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Original article

Iphosphamide-induced nephrotoxicity in children

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Abstract. The nephrotoxic potential of iphosphamide was evaluated in a retrospective analysis of all children receiving the drug at The Hospital for Sick Children in Toronto. The 25 children exhibiting nephrotoxicity did not receive more cycles or higher doses per square metre than the 78 with normal renal function. Similarly, the two groups received comparable doses and number of cycles of sodium 2-mercaptoethanesulphonate, and had similar rates of exposure to nephrotoxic drugs (except for *cis*-platinum). Children exhibiting nephrotoxicity were significantly younger (78.1 ± 64.1 months) than those having normal kidney function (103.8 ± 66.6 months) ($P < 0.05$). Children exhibiting nephrotoxicity were more likely to have received *cis*-platinum prior to the iphosphamide (10/25, 40%) than those with normal renal function (14/73, 18%) ($P < 0.05$). Nephrotoxicity was associated with a significant effect on growth. Careful follow-up of renal function should take place in children receiving iphosphamide, with special attention paid to children younger than 5 years of age and those who have received *cis*-platinum.

Introduction

Iphosphamide is a structural analogue of cyclophosphamide which has been introduced into chemotherapy protocols in recent years [1]. While its relative superiority to cyclophosphamide is still debated [2], its renal toxicity has created a limiting factor; the dose and frequency of treatment has to be limited in many cases, and this has been a significant deterrent to the use of iphosphamide. In the 1980s, sodium 2-mercaptoethanesulphonate (MENSA) became available and has provided some protection, enabling higher doses of iphosphamide to be used and the frequency of dosing to be increased [1]. With this extended use of iphosphamide, a new pattern of side effects has emerged consisting of renal tubular and/or glomerular dysfunction [3]. Case reports have described renal damage mainly in children [4–6]. However, by their nature, case reports cannot answer a variety of questions important for the safe use of iphosphamide:

1. What is the prevalence of nephrotoxicity?
2. Which patients are more likely to suffer these side effects?
3. Are these changes temporary or permanent?
4. Can these patients be identified earlier?

In an attempt to answer these questions, we performed a retrospective analysis identifying all the children who have received iphosphamide at The Hospital for Sick Children in Toronto, as part of their cancer chemotherapy.

Patients and methods

Pharmacy records were reviewed to identify patients who had received iphosphamide during their treatment at The Hospital for Sick Children between 1 January 1984 (when iphosphamide was first introduced) and 31 December 1989. Chart and laboratory review continued through 31 March 1990.

For each patient, the following information was retrieved: age at diagnosis; diagnosis; number of treatment cycles containing iphosphamide; iphosphamide dose (mg/cycle, total mg, mg/m^2); MENSA dose (mg/cycle, total mg, mg/m^2); MENSA frequency; the use of frusemide, *cis*-platinum and other drugs with nephrotoxic potential (gentamycin, tobramycin, vancomycin, amikacin, amphotericin B); the use of radiation therapy; patients' heights before and following iphosphamide therapy.

Renal function was evaluated by recording the following values prior to, at the end of iphosphamide cycles, and after completing the treatment with the drug: venous pH, bicarbonate, electrolytes, urea, creatinine, calcium, phosphate, magnesium, alkaline phosphatase, creatinine clearance derived from serum creatinine according to the Schwartz method and urinalysis.

Studies were performed within a month of the end of a cycle or of the whole treatment.

Laboratory values fell into one of four categories:

1. Normal prior to iphosphamide exposure and became abnormal following use. These were attributed by us to iphosphamide.

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2. Abnormal prior to iphosphamide exposure and stayed abnormal. These were not considered to be related to iphosphamide use. This may not be completely true as iphosphamide may have aggravated pathological processes; however, we have arbitrarily chosen not to attribute such changes to the drug in order not to "dilute" a true effect.
3. Abnormal prior to iphosphamide exposure, normalized during treatment with iphosphamide and remained normal.
4. Never tested. Not all patients had all laboratory tests performed with each cycle of iphosphamide. Therefore, no conclusion could be drawn about the effect of iphosphamide on renal function.

To evaluate changes in renal function associated with iphosphamide, all laboratory tests performed prior to or within 24 h of admission to the hospital for the particular cycle of chemotherapy were recorded.

Six criteria were used to define abnormal renal tubular and glomerular function [7]. These were:
(1) proteinuria (2+ or greater), (2) glycosuria (any amount), (3) Hypophosphataemia (>2 SD for age), (4) hypocarbia (bicarbonate $\leq$20 mEq/l), (5) hypomagnesaemia (<0.70 mmol/l), (6) decreased creatinine clearance (<80 ml/min per 1.73 m^2).

Patients were then divided into two groups:
1. Normal. No abnormality was ever found or one abnormality occurred on one occasion only.
2. Nephrotoxic. These patients had two or more (of the 6) abnormal criteria occurring on the same date or two or more (of the 6) abnormal criteria occurring on different dates, but each occurring more than once. Patients were excluded from analysis if they had two or more (of the 6) abnormal criteria occurring on different dates, each one not necessarily occurring more than once, or one abnormal criterion occurring on two or more occasions. Two additional patients who would have been included in the nephrotoxic group were excluded: one had bilateral Wilms' tumour and the other had neuroblastoma involving the kidneys. Each had undergone nephrectomy and therefore we could not study the relationship between iphosphamide and deterioration in renal function.

Results

One hundred and twenty-one patients were treated with iphosphamide between 1 January 1984 and 31 December 1989 (Table 1). Of these, 25 (21%) were found to have nephrotoxic changes, 77 (64%) were found to have no changes, and 19 (15%) could not be grouped and, therefore, were excluded according to the above criteria. When reviewing the type of renal damage that occurred, 24 of 25 nephrotoxic patients had evidence of renal tubular dysfunction, while glomerular dysfunction occurred in 12 of 25 patients. No patient had glomerular dysfunction without tubular dysfunction, while 7 patients demonstrated tubular dysfunction without glomerular dysfunction. Table 2 shows the incidence of each of the six criteria used to define nephrotoxicity, and shows hypophosphataemia to be the most common (84%), followed by proteinuria (74%), and hypomagnesaemia (67%), while the other criteria occurred in half of the patients.

The 25 nephrotoxic patients had a mean age of 78.1 $\pm$ 64.1 months and were significantly younger than the 77 normal patients (103.75 $\pm$ 66.6 months, P <0.05) (Table 3). There was a greater representation of patients 48 months (4 years) and less in the nephrotoxic group. Of the 25 patients, 13 (52%) were 48 months or under whereas in the normal group, of the 77 patients only 24 (31%) were 48 months or under and 39 (51%) were 10 years or under.

The 25 nephrotoxic patients had a mean of 7 $\pm$ 4 cycles/patient of iphosphamide chemotherapy. This is in contrast to a mean of 5.4 $\pm$ 2.8 cycles/patient received by the 77 normal patients (P = 0.05). However, when comparing the mean number of cycles per patient before nephrotoxic changes occurred the difference was not significant (4.96 $\pm$ 2.88 in nephrotoxic and 5.37 $\pm$ 3 in normals).

The nephrotoxic group received a mean total dose of iphosphamide of 33.7 $\pm$ 31.9 g/patient. This was not different from a mean of 33.9 $\pm$ 23.1 g/patient in the normal group. When comparing the mean iphosphamide dose per

Table 1. Diagnoses of children receiving iphosphamide

	Nephrotoxic		Normal	
Brain tumour	12	(48%)	21	(27%)
Rhabdomyosarcoma	6	(24%)	20	(26%)
Osteogenic sarcoma	4	(16%)	14	(18%)
Ewing's sarcoma	1	(4%)	6	(8%)
Sarcoma	1	(4%)	10	(13%)
Wilms' tumor	0		2	(3%)
Germ cell tumor	1	(4%)	0	
Malignant mesonchioma	0		1	(1%)
Neuroblastoma	0		1	(1%)
B-cell acute lymphocytic leukaemia	0		1	(1%)
Choroid carcinoma	0		1	(1%)
	25 patients		77 patients	

Table 2. Incidence of each of the six criteria used to define nephrotoxicity in children receiving iphosphamide

	Incidence (%)
Hypophosphataemia	84
Proteinuria	74
Hypomagnesaemia	67
Change in creatinine clearance	53
Hypocarbia	50
Glycosuria	50

Table 3. Comparison of children exhibiting iphosphamide-induced nephrotoxicity and those who did not

	Nephrotoxic	Normals	P
Age	78.1 $\pm$ 64.1 months (median 76)	103.75 $\pm$ 66.6 months (median 102)	< 0.05
Cycles	5.0 $\pm$ 2.9 (median 5)	5.4 $\pm$ 2.8 (median 5)	NS
Iphosphamide dose (g/m^2 per cycle)	5.7 $\pm$ 1.13	5.9 $\pm$ 0.9	NS
MENSA dose g/m^2 per cycle	6.1 $\pm$ 1.9	6.2 $\pm$ 1.6	NS
Change in height SDS	–1.2 $\pm$ 1.3	–0.2 $\pm$ 0.6	< 0.0005
Previous exposure to *cis*-platinum	10/25 (40%)	14/77 (18%)	< 0.05

MENSA, Sodium 2-mercaptoethanesulphonate; SDS, standard deviation score; NS, not significant

square metre per cycle before nephrotoxic changes occurred, there were no differences between the groups (5.67 ± 1.13 g/m^2 vs. 5.89 ± 0.85 g/m^2).

The nephrotoxic group received a mean total dose of MENSA of 37.66 ± 36.6 g/patient; the normal group received a mean of 35.12 ± 24.5 g/patient (not significant). When the mean MENSA dose per square metre per cycle before nephrotoxic changes occurred was compared with the normal group (6.06 ± 1.87 g vs. 6.18 ± 1.62 g) this difference was not significant. The frequency of MENSA dosing was not significantly different between the two groups. In the nephrotoxic group, 9 patients (38%) received continuous infusions, 10 patients (42%) received interval dosing, and 5 (21%) received mixed dosing (some cycles were continuous and others were interval dosing). In the normal group, 33 patients (45%) received continuous infusions, 25 (34%) received interval dosing, and 15 (21%) received a mixed regimen.

In both groups, 92% of patients received their iphosphamide over a 2-day cycle. The others either received their dose over a 5-day cycle (1 nephrotoxic patient and 3 normal patients) or both cycles over their treatment course.

The rates of use of furosemide, of other nephrotoxic antibiotics, of exposure to radiation therapy, and the occurrence of cystitis were not statistically different between the two groups. Conversely, there was a significant difference between the 10 (40%) nephrotoxic patients and the 14 (18%) normal patients ($P < 0.05$) with respect to exposure to *cis*-platinum prior to receiving iphosphamide. There was no difference in amounts of *cis*-platinum used in children who received it, between the two groups.

Only 52 patients had sufficient data to allow evaluation of changes in height percentiles. The change in height percentile of 20 nephrotoxic patients was compared with the 32 normal patients. A significant decrease in height percentiles was observed only in the nephrotoxic group ($P < 0.0005$, Table 3).

Discussion

Due to the retrospective nature of this study, we have chosen to adhere to a conservative estimation of changes in renal function. Hence, 19 patients (15%) were excluded from analysis because abnormal results were not documented on more than one occasion. The most obvious finding of this study is that at least 21% of all the patients treated with iphosphamide developed nephrotoxic changes. If one included some of the patients we excluded, the incidence would be even higher. Younger children appear to be at a higher risk of developing nephrotoxic changes. There is no known reason why younger children should be more likely to be affected by the drug. In our cohort, the younger children (<4 years) were not sicker and their survival was not worse than the older children; hence their more common deterioration in renal function cannot be attributed to their poorer general health. It is possible that there are age-related differences in renal handling of this drug. For example, if the young have more predominant tubular secretion of iphosphamide (as is the case for example with digoxin), then their kidney cells may be exposed to more drug. Alternatively, toxicity may be related to the rate of epithelial growth in younger children, since kidneys grow till adolescence.

Our study indicates that children receiving *cis*-platinum prior to iphosphamide are at an increased risk of developing nephrotoxic changes. Synergistic nephrotoxic effects of *cis*-platinum have been shown with many other drugs [8]. This tendency is supported by a previous study by Goren et al. [9] who showed that previous *cis*-platinum therapy potentiated iphosphamide nephrotoxicity, as evidenced following the first dose of iphosphamide by excretion of *N*-acetylglucosaminidase and urinary total protein.

The decrease in height percentiles in nephrotoxic children is biologically plausible as renal damage is commonly associated with stunted growth. This finding is of no clinical importance, but it may indicate that the changes in renal function are severe enough to affect growth. Alternatively, the nephrotic children had a tendency towards more brain tumours ($P = 0.06$) and therefore to more cranial radiation. Cranial irradiation is a well-recognized cause of impaired growth. It is conceivable that there is, in these patients, a synergistic effect of nephrotoxicity and cranial irradiation on growth impairment. These relationships will have to be further clarified in future studies. It is of interest that the most common impairment found by us (hypophosphataemia) is more deleterious to growth than some other transtubulopathies (i.e. glycosuria). In a recent study, Skinner et al. [10] studied 11 children and adolescents with previously normal renal function who received iphosphamide for solid tumours, and none of whom received *cis*-platinum. All 11 had evidence of proximal tubulopathy, phosphaturia, hypophosphataemia, glycosuria, aminoaciduria, and β_2-microglobulin. Distal tubular damage, evidenced by decreased urine osmolality, was documented in 6; a similar number had a decreased glomerular filtration rate. These rates of renal damage are higher than in this study, and may be explained by a substantially higher number of iphosphamide cycles (median 11.3) than in this study ($n = 5$), and a two to fourfold higher cumulative dose of iphosphamide. This dose-response behaviour is also evident when comparing our nephrotoxic and normal patients nephrotoxicity was associated with a larger number of cycles.

At present, we recommend that renal function in all patients receiving iphosphamide should be monitored regularly. Because of our evidence of a possible long-term effect on growth in patients exhibiting iphosphamide nephrotoxicity, the use of the drug should be very carefully reviewed in such patients.

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Literature abstracts

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Twenty-four-hour profile of plasma growth hormone-binding protein

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In experimental animals each burst of GH pulse is followed by a wave of receptor turnover and an increase in serum GH-binding protein (GH-BP), which occurs 60 min after the GH peak. The present report describes the 24-h profile of plasma GH-BP and its correlation to GH pulsatility in normal individuals. Four normally growing children in early puberty were the subjects of this study. Blood was withdrawn continuously for 24 h in 30-min fractions. Pulse analysis of both GH and GH-BP was performed by the Pulsar program. The vast majority of the GH pulses were accompanied by GH-BP pulses within 30 min. Correlation of plasma GH levels to GH-BP levels on the residual series above the smoothed baseline of all 172 individual samples was r = 0.447 (P <0.001). Thus, plasma GH-BP levels fluctuate rapidly in relation to the pulsatility of plasma GH levels. This may influence the GH disappearance rate and brings into question some of the deconvolution calculations of GH secretory impulses.

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Vaccination for prevention of CAPD associated staphylococcal infection: results of a prospective multicentre clinical trial

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124 stable CAPD patients from 8 Australian and 3 New Zealand centers were randomly assigned in a blinded fashion to one of two groups to study the effect of vaccination using commercial preparations consisting of a combined staphylococcus toxoid and whole killed staphylococci (SB) or normal saline solution (SS) on the incidence of peritonitis and exit site infection and *S. aureus* nasal carriage over a 12-month prospective period. In addition, levels of IgG, IgA, IgM, C3 and C4 were monitored during the trial period in serum and dialysate; serum levels of anti-α hemolysin and dialysate levels of fibronectin and specific antistaphylococcal antibodies were also measured. Over the period, treatment with SB or SS did not affect the incidence of peritonitis, catheter-related infection or *S. aureus* nasal carriage. However, vaccination with SB elicited a significant increase in the level of serum anti-α hemolysin throughout the 12 month duration of the study, although the level of increase was unrelated to the subsequent rate of peritonitis. Vaccination with SB but not SS elicited a significant increase in the dialysate level of specific antibodies against *S. aureus*. Serum levels of IgG, IgA, IgM, complement C3 and C4 were within the normal range in the CAPD patients studied and remained unaffected by vaccination with SB. In addition, dialysate levels of IgG, IgA, IgM, complement C3 and C4 were 50–100 times lower than corresponding serum levels and remained unaffected by vaccination. In summary, immunisation with an anti-staphylococcal agent was not successful in reducing peritonitis or exit site infection in CAPD patients.