotype might allow treatment to be tailored to each patient to reduce this risk.

In conclusion, further study is needed to assess the toxicity of different regimens of ifosfamide in children, to investigate risk factors, and to determine the long term consequences. Research into the possible causative factor(s) may well be rewarding. In the meantime, great care should be taken in continuing the use of ifosfamide in children to avoid severe nephrotoxicity while retaining the benefits of its cytotoxic effect. Renal and bone biochemistry should be monitored, and the drug should be withheld if there is renal impairment (when cyclophosphamide could be considered as an alternative).

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