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ORIGINAL ARTICLE

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Effects of sodium in hydration solution on plasma methotrexate concentrations following high-dose methotrexate in children with acute lymphoblastic leukemia

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Abstract *Purpose*: To test whether a higher sodium dose in the hydration solution may facilitate faster methotrexate (MTX) elimination as compared with a lower sodium dose following high-dose MTX (HDMTX) treatment. *Methods*: Intravenous solutions with alternate doses of sodium (regimen A 70 mEq/l, regimen B 100 mEq/l) were given to 30 children with acute lymphoblastic leukemia in two courses of HDMTX in a randomized crossover fashion. The plasma MTX concentrations every 24 h from the beginning of MTX administration and the adverse events associated with HDMTX were compared between the two hydration regimens. *Results*: The plasma MTX concentrations were similar in the two hydration regimens at 24 h (A 50.9 ± 7.4 vs B 40.9 ± 5.4 μM, means $\pm$ SE, $P = 0.17$), but was significantly lower in regimen B at 48 and 72 h (A 0.65 ± 0.17 vs B 0.27 ± 0.03 μM, $P = 0.04$; and A 0.14 ± 0.03 vs B 0.05 ± 0.01 μM, $P = 0.003$). The time during which MTX plasma concentrations exceeded 0.1 μM was significantly longer in regimen A than in regimen B (A 3.83 ± 0.18 vs B 3.13 ± 0.06 days, $P = 0.001$). The incidences of adverse events were similar between the two regimens ($P = 0.78$), and severe adverse events were not seen in either regimen. *Conclusions*: Hydration with a higher sodium dose facilitated faster MTX elimination following HDMTX. Sodium may have a beneficial effect on MTX-induced nephrotoxicity.

Keywords High-dose methotrexate · Hydration · Sodium · Glomerular filtration rate · Nephrotoxicity

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Introduction

High-dose methotrexate (HDMTX) is widely used in the treatment of a variety of malignant diseases. HDMTX is often administered in doses up to 12 g/m^2 over 4 h, shortly followed by multiple doses of leucovorin to counteract the toxic effects of methotrexate (MTX) [1, 2, 3, 4]. In each regimen, rapid elimination of MTX by the kidney is critical. During and after HDMTX treatment, MTX concentrations in the urine may exceed the solubility of the drug, particularly if the urine is acidic. Subsequent precipitation of the drug in the renal tubules and collecting ducts has been considered to be responsible for MTX nephrotoxicity, leading to delayed drug elimination [5, 6]. Hence, most centers now employ vigorous hydration and urinary akalinization to prevent precipitation. These hydration regimens and the monitoring of plasma MTX concentrations and appropriate alterations in leucovorin dosage have helped to decrease the incidence of overt renal failure and serious toxicity [7], but some patients develop delayed MTX elimination despite careful attention to the details of hydration and alkalinization [8].

Direct toxicity in the renal tubule is another possible pathogenetic mechanism of MTX nephrotoxicity [9, 10]. It has also been observed that aminopterin, a compound with the same solubility as MTX, may also have a nephrotoxic effect even when administered at one-tenth of the normally administered dose of MTX, a dose unlikely to cause intratubular precipitation [11]. Direct toxicity in the renal tubule eventually result in alterations in glomerular function via a physiological mechanism known

as tubuloglomerular feedback. Indeed, a rapid and dose-related decrease in glomerular filtration rate (GFR) has been observed in patients during and after HDMTX treatment [11, 12]. Although the decrease in GFR is usually transient with spontaneous recovery, elimination of MTX may be delayed in the setting of a decreased GFR since MTX is virtually exclusively excreted by the kidney [13]. Sodium is important in the regulation of the feedback mechanism, and sodium loading is known to minimize the fall in GFR caused by tubuloglomerular feedback in modes of drug-induced nephrotoxicity such as amphotericin B-induced nephrotoxicity [14, 15]. Thus, we tested the hypothesis that sodium would prevent direct toxicity of MTX and delayed MTX elimination following HDMTX.

Material and methods

Previously untreated patients with acute lymphoblastic leukemia (ALL) treated with the L95-14 protocol of the Tokyo Children's Cancer Study Group were enrolled in this study with the informed consent of their parents. The treatment with the L95-14 protocol will be reported separately. Briefly, induction therapy consisted of prednisolone, vincristine, L-asparaginase and THP-Adriamycin. The patients without extremely high-risk features were treated on three consecutive courses of HDMTX at intervals of 7–10 days after obtaining a complete hematological remission. First, 3 g/m^2 of MTX was administered as a 12-h continuous intravenous infusion, and then the same dose of MTX was administered as a 24-h continuous intravenous infusion in the second and third courses. Each HDMTX course was accompanied by intrathecal injections of MTX, hydrocortisone and cytarabine (age-adjusted doses). This study was performed in the latter two courses of HDMTX as a crossover modality.

Hydration was started from 3 h before the beginning of MTX with 3000 ml/m^2 per day of fluids, and each patient received alternate hydration regimens in these two courses. During one HDMTX course, the patients received regimen A which comprised 35 mEq/l of sodium chloride, 20 mEq/l of potassium chloride, and 35 mEq/l of sodium bicarbonate, provided by a hydration solution product (Solita T3, Shimizu Pharmaceuticals, Nagoya City, Japan) and 7% sodium bicarbonate. During the other HDMTX course, they received regimen B which comprised 65 mEq/l of sodium chloride, 20 mEq/l of potassium chloride, and 35 mEq/l of sodium bicarbonate, provided by the same hydration solution as regimen A and 10% sodium chloride. The sodium concentration was 70 mEq/l in regimen A and 100 mEq/l in regimen B. The order in which each patient received the two hydration regimens was randomized. Hydration was maintained until the plasma MTX concentration dropped to 0.1 μM. The plasma MTX concentrations of all patients were measured by a fluorescence polarization immunoassay using a commercial kit (Abbott Laboratories, North Chicago, Ill.) at 24, 48 and 72 h from the beginning of MTX. The measurement was repeated every 24 h until the plasma concentrations fell below 0.1 μM. Administration of trimethoprim/sulfamethoxazole was postponed until the plasma MTX concentration dropped to 0.1 μM. Urine pH was checked with each void, and additional sodium bicarbonate was on hand for administration if the pH fell below 6.5.

At 36 h from the beginning of HDMTX, leucovorin at 15 mg/m^2 was initiated at 6-h intervals. If the plasma concentration at 48 h exceeded 1.0 μM, patients received higher doses of leucovorin until the plasma MTX concentration fell below 0.1 μM. The protocol for increasing the leucovorin dose at 48 h was: 1.0 to 2.4 μM, 30 mg/m^2 every 6 h; ≥2.5 μM, 90 mg/m^2 every 6 h.

Patients were monitored daily for weight and urine output. Serum electrolytes, creatinine, and BUN were checked daily until the plasma MTX concentration dropped to 0.1 μM. Complete blood counts with differential counts, bilirubin, and ALT and AST were determined three times weekly. The GFR was calculated from creatinine clearance daily during hydration. Toxicities were assessed and graded according to the World Health Organization criteria [16].

The MTX concentrations at 24, 48 and 72 h, the time during which MTX plasma concentrations exceeded 0.1 μM, the leucovorin dosage used, and GFR changes following HDMTX were compared between regimen A and regimen B by the Wilcoxon signed-rank's test. The numbers of patients whose plasma MTX concentrations exceeded 0.1 μM at 72 h after the start of HDMTX and the incidences of adverse events were compared by the Chi-squared statistic between the two regimens. All results are expressed as means ± SE. All P values are two-tailed.

Results

Between April 1996 and December 1998, 30 patients (14 boys and 16 girls) were eligible for the study. Their median age was 6 years (range 2 to 13 years). The serum creatinine values prior to all MTX infusion were less than 1.0 mg/dl. Urinary pH was kept between 6.5 and 8.0 in each patient during the study, so none of the patients received additional sodium bicarbonate. No patient gained more than 5% of his or her baseline body weight during the study.

Figure 1 shows the 24-, 48- and 72-h MTX concentrations after the start of HDMTX administration in regimen A and regimen B. The mean plasma MTX concentrations were similar between the two hydration regimens at 24 h (A 50.9 ± 7.4 vs B 40.9 ± 5.4 μM, $P = 0.17$), but were significantly lower in regimen B at 48 and 72 h after (A 0.65 ± 0.17 vs B 0.27 ± 0.03 μM, $P = 0.04$; and A 0.14 ± 0.03 vs B 0.05 ± 0.01 μM, $P = 0.003$).

The mean time during which plasma MTX concentrations exceeded 0.1 μM was significantly longer in regimen A than in regimen B (A 3.83 ± 0.18 vs B 3.13 ± 0.06 days, $P = 0.001$). At 72 h after administration of HDMTX, 16 patients in regimen A, but only 4 in regimen B ($P = 0.001$), had plasma MTX concentrations exceeding 0.1 μM. The mean leucovorin dose used was significantly higher in regimen A than in regimen B (A 181.6 ± 26.6 vs B115.0 ± 4.1 mg/m^2, $P = 0.02$).

Data regarding GFR were available for 26 patients. The mean GFR values before the start of HDMTX were similar in the two regimens (A 135.9 ± 4.7 vs B126.2 ± 5.0 ml/min per 1.73 m^2, $P = 0.20$). Although the mean GFR values during HDMTX were not different in the two regimens on day 0 (A 79.5 ± 3.8 vs B 80.7 ± 2.8 ml/min per 1.73 m^2, $P = 0.57$), there was a trend for the mean GFR value after HDMTX to be lower in regimen A than in regimen B: A 77.2 ± 3.8 vs B 93.8 ± 2.8 ml/min per 1.73 m^2 ($P = 0.07$) on day 1, and A 80.4 ± 2.8 vs B 89.2 ± 3.6 ml/min per 1.73 m^2 ($P = 0.08$) on day 2.

Table 1 summarizes the findings from the patients who showed delayed MTX elimination (defined as plasma concentration ≥1.0 μM at 48 h) in regimen A. Among the four patients with delayed MTX elimination,

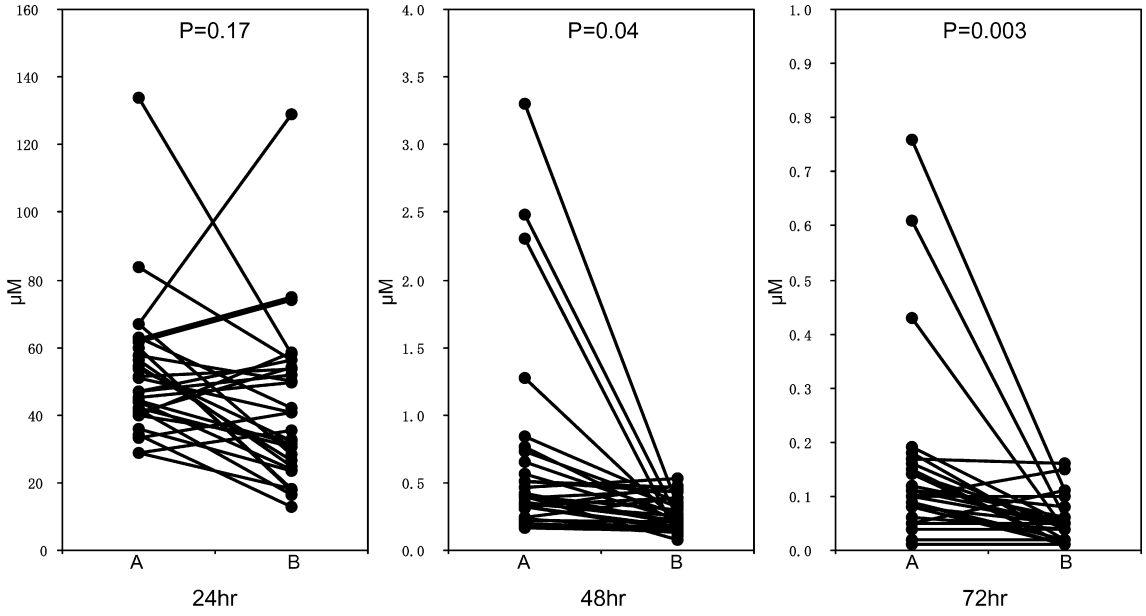

Fig. 1 MTX pharmacokinetics following high-dose infusion in patients receiving hydration with regimen A and regimen B. The MTX concentrations measured for each patient at 24, 48 and 72 h are connected

three received regimen A first, and one received regimen B first. Creatinine clearance was decreased by 51% to 59% with delayed MTX elimination. None of the patients developed life-threatening toxicity with the use of increased leucovorin doses, but they required longer intravenous hydration and higher doses of leucovorin. Delayed MTX elimination was not observed in these four patients while receiving regimen B.

HDMTX was generally well tolerated in this study. The common adverse events were hematological and gastrointestinal symptoms including anemia, leukopenia, thrombocytopenia, nausea, vomiting, mucositis, and the elevation of ALT, but severe adverse events (grade 3 and grade 4) were not recognized (Table 2). The overall incidences of adverse events were similar between regimen A and regimen (70% vs 67%, $P = 0.78$). Adverse events associated with fluid management were not seen in this study.

Discussion

The present study demonstrated that sodium facilitates MTX elimination following HDMTX. Since MTX clearance may be variable among patients [17, 18], we compared the two hydration regimens containing different sodium doses in a randomized crossover manner. We also used virtually identical treatment regimens for induction and post-remission therapies, as the treatment before HDMTX and the dosage used may affect MTX clearance following HDMTX [19, 20].

To our knowledge, there have been no reports that sodium affects MTX elimination following HDMTX treatment. Although Abelson et al. showed that plasma MTX decay does not change when sodium bicarbonate in the hydration solution is replaced with an equivalent amount of sodium chloride [10], these findings do not exclude the possibility that sodium doses in the hydration solution may affect MTX elimination.

Although we hypothesized that sodium may alter tubuloglomerular feedback, direct evidence for this hypothesis was not found in our study. We observed a

Table 1 Patient characteristics and variables with delayed MTX elimination

Age (years) Gender	Patient			
	1 5 Female	2 4 Female	3 3 Female	4 9 Male
MTX concentration (μM)[a]				
24 h	31.3	84.3	53.6	134.0
48 h	3.30	2.48	1.12	2.31
72 h	0.61	0.76	0.44	0.43
Creatinine clearance (ml/min/1.73 m^2)[b]				
Before	143	124	168	140
Day 0	68	75	81	88
Day 1	61	65	70	62
Day 2	63	61	72	65
Day3	89	67	69	82

[a]MTX concentrations were measured every 24 h after the start of HDMTX
[b]Creatinine clearance was calculated daily while receiving hydration

Table 2 Adverse events (more than one adverse event occurred in some patients)

Adverse event	WHO grade	No. of patients	
		Regimen A	Regimen B
Overall		21	20
Hematologic			
Hemoglobin	1	9	11
	2	4	3
Leukocytes	1	5	4
	2	2	3
Granulocytes	1	4	6
	2	2	2
Platelets	1	2	1
	2	1	1
Gastrointestinal			
Nausea/vomiting	1	6	4
	2	3	4
Oral	1	2	1
	2	0	1
SGOT/SGPT	1	4	2
	2	2	3
Infection	1	1	0

trend for rapid recovery from the GFR fall following HDMTX with the use of a hydration solution containing a higher amount of sodium, but the difference was not statistically significant. The method for calculating GFR might be an explanation for this result, since creatinine clearance is not a reliable estimate of GFR in the setting of decreased renal function. However, delayed elimination of MTX was always accompanied by a fall in GFR in our patients. These observations suggest that the protection against the GFR fall is a clue to the rapid elimination of MTX following HDMTX.

It is possible that the addition of sodium could impair the antitumor effect of HDMTX. Although data regarding MTX exposure were not available in our study, the addition of sodium did not changed the plasma MTX concentrations at 24 h. Moreover, the addition of sodium decreased the total dosage of leucovorin used. These observations suggest that the addition of sodium may contribute to the antitumor effect of HDMTX.

Notably, our results suggest that HDMTX could be repeated by refining the hydration regimen even in patients who have previously experienced delayed MTX clearance. HDMTX is an important component in the treatment of cancer, especially in children. In patients with delayed MTX clearance, subsequent HDMTX infusions tend to be avoided or may be performed at a reduced dose [21]. However, dose reduction could abrogate the antitumor effect of MTX. In fact, relapse-free survival is related to the plasma concentrations of MTX in children with ALL [22] and osteosarcoma [23]. Hence, it is clinically important to exploit interventions to prevent delayed MTX elimination following HDMTX.

No adverse reactions to sodium loading were observed in the children in this study. It should be noted, however, that sodium loading might be harmful in older patients or patients with preexisting sodium or fluid overload, and in those with impaired left ventricular function.

In conclusion, hydration containing large amounts of sodium was well tolerated and useful for preventing delayed drug elimination in children receiving HDMTX. Our results suggest that HDMTX courses can be repeated with the use of refined fluid management, even in patients who have previously experienced delayed MTX clearance. Further studies are needed to elucidate the precise mechanism by which sodium is involved in MTX pharmacokinetics following HDMTX.

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