İfosfamid Kullanımı Sonrası Gelişen Fanconi Sendromu

Fanconi's Syndrome Following Administration of Ifosfamide

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ÖZET

Çocuklarda ifosfamid tedavisi sonrasında en sık proksimal tübüler fonksiyon bozukluğu olmak üzere nefrotoksisite ile karşılaşılmaktadır. Nefrotoksisite gelişiminde hastalara uygulanan ifosfamid dozu en önemli risk faktörüdür. Biz tedavi protokollerinde ifosfamid yer alan ve izleminde Fanconi sendromu gelişen iki olguyu sunduk. Hastalarda sıvı elektrolit bozukluklarına bağlı komplikasyonların önlenmesinde sendromun erken tanı ve tedavisi önemlidir. Bu hastalarda tübüler bozuklukların erken tanısı ve tedavisi için idrar miktarlarının ve serum elektrolit düzeylerinin takibi gereklidir.

Anahtar sözcükler: ifosfamid, Fanconi sendromu, proksimal tübüler asidoz

ABSTRACT

Nephrotoxicity is a frequent complication of treatment with ifosfamide in children. Proximal tubular dysfunction is the commonest presentation, and may lead to a Fanconi's syndrome, including hypophosphataemic rickets and proximal renal tubular acidosis. The cumulative dose of ifosfamide is the most important risk factor for nephrotoxicity. We present two cases who received ifosfamide according to their treatment protocol and developed Fanconi's syndrome. Early diagnosis and therapy becomes an important issue in prevention of complications resulting from fluid and electrolyte defects. Prospective monitoring of urine volume and serum electrolytes may lead to early detection of tubulopathy and allow early replacement therapy.

Keywords: ifosfamide, Fanconi's syndrome, proximal renal tubular acidosis

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Introduction

Ifosfamide, a structural analogue of cyclophosphamide, is widely used to treat patients with soft tissue and osseous sarcomas. Its early use was limited by severe hemorrhagic cystitis, the introduction of sodium-2-mercaptoethanesulphonate (mesna) has provided bladder protection, enabling ifosfamide to be used in higher and more frequent doses. With the extended use of this agent, evidence for nephrotoxicity in children has been accumulated. Ifosfamide administration leads to impaired function of the glomerulus and both the proximal and distal tubule (1-9). Some studies have called attention to an uncommon serious complication of ifosfamide treatment, namely, the development of Fanconi's syndrome (2,3). We present two cases who received ifosfamide according to their treatment protocol and developed Fanconi's syndrome.

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Case Reports

Case 1

A 7-year-old boy had been followed up in Pediatric Oncology department until 6 years of age as Nijmegan breakage syndrome and rhabdomyosarcoma. He was treated with vincristine, actinomycin-D and ifosfamide for eight courses in addition to local radiotherapy. Ifosfamide was administered at a dose of 1.8 g/m^2/day x 5 days. He was referred to Pediatric Nephrology department because of polyuria and polydipsia that was noted 18 months after the cessation of therapy. Microcephaly, growth retardation (height

91 cm<3rd percentile, weight 8 kg<3rd percentile) and severe dehydration were detected on his physical examination. Laboratory findings revealed severe Fanconi's syndrome with hyperchloremic metabolic acidosis, phosphaturia, glycosuria, aminoaciduria, uricosuria, hypercalciuria, proteinuria, and polyuria (Table I). The treatment consisted of supplementation of alkali in the form of a mixture of potassium citrate and sodium citrate, calcium, and phosphorus.

Case 2

A 3-year-old girl was referred to Oncology department for evaluation of abdominal pain and fever. Radiological findings showed intraabdominal mass and pulmonary lesions identified on CT of the chest. Histological evaluation revealed Wilms' tumor. Unilateral nephrectomy and surrenalectomy were performed followed by combination chemotherapy including vincristine, actinomycin-D and adriamycin for eight weeks. When response to therapy was assessed at the 12th week induction therapy, although the pulmonary lesions had resolved, both tumor recurrence at the primary site and liver metastases were detected. Radiotherapy was also given to her. Radiological examination demonstrated evidence of relapse of tumor at the ninth week of treatment and her chemotherapy protocol was changed to ifosfamide, VP16 and carboplatin. Ifosfamide was administered at a dose of 3 g/m²/day x 3 days. At the seventh month of treatment, she was referred to Pediatric Nephrology department because of polyuria and polydipsia. Growth retardation (height 83 cm<3rd percentile, weight 11 kg<3rd percentile) and severe dehydration were detected on her physical examination. Fanconi's syndrome was diagnosed according to the laboratory findings in addition to the clinical features (Table I). The patient was treated with alkali in the form of a mixture of potassium citrate and sodium citrate. She was also given calcium and phosphorus. Her symptoms had improved with this treatment. However, she died of progressive disease after six months.

Discussion

The great improvements in the treatment of malignant diseases in childhood have led to a major

Table I. Summary of clinical and laboratory characteristics of the patients

	Patient 1	Patient 2
Age (year)	7	4.5
Ifosfamide cumulative dose (g/m²)	72	63
Serum creatinine (mg/dL)	1.4	1
Serum urea nitrogen (mg/dL)	30	25
Potassium (mEq/L)	2.0	2.5
Cloride (mEq/L)	115	113
Calcium (mg/dL)	8.9	8.2
Phosphorus (mg/dL)	1.2	1.2
Blood pH	7.21	7.33
pCO_2	18	20.5
HCO_3	6.1	14.9
BE	-21.3	-11
Urine pH	5	5
Urine specific gravity	1005	1009
Urine glucose	+++	+++
Aminoaciduria	Generalised	Generalised
Polyuria (mL/kg/h)	13	6
Tubular phosphorus reabsorbtion (%)	58	18
β_2 microglobulin (ug/L)	350	2180
N-acetyl-β-glucosaminidase (U/L)	15	45
Creatinine clearance (ml/min/1,73m²)	9	62

increase in the number of long-term survivors. Much of the improvement in prognosis over the last 30 years has been due to the use of effective multiagent chemotherapy. With the extended use of these agents, evidence for nephrotoxicity in children has been accumulated (1).

The reported incidence of ifosfamide nephrotoxicity has been variable; decreased glomerular filtration rate (GFR) in 6.3-45% of cases and clinically significant proximal dysfunction and/or Fanconi's syndrome were shown in 1.3-30% of the cases (3). We have detected moderate decrease of glomerular filtration rate and Fanconi's syndrome in our patients as ifosfamide therapy-related side effects.

Many risk factors have been proposed to play a role in the development of nephrotoxicity in children receiving ifosfamide. The cumulative dose of ifosfamide is the most important risk factor for nephrotoxicity (1,3,5-7). Ifosfamide nephrotoxicity has primarily been reported with cumulative doses of ≥60 g/m^2 or in the presence of other factors such as unilateral nephrectomy, radiation therapy and previous or concurrent use of platinum compounds or other nephrotoxic agents. Furthermore, quantitative inter-patient variability in ifosfamide metabolism may determine individual risk (1,5,6). Most published reports of severe toxicity have been in young children, who may be more susceptible to proximal tubular toxicity (7).

In our patients, cumulative doses were more than 60 g/m^2. Although there is evidence that the greatest risk of developing Fanconi's syndrome is when ifosfamide total doses exceed 60 g/m^2, oncologists must weigh the risk and benefit of this agent in treating childhood cancers. Some studies have reported an increased incidence of severe ifosfamide nephrotoxicity in patients, who have also received cisplatin or who had previously undergone unilateral nephrectomy (1,7). Similarly, the latter patient's kidney was removed and she was given carboplatinum combined with ifosfamide. We suggested that the patient's age, unilateral nephrectomy, radiotherapy and previous administration of platinum compounds had contributed to the development of nephrotoxicity. In the light of the risk of developing Fanconi's syndrome after ifosfamide therapy, thought must be given to the contribution of other nephrotoxic chemotherapeutic agents and antimicrobials.

Many authors have described persistent ifosfamide nephrotoxicity one year or longer after the completion of treatment (8,9). It is clear that there is much inter-individual variability in the onset, nature and severity of renal toxicity due to ifosfamide. Ifosfamide-induced nephrotoxicity has been reported as temporary or persistent.

In conclusion, in patients receiving chemotherapy, as life span gets longer, long term side effects seem to be more important. As it was seen in our first patient, Fanconi's syndrome can occur so soon after therapy. For this reason, urine volume and serum electrolytes should be carefully monitored in these patients' further follow-up. Early diagnosis and therapy becomes an important issue in life quality and in prevention of complications resulting from fluid and electrolyte defects.

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