Cancer Chemother Pharmacol (1993) 33: 262–263

Cancer Chemotherapy and Pharmacology

Short communication

Proteinuria due to suboptimal hydration with high-dose methotrexate therapy

G. T. Kovács, Ch. Paál, P. Somló, R. Koós, D. Schuler, J. D. Borsi

Second Department of Pediatrics, Semmelweis Medical School, Budapest, Hungary

Received: 8 April 1993/Accepted: 18 August 1993

Abstract. One of the major complications after high-dose methotrexate (HDMTX) infusions is renal damage. We investigated the occurrence of proteinuria after HDMTX administration in children with pediatric malignancies (acute lymphoid leukaemia, osteosarcoma Burkitt's lymphoma). In the period 1989–1990 we gave 52 HDMTX courses to 24 children. During this period, prehydration and extra urinary alkalisation were performed only if the urinary specific gravity was over 1010 or if the urinary pH fell below 7. Using this schedule the mean values obtained for protein extraction were: before the therapy, 0.12 ± 0.03 g/m^2; on day 1 after MTX treatment, 0.38 ± 0.06 g/m^2; and on day 2 after the MTX infusion, 0.39 ± 0.11 g/m^2 ($P < 0.01$). A significant increase in proteinuria (>0.2 g/m^2 post- vs pretreatment) was detectable in 54% of the patients. In the period 1991–1992 we modified the hydration-alkalisation schedule to include i. v. prehydration for 18–24 h at 3 l/m^2/day with a 0.45% NaCl-5% glucose solution along with sodium bicarbonate and posthydration for 72 h with the same solution. On this protocol the mean values determined for the urinary protein content were all in the normal range (pretreatment, 0.03 g/m^2/day; day 1, 0.05 g/m^2/day; and day 2, 0.08 g/m^2/day). These findings were significantly different from the previous results ($P < 0.05$).

Introduction

The dihydrofolate reductase inhibitor methotrexate (MTX) is widely used in the treatment of various malignancies and other conditions [1]. The application of folinic acid rescue allows the administration of very high doses of MTX [2, 3]. The major complications of MTX therapy are myelosuppression, mucositis and renal damage [4]. The nephrotoxicity is attributed to a direct effect of MTX and to the cristallisation of 7-OH-MTX molecules in the renal tubuli at acidic urinary pH [5, 6], usually resulting in a reduction in the glomerular filtration rate. Generally, MTX-related nephrotoxicity can be prevented by intensive hydration and alkalisation of the urine [7, 8]. However, we report herein the relatively frequent occurrence of slight to moderate proteinuria after high-dose MTX administration in children.

Patients and methods

In the period 1989–1990 we investigated 24 children (10 boys and 14 girls; mean age, 14.2 ± 4.1 years) with pediatric malignancies [osteosarcoma (OSC), 10 patients; Burkitt's lymphoma (BYL), 5 patients; acute lymphoid leukaemia (ALL), 9 patients] during 52 HDMTX courses. Prehydration was performed only if the specific gravity was over 1010. On the previous day the patient was advised to take oral $NaHCO_3$. Posthydration was carried out at 3 l/m^2 for 3 days (0.45% NaCl-5% glucose infusion or oral hydration). HDMTX infusions were started at urinary pH of 7 and extra sodium bicarbonate was given if the urinary pH fell below 7.

In the period 1991–1992 we investigated 15 patients (11 boys and 4 girls; mean age, 11.4 ± 4.6 years) with OSC (7 patients) or ALL (8 patients) during 45 HDMTX courses given a modified hydration/alkalisation schedule. The intensive hydration and alkalisation regimen consisted of i. v. prehydration for 18–24 h at 3 l/m^2/day with a 0.45% NaCl-5% glucose solution together with sodium bicarbonate at 3 g (36 m*M*)/m/day and posthydration for 72 h with the same solution.

MTX doses and rescue schedules were similar in both groups. The doses of MTX were 12 g/m^2 given over 6 h for OSC [COSS-86], 200 mg/kg given over 6 h for BYL [POG] and 5 g/m^2 given over 24 h for ALL [BFM-90] as i. v. infusions. The Ca-leucovorin rescue was carried out ten times at 15 mg/m^2 6 h starting at 24 (OSC, BYL) or 36 h (ALL) after the beginning of HDMTX administration. The rescue dose was given according to the individual serum MTX levels. Urine samples (24 h) were collected prior to MTX administration and for two 24-h periods following the completion of the drug infusions.

In 97 HDMTX courses the following parameters were studied: blood electrolytes blood urea nitrogen, creatinine, serum and urine proteins, and serum MTX levels. Creatinine clearance was also calculated with 24-h urine collection. Student's *t*-test, Fischer's exact test and other standard statistical methods were used for analysis of the data.

Results

In patients treated in the period 1989–1990 we found frequent development of and a significant increase in the

Table 1. Degree of proteinuria observed before and after HDMTX infusions

	Proteinuria ($g\ m^{-2}\ day^{-1}$)	Before MTX (%)	1st day after MTX (%)	2nd day after MTX (%)
Normal	0 –0.15	77.4	54.8	46.6
Slight	0.16–0.5	16.1	25.8	40.0
Moderate	0.51–1.00	6.5	12.9	6.7
Severe	⩾1.01	0	6.5	6.7

degree of proteinuria after HDMTX therapy. The mean values observed for protein excretion were 0.12 ± 0.03 g/m² before the treatment 0.38 ± 0.06 g/m² on day 1 and 0.39 ± 0.11 on day 2 after HDMTX administration (P <0.01). In the analysis of individual trends a significant increase (>0.2 g/m² post vs pretreatment) in proteinuria was detectable in 50% of the patients on day 1 and in 54% on day 2 after the treatment. Table 1 shows the degree of proteinuria seen before and after HDMTX infusions.

The mean value determined for the glomerular filtration rate (GFR; creatinine clearance) did not change, being 94 ± 44 ml/min/1.73 m² before treatment with HDMTX and 116 ± 58 and 97 ± 38 ml/min/1.73 ml, respectively on days 1 and 2 after HDMTX therapy. However, a significant decrease (>20 ml/min/1.73 m²) in GFR was found in 18% of the patients. Acute renal failure (GFR <30 ml/min/1.73 ml) was not observed.

Analysis of the data revealed no change in the investigated laboratory parameters (electrolytes, kidney function, Ca excretion); however, the analysis of individual trends showed increased Ca excretion (Ca/creatinine ratio in the urine) in 43%–48% of the patients following HDMTX therapy, whereas the influx of Ca was similar before and after MTX therapy.

Increased MTX levels (at 48 h after treatment, >2 × 10^{-6} M/l) were found in only three children and clinical signs of toxicity (vomiting, fever, rash, mucositis) were observed in eight patients. We found no correlation between proteinuria, GFR and/or the age of the patients, the 48-h MTX level, signs of clinical toxicity, urinary pH and the cumulative number of MTX administrations. In view of the above-mentioned observations, we modified the hydration-alkalisation schedule for HDMTX administration.

In most of the patients treated in the period 1991–1992 the intensive hydration and alkalisation prevented the development of proteinuria caused by MTX. In 37 cases (82.2%), no proteinuria was detected after MTX treatment. We found slight (0.2–0.5 g/m/day) proteinuria in only 5/45 cases (11.1%) and moderate proteinuria (0.51–1.0 g m^{-2} day –1) 2 patients (4.4%); only 1 patient (2.2%) had severe (>1.0 g/m/day) proteinuria. These results are significantly different from our previous findings with the first hydration regimen (see above; P <0.05).

The mean values determined for the protein content of the urine were all in the normal range (pretreatment, 0.03 g/m/day; day 1, 0.05 g/m/day; and day 2, 0.08 g/m/day). Interestingly, more cases of severe proteinuria were found in boys after the use of both the original and the modified hydration schedule (5/6 vs 3/3). The mean creatinine-clearance values did not change following MTX treatment with intensive alkalisation (pretreatment, 69.2 ± 57 day 1, 68.2 ± 35.8 ml/min/1.73 m²; and day 2, 67.9 ± 45 ml/min/1.73 m²). However, in 26.7% of the patients a significant decrease (>20 ml/min/1.73 m²) in the GFR was found.

Discussion

We found frequent occurrence of and both a significant increase in the degree of proteinuria and a decrease in the GFR after HDMTX therapy. According to our results the hydration protocol seems to be an important factor in the development and severity of proeinuria. The intensive hydration and alkalisation schedule prevented proteinuria in most of the patients. Interestingly, the GFR did not change with the different protocols, and in about 20% of the cases a slight degree of renal damage was detectable (decrease in creatinine clearance). The more frequent occurrence of proteinuria in boys may be explained by the higher rate of 7-OH-MTX formation in males, which has been shown previously [9]. These findings need further investigation by the simultaneous measurement of levels of MTX and its metabolite in serum and in the urine. The importance of our observations and the late outcome of the renal damage caused by HDMTX need further investigation.

Acknowledgements. This work was supported by the Foundation for Hungarian Science and by a United States Agency for International Development POOH Program Project grant.

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