Eur J Cancer Clin Oncol. Vol. 20, No. 3, pp. 435–436, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Letter to the Editor

Failure of 2-Mercaptoethane Sulphonate Sodium (Mesna) to Protect against Ifosfamide Nephrotoxicity

GRAEME SANGSTER,* STANLEY B. KAYE,* KENNETH C. CALMAN* and JOAN F. DALTON†

**Department of Clinical Oncology, Gartnavel General Hospital, Glasgow, U.K. and †W.B. Pharmaceuticals Ltd, Bracknell, U.K.*

THE UROTOXICITY of both cyclophosphamide and its analogue ifosfamide is related to the renal excretion of a metabolite, acrolein [1]. Sodium-2-mercaptoethane sulphonate (mesna; W.B. Pharmaceuticals Ltd, Bracknell, U.K.) is a synthetic thiol-containing compound which protects against this toxicity [2, 3] by forming a non-toxic additive compound with acrolein. Prior to the use of mesna, the urothelial toxicity most commonly manifested as haematuria or cystitis [4], although renal glomerular or, even more rarely, tubular abnormalities [5] had been recorded separately. We report a case of adult Fanconi syndrome and progressive glomerular failure occurring with ifosfamide treatment despite the regular use of mesna.

CASE REPORT

A 35-yr-old woman with metastatic small bowel leiomyosarcoma received eight one-monthly treatments with ifosfamide 12 g (8 g/m^2) in a 24-hr infusion. Intravenous fluids were administered to maintain a minimum urine output of 4 l/24 hr, and mesna 1 g (600 mg/m^2) was given by intravenous bolus injection 4-hourly from the commencement of the ifosfamide infusion until 4 hr after the completion, giving a total course dose of 8 g.

All serum biochemical parameters were normal until after the eighth treatment and urine microscopy was consistently negative for blood, as were regular urine tests by Labstix (Ames), although false-positive results for ketones did occur [6].

On day 8 after the eighth treatment the patient was re-admitted with malaise accompanied by excessive thirst and polyuria. She was normotensive but clinically dehydrated. Investigations showed serum sodium 142 (normal, 135–145) mmol/l, potassium 2.0 (3.5–5.2) mmol/l, chloride 115 (97–107) mmol/l, bicarbonate 18 (23–29) mmol/l, urea 6.2 (2.5–7.5) mmol/l, creatinine 156 (35–115) μmol/l, phosphate 0.32 (0.8–1.5) mmol/l, calcium 2.16 (2.20–2.65) mmol/l, uric acid 0.07 (0.15–0.35) mmol/l, fasting serum glucose 3.8 (2.8–9.9) mmol/l, serum osmolality 290 mOsm/kg and urine osmolality 175 mOsm/kg. Urinalysis showed urine pH 5, proteinuria (2 g/24 hr), glycosuria (2%), ketonuria (++) but no haematuria: urine phosphate 50 mmol/24 hr, urate 20 mmol/24 hr and potassium 90 mmol/24 hr.

Rehydration was commenced but daily urine outputs of up to 7 l were recorded for several days, until on day 23 a urine osmolality of 329 mOsm/kg was achieved. On day 11, at the time of maximal systemic acidosis (arterial blood pH 7.35, serum bicarbonate 15 mmol/l) the urine pH was 5 and the urine was free of bicarbonate.

Despite potassium replacement of 100–150 mmol/24 hr, the serum potassium did not rise significantly until sodium bicarbonate, 2.4 g/day was introduced on day 15. Thereafter, the serum bicarbonate did not rise above 20 mmol/l. Glycosuria and proteinuria (≥1.5 g/day) persisted for more than 3 months.

Glomerular function was initially normal, but over the next 4 months the serum urea rose to 20 mmol/l and the serum creatinine to 500 μmol/l,

Accepted 29 July 1983.

and the creatinine clearance fell from 93 to 8 ml/min. No obstructive uropathy was demonstrated on ultrasound examination.

COMMENT

After ifosfamide treatment this patient developed an adult Fanconi syndrome with generalised proximal renal tubule disturbance, accompanied by a proximal renal tubular acidosis. The later development of progressive glomerular failure was thought to indicate direct glomerular damage by ifosfamide metabolites rather than a secondary effect of the tubular lesion.

In our patient mesna gave apparently effective protection against the more common manisfestations of ifosfamide urothelial toxicity, and the failure to protect completely against nephrotoxicity may have been due to inappropriate scheduling of mesna, although it would also be important to establish that both glomerular and tubular damage are indeed mediated by the same mechanism involving acrolein.

We conclude that significant renal tubular and glomerular damage may develop following high-dose ifosfamide therapy despite apparently adequate treatment with mesna, and this complication should be borne in mind as the use of high-dose ifosfamide increases.

REFERENCES

1. BROCK N, STEKAR J, POHL J, NIEMEYER U, SCHEFFLER G. Acrolein, the causative factor of urotoxic side-effects of cyclophosphamide, ifosfamide, trofosfamide and sufosfamide. *Arzneimittelforsch* 1979, **29,** 659–661.
2. SCHEEF W, KLEIN HO, BROCK N *et al.* Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphorines: preliminary results. *Cancer Treat Rep* 1979, **63,** 501–505.
3. BRYANT BM, JARMAN M, FORD HT, SMITH IE. Prevention of isophosphamide induced urothelial toxicity with 2 mercaptoethane sulphonate sodium (mesna) in patients with advanced carcinoma. *Lancet* 1980, **ii,** 657–659.
4. VAN DYK JJ, FALKSON HC, VAN DER MERWE AM, FALKSON G. Unexpected toxicity in patients treated with iphosphamide. *Cancer Res* 1972, **32,** 921–924.
5. DE FRONZO RA, ABELOFF M, BRAINE H, HUMPHREY RL, DAVID PJ. Renal dysfunction after treatment with isophosphamide (NSC-109724). *Cancer Chemother Rep* 1974, **58,** 375–382.
6. GORDON-SMITH EC, HOWS JM, WARD L, WOODS K, DALTON JIF. Mesna and false-positive results in ward testing for urinary ketones. *Lancet* 1982, **i,** 563.