Medication Safety

Occurrence and Impact of Unanticipated Variation in Intravenous Methotrexate Dosing

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BACKGROUND: Studies using direct measurement suggest that the doses of up to 65% of drug infusions are outside industry standards. These preparation-associated errors occur despite routine safety procedures. As of April 5, 2006, the clinical impact of these errors had not been evaluated.

OBJECTIVE: To measure the occurrence and associated clinical outcomes of variations in intravenous methotrexate dosing.

METHODS: A prospective observational study was performed on 47 methotrexate infusions of 800 mg/m² that were administered to 19 children with acute lymphoblastic leukemia. Serum methotrexate concentrations were measured at the end of the infusions, which were administered over 24 hours. The total methotrexate dose was determined by direct measurement of the concentration and the volume of each infusion.

RESULTS: Dosing errors greater than or equal to 10% occurred in 11 (23%) infusions and ranged from –61% to 55% of the ideal dose. Repeated measures regression analysis found the measured total methotrexate dose was not significantly associated with the serum methotrexate concentration ($p = 0.58$) or with clinical toxicities. The methotrexate dose administered over the last hours of infusion ($p = 0.006$) and the serum creatinine level at diagnosis ($p = 0.05$) were the most significant predictors of the methotrexate concentration. High methotrexate concentrations were significantly associated with increased hepatic aminotransferase levels; however, the degree of elevation was of limited clinical relevance.

CONCLUSIONS: While unexpected errors in drug dosing are more common than is suggested by other methods, the clinical impact observed in this model of methotrexate infusion was not demonstrably greater than medication errors described by other methods. Subsequent studies in this model of dosing error will require larger sample sizes, and other drugs should be evaluated.

KEY WORDS: adverse drug event, medication error, methotrexate.

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Despite the accumulating evidence of unexpected variability between ordered and measured concentrations in up to 65% of drug infusions and concern about the assumption of accurate dosing made in pharmacokinetic studies, the investigation of the clinical impact of these dosing errors has been limited.[1-5] These preparation-associated errors occur despite routine safety procedures. There is great potential for clinically significant effects arising from dosing errors in medications with a low therapeutic index such as methotrexate.[6]

Methotrexate, which is routinely administered to children with malignancy, causes dose- and serum concentration–related nephrotoxicity, hepatotoxicity, and myelosuppression.[7-11] Serum drug concentrations are measured as part of routine care; significant but unexplained variability in the levels with methotrexate infusions exists.[7,12-14] Preparation-associated error may explain much of this variability. We performed a prospective observational study of directly measured drug doses and the associated clinical outcomes.

Methods

Children receiving 800 mg/m², 24 hour methotrexate infusions as part of treatment for acute lymphoblastic leukemia on the current Children's Oncology Group (COG) protocols 9904 and 9905 arms A or C were eligible for study. We excluded children receiving infusions who had congenital leukemia or Down's syndrome, who were older than 18 years at diagnosis, or who were scheduled to receive nonstandard methotrexate dosing.

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METHOTREXATE INFUSION

The current practice of our institution is to accept up to a 10% difference between the ordered dose and the ideal (protocol) dose. Sodium bicarbonate (30 mmol/L) is added to the infusion solution of dextrose 5% and sodium chloride 0.2%, and additional intravenous sodium bicarbonate boluses are administered to maintain alkaline urine. Folinic acid (leucovorin) rescue therapy (10 mg/m²) is started 42 hours after the initiation of the methotrexate infusion. These therapies are discontinued at the discretion of the treating physician after the methotrexate concentration is below 0.2 μmol/L.

Infusions were prepared using 25 mg/mL methotrexate stock solution (Faulding, Quebec, Canada). This was diluted to the prescribed volume and concentration by addition of the stock solution to the diluent. One to 3 sterile intravenous bags were used depending upon the total volume required. Following standardized prehydration, children received the methotrexate infusion. Each infusion began with a 200 mg/m² bolus of methotrexate over 20 minutes and was followed by a separate 800 mg/m² infusion administered over the remaining 23 hours and 40 minutes. Bags were administered in labeled order.

PRIMARY OUTCOMES

There were 2 primary outcomes for this study: the total dose administered and the 24 hour serum methotrexate concentration. The total dose administered was calculated from the volume and concentration of the infused methotrexate solution. The methotrexate concentration was determined by direct measurement using HPLC with ultraviolet detection. The volume infused was measured by weighing the bag with prescribed chemotherapy before and after administration (CA11274888, Mettler, Toledo, OH; accuracy ± 0.01 g). Correction for the infusion density (~1054.8 g/L) was made ignoring variations due to methotrexate (assumed <0.06%). The missing weights of emptied bags were imputed. The percentage error of the total dose administered was also calculated versus the ideal (protocol) infusion dose (800 mg/m²), the prescribed dose, and the stated dispensed dose.

Methotrexate concentrations were measured at the completion of a 24 hour infusion. Methotrexate concentrations are a surrogate for toxicity, are collected routinely as a part of standard care, and are not affected by the site of venous sampling.[7-11,15] The serum methotrexate concentration was measured using the TDx Methotrexate II assay system (Abbott Laboratories, Chicago, IL). This fluorescence polarization immunoassay is linear over the range 0.05–1.0 μmol/L, is calibrated regularly, and has a coefficient of variation (CV) of 5% (product information). A 1:100 dilution that is required for analysis introduces less than 1% additional error. Independent evaluation in our laboratory found CV values between 5% and 10%.

SECONDARY OUTCOMES

The secondary outcomes were rates of hepatotoxicity, nephrotoxicity, and myelotoxicity over the 4 weeks following a methotrexate infusion. The maximum values of creatinine, aspartate aminotransferase, and alanine aminotransferase were recorded. Myelosuppression was assessed by the minimum neutrophil, platelet, and hemoglobin counts.

POTENTIAL FACTORS AFFECTING THE 24 HOUR METHOTREXATE CONCENTRATION

Seven factors that could explain variability in serum methotrexate concentrations were recorded: (1) the total dose/m², (2) the dose/m² in the last bag administered, (3) the amount of methotrexate administered in the last hours of the infusion, (4) glomerular function at diagnosis, (5) glomerular function within 48 hours before the start of the infusion, (6) the time that the methotrexate concentration was determined relative to the documented completion of the methotrexate infusion, and (7) the study protocol on which a patient was treated. The contributions of active tubular secretion and concomitant medication administration were not evaluated.

Glomerular function was assessed twice by using the serum creatinine level and the calculated creatinine clearance from the formula of Schwartz et al.[16] due to concerns about the validity of the calculated value in this population and changes in muscle mass during therapy.[17] The dosing rate of methotrexate in the last hours of the methotrexate infusion was included because administration rates may be altered to ensure infusion completion close to the prespecified time. The dosing rate in the last hour of infusion was calculated as the rate of administration determined from the last recorded volumes of methotrexate infusion administered divided by the time interval over which it was given. The dosing rate per meter squared was then calculated using the child's surface area and the methotrexate concentration measured from the bag being administered.

VALIDATION OF METHOTREXATE INFUSION SAMPLING

We validated the methotrexate infusion sampling method by taking 3 samples from each of 2 bags made with a concentration similar to that of standard methotrexate infusions (0.33 μmol/L). Samples were taken from the full bag, the half-emptied bag, and when the bag was nearly empty. The methotrexate concentration was measured, and the CV was calculated for the set of measurements from each bag.

ANALYSIS

The percentage error in volume, concentration, and dose were determined for each bag prepared. The total dose per meter squared was calculated using the most recent measurements, and the percentage error between ideal (800 mg/m²), prescribed, dispensed, and administered infusions was determined. The body surface area was calculated as BSA (m²) = $\sqrt{}$ [(height in cm × weight in kg) /3600].

Regression analyses were used to evaluate the relationship between predictive factors and serum methotrexate concentrations and the relationships between late toxicity outcomes and the 2 potentially predictive factors: the serum methotrexate concentrations and the total dose administered. The proportion of variability in the methotrexate concentration that was explained by the predictive factors was estimated using the r^2 value.

A repeated measures regression analysis was used to accommodate the inclusion of multiple methotrexate infusions from one patient and the potential impact of the order of infusions. The regression analysis began with all 7 variables. These were sequentially removed using a backwards-stepwise method until only variables significant at the $p = 0.05$ level remained.

The secondary outcomes were divided into quartiles of the total measured dose per meter squared and the methotrexate concentration; the mean values from each quartile were compared using linear regression.

SAMPLE SIZE

The sample size was determined using the methotrexate concentrations from a historical cohort. Forty infusions were required to describe differences among concentrations of 2 μmol/L with 90% power and a risk of a type one error of 2.5%. This difference was suggested to be the smallest clinically important difference by local content experts. The approach was selected recognizing that variations in infusion dose (volume and concentration) were not precisely known, and toxicities were secondary outcomes.

This study was reviewed and approved by the institutional research ethics board. The need for consent was waived due to the lack of direct patient contact and the observational design.

Results

A total of 47 infusions administered to 19 patients over 8 months were studied. There were 8 children on the COG 9904 protocol (20 infusions), and 11 children on the COG 9905 protocol (27 infusions). The maximum number of infusions per child was 4. Each infusion was comprised of 1 (n = 22), 2 (n = 19), or 3 (n = 6) bags of methotrexate.

The prescribed doses were identical to the dispensed doses, suggesting that the infused concentration should be between 0.323 and 0.346 μg/mL. The oncology pharmacists did not change physicians' orders. Differences between documented and recalculated BSA were minimal (–0.01 to 0.02 m²).

The sampling method appeared to be reliable. Two bags of methotrexate were made. The 3 concentrations obtained from each bag were similar (0.339, 0.351, and 0.355 μg/mL [CV 2.4%]; and 0.309, 0.332, and 0.338 μg/mL [CV 4.8%]), suggesting that the method used was representative of the true concentration in the bag. One infusion was excluded from analysis on the basis of assumed incomplete mixing. It had a measured concentration and volume suggesting that an extremely high dose of 3391 mg/m² (vs 800) would be administered. This dose resulted in an unexpectedly low 24 hour serum methotrexate concentration of 3.9 μmol/L.

DOSING ERRORS

Seventy-eight bags of methotrexate solution were prepared for the 47 infusions studied. All bags were weighed when full, and 62 (79%) were weighed after the infusion was administered. Seven (11%) of the 62 bags with initial and final weights had errors of 5% or more between the stated dispensed volume and the administered volume (range –6.6% to 1.4%).

Errors in the measured concentration of each bag of 10% or more were found in 24 (31%) of the 78 bags comprising the 47 infusions. Measured concentrations ranged from 0.08 to 0.54 μg/mL, with a mean concentration of 0.34 μg/mL. The percentage error ranged from –76% to 63%.

The measured dose in each bag differed by 10% or more from the stated dispensed dose in 20 (26%) of the bags. Errors ranged from –77% to 56%, with a mean percentage error of –1.3%. When the last bag infused was evaluated in isolation, errors of 10% or more were found in 14 (30%) bags from the 47 infusions, and the magnitude of the errors ranged from –52% to 57% (mean –0.51%).

The ideal (800 mg/m²) and the prescribed total doses were similar (mean difference –0.5%, range –3.8% to 2.6%). Eleven (23%) of the measured total doses infused had errors of 10% or more. The errors ranged from –61% to 55% (mean –1.3%; Figure 1).

SERUM METHOTREXATE CONCENTRATIONS

Serum methotrexate concentrations were obtained for all infusions. Concentrations were drawn at the documented time of infusion completion in 24 (51%) infusions and varied from 15 minutes before to 140 minutes after (mean 16, median 0) the documented infusion completion time. The mean steady-state serum concentration was 7.9 μmol/L (range 3–16, median 7.8).

PATIENT FACTORS

Serum creatinine level measurements were available for all children at the time of diagnosis and within 48 hours before infusion started in 46 of the 47 infusions. The mean calculated creatinine clearance values using the Schwartz et al.[16] formula and serum creatinine levels were 141 mL/min/1.73 m² and 0.46 mg/dL, respectively, at diagnosis, and 171 mL/min/1.73 m² and 0.39 mg/dL, respectively, at the start of each infusion (Table 1).

ASSOCIATIONS WITH SERUM METHOTREXATE CONCENTRATION

Analysis of isolated predictor variables with linear regression suggested that lower serum creatinine values were

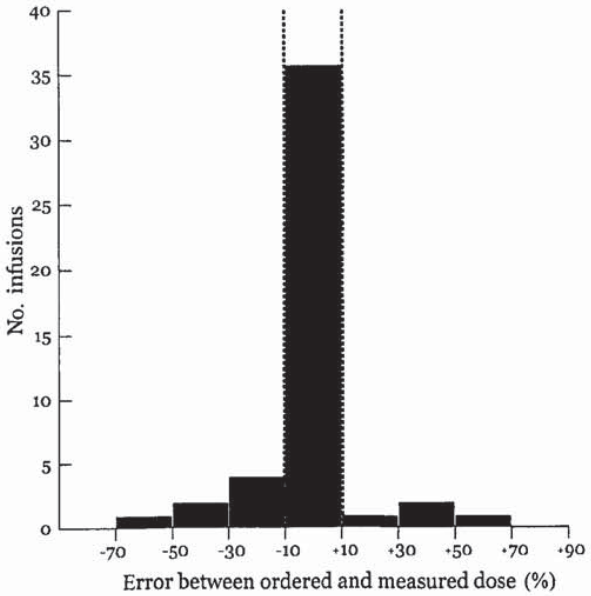

Figure 1. Histogram of the percentage difference between the methotrexate dose administered and the ordered dose in 47 methotrexate infusions of 800 mg/m² administered to 19 children with acute lymphoblastic leukemia. Doses were calculated using concentration measurements by HPLC and volume assessments of bags before and after infusion. The area bounded by the dashed lines represents the acceptable range of dose variation (±10%).

significantly associated with lower methotrexate concentrations. The dose administered in the last hours of the methotrexate infusion was also significantly associated with its serum concentration. The mean interval between the last and second-last times that volumes of methotrexate infusion were charted was 1.13 hours (range 0.41–4.2).

Regression analysis suggested that changes in the rate of methotrexate infusion in the last hours of infusion affected the serum methotrexate concentration by 0.5–4.9 μmol/L. When all variables were used in multiple regression, 43% of the variability in methotrexate concentrations could be explained. The serum creatinine level at the time of diagnosis explained more than half (24%) of this variability (Table 1).

Repeated measures regression found that the dose administered over the last hours of infusion ($p = 0.006$) and the serum creatinine level at diagnosis ($p = 0.05$) were the only variables significantly associated with the serum methotrexate concentration.

SECONDARY OUTCOMES

The total dose administered per meter squared was not significantly associated with any of the clinical toxicities assessed. The serum methotrexate concentration was associated with modest elevations in both aspartate and alanine aminotransferases, but not postinfusion renal or hematologic measurements (Table 2).

Table 1. Prediction of the 24 Hour Serum Methotrexate Concentration[a]

Parameter	Mean	Min	Max	Estimate	p Value	r^2
CCC at diagnosis (mL/min/1.73 m^2)	141	92	193	−0.02	0.34	0.02
Creatinine at diagnosis (mg/dL)	0.47	0.32	0.92	6.16	0.04	0.09
CCC at start of infusion (mL/min/1.73 m^2)	171	65	221	−0.003	0.85	0.0008
Creatinine at start of infusion (mg/dL)	0.39	0.25	0.86	4.6	0.19	0.04
Time between obtaining serum concentration and documented completion of infusion (min)	16	−15	140	−0.00009	0.73	0.002
Protocol					0.66	0.004
Total dose (mg/m^2)	784	316	1233	0.0022	0.48	0.01
Last bag dose (mg/m^2)	563	194	1233	−0.0030	0.11	0.06
Dose administered in the last 1–2 h of infusion (mg/m^2/h)	29	6	94	0.0856	0.01	0.13
Height (cm)	116	79	175	0.04	0.06	0.08
Weight (kg)	28.5	11	87	0.03	0.09	0.06
BSA (m^2)	0.94	0.49	2.0	1.43	0.23	0.03
All of the above					0.05	0.43
Creatinine at diagnosis and last hours dose only					0.002	0.24

BSA = body surface area; CCC = calculated creatinine clearance; Max = maximum; Min = minimum.
[a]Single variable linear regression comparing the 24 hour serum methotrexate concentration with potentially predictive factors.

Discussion

We found errors outside pharmaceutical industry standards in 23% of methotrexate infusions administered to children with leukemia and among 31% of the methotrexate admixtures prepared for treatment. The impact of these errors on measured drug concentrations was small, and most of the variability (58%) in steady-state methotrexate concentrations remains unexplained. In this model of drug error, patient-related differences in renal drug elimination and the dose administered in the final hours of infusion were more important predictors of the serum drug concentration than variations in the total dose administered.

The results of our study are consistent with previous observations of methotrexate pharmacology.[13] The finding that serum creatinine level was more strongly associated with a serum methotrexate concentration than a calculated creatinine clearance may be related to previous descriptions of the limitations of calculated creatinine clearance in children with malignancy.[17,18] One previous study found that a calculated creatinine clearance could explain only 10% of the variability in methotrexate clearance in children.[14] The serum creatinine level at diagnosis was more strongly associated with the serum methotrexate concentration than the serum creatinine at the time of infusion. The serum creatinine at diagnosis was 0.08 mg/dL higher than at the time of infusion. This most likely reflects reduced muscle mass during treatment rather than altered renal function.[19,20]

The variable most significantly associated with a 24 hour serum methotrexate concentration was the dose administered during the last hours of infusion. This finding raises 3 issues. First, it highlights the importance of considering drug administration as an explanation for apparent variability in therapeutic drug concentrations such as peak antibiotic concentrations and other clinical outcomes.[21-23] Second, it questions the value of 24 hour serum methotrexate concentrations as a measurement of steady-state. The wide variability of the dose per meter squared per hour administered during the last 1–2 hours of infusion is apparent from Figure 2. Because the half-life of methotrexate is 6–8 hours in this population, it should be expected that the serum methotrex-

ate concentration would change in this 1- to 2-hour period, although a new steady-state would not be reached for at least 18 hours.[12] Our data suggest that the clinical impact of the change in serum methotrexate concentration is small.

Finally, if the 24 hour serum methotrexate concentration is not a true steady-state level, then the assumptions about the nature of relationships between potential explanatory variables and this concentration may be attenuated. This in turn may have impacted the ability of this study to show a significant effect of dosing error in the relatively small sample studied.

LIMITATIONS

There are 5 limitations to this study. First, the method used to determine the methotrexate dose may be less accurate than suggested. We excluded one under-mixed sample. However, the pharmacy technicians making the infusions were aware of the purpose of the study and the importance of thorough mixing, and our previous work suggests that incomplete mixing is uncommon.[1] At most, the measurements varied by 5% in the sampling study. The other sources of measurement error were the weight and methotrexate assay. We estimate maximum errors of 1% from weighing measurements (precision 0.1 g) and 5% from the methotrexate assay from the measuring instruments used (CV ~2%). These errors are multiplicative and could suggest a measured dose between 89% (0.95 × 0.95 × 0.99) and 111% (1.05 × 1.05 × 1.01) of the actual dose. Thus, in the worst-case scenario, the process of measurement could have added up to 11% error. This is considerably less than the majority of the errors found (Figure 1).

Second, the study may have been underpowered to detect important differences in each of the predictor variables.[24] There were 11 infusions with 10% or more error. Aggressive preemptive toxicity management may have prevented the development of the historically well-recognized complications. However, variations in folinic acid rescue, postchemotherapy hydration, urinary alkalinization, and the duration of methotrexate exposure may be important determinants of later toxicities.[25-28] Further observational studies are needed to evaluate the effect of variations from protocol on methotrexate-associated toxicity. Third, as the largest prospective study reported that 4% of medication errors are associated with adverse events, a sample of 11 errors may not be large enough to demonstrate adverse drug events.[29] Dosing errors may also contribute to subclinical adverse drug events.

Fourth, our results are from a single institution and a single drug and may not be generalizable to other centers or medications. However, results from studies in other institutions and with other drugs suggest that this is not the case.[1-4] We did not evaluate the origins of variability and, consequently, were not able to exclude the stock solution (from the vial) as a major source of error.

Finally, the inaccuracies of the serum methotrexate concentration assay may have contributed to the limited corre-

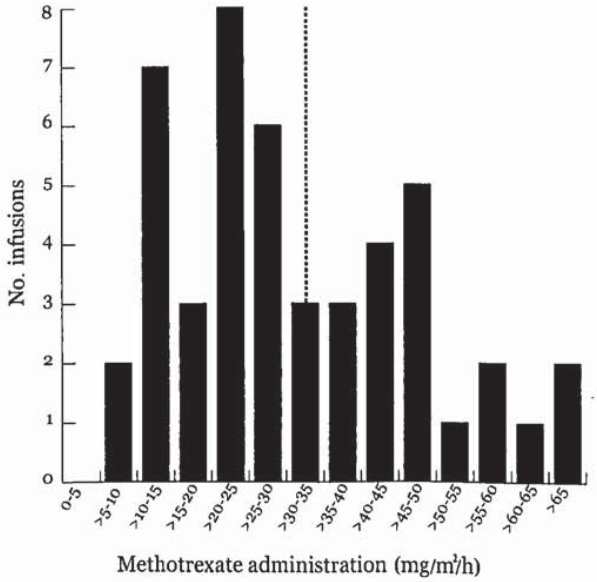

Figure 2. Histogram of the rate at which methotrexate was administered during the last documented period of the infusion. The infusion rate in mL/h was determined from the volumes infused divided by the time over which the volume was infused. The dose per hour was calculated from the measured methotrexate concentration. The dashed line represents the anticipated infusion rate if the 800 mg/m² dose was administered consistently throughout the 23 hour and 40 minute infusion. Greater doses were associated with greater serum concentrations at the completion of the infusion (p = 0.01).

Table 2. Mean Laboratory-Based Toxicity Measurements[a]

Methotrexate Parameters	Quartiles			p Value[b]
	Lowest	Middle	Upper	
Total dose m²				
AST (max; U/L)	43	43	59	0.45
ALT (max; U/L)	90	73	114	0.97
creatinine (max; mg/dL)	0.40	0.42	0.41	0.76
neutrophils (min; 10^9/L)	1.50	1.28	1.42	0.47
platelets (min; 10^9/L)	317	346	298	0.69
hemoglobin (min; g/dL)	11.4	10.9	11.5	0.70
24 h concentration				
AST (max; U/L)	33	41	65	0.0003
ALT (max; U/L)	47	87	112	0.0073
creatinine (max; mg/dL)	0.34	0.44	0.40	0.23
neutrophils (min; 10^9/L)	1.33	1.41	1.31	0.93
platelets (min; 10^9/L)	325	338	313	0.98
hemoglobin (min; g/dL)	11.3	11.3	11.0	0.65

ALT = alanine aminotransferase; AST = aspartate aminotransferase; max = maximum; min = minimum.

[a]Presented for the 4 weeks beginning at the completion of each of 47 methotrexate infusions administered to 19 patients. Mean values are presented by quartiles of total dose per meter squared and the 24 hour serum methotrexate concentration.

[b]From linear regression of continuous toxicity values versus the total dose or 24 hour concentration.

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