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# Reduced time for urinary alkalinization before high-dose methotrexate with preadmission oral bicarbonate

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## Abstract

**Purpose:** Hydration and urinary alkalinization are essential for reducing renal dysfunction with high dose methotrexate (HDMTX). This report presents an analysis of institutional methods used to achieve adequate urinary alkalinization and output for patients receiving single agent HDMTX. Renal and metabolic parameters of tolerance were examined.

**Methods:** Medical records of adult patients receiving HDMTX during the calendar years of 2008–2009 were retrospectively reviewed to determine the time to achieve urine pH $>$ 7. Number of hospital days, bicarbonate dose, ordered hydration rate, urine output, and urine pH were assessed. A survival analysis model was run for time to urine pH $>$ 7 using preadmission oral bicarbonate as a predictor variable and including a frailty term. Observational statistics were performed for other parameters.

**Results:** The analysis included 79 encounters for ten patients. Urine pH $>$ 7 was achieved more rapidly in patients receiving preadmission oral bicarbonate ($P = 0.012$). The number of patients receiving HDMTX on the same day as admission was greater for those receiving preadmission oral bicarbonate (47%) in comparison to those who did not (2%), and they spent less time in the hospital. A standard regimen for hydration and urinary alkalinization based on this project is reported. The nature and frequency of adverse events were as expected for this treatment.

**Conclusion:** At our institution, the time to achieve urinary alkalinization was reduced for patients receiving preadmission oral bicarbonate which facilitated chemotherapy infusion on the same day as admission and decreased the number of calendar days that patients stayed in the hospital.

## Keywords

Methotrexate, lymphoma, nonHodgkin, drug toxicity, quality improvement, sodium bicarbonate, infusions, parenteral

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High-dose methotrexate (HDMTX) 3.5–8 g/m$^2$ administered every 14 days is an integral part of therapy for the treatment of primary central nervous system lymphoma (PCNSL).[1,2] There is a risk of regimen-related renal impairment with administration of HDMTX.[3] The rate of nephrotoxicity attributed to administration of HDMTX 3–8 g/m$^2$ ranges from 18 to 81% of patients.[4–7] Obstructive uropathy due to precipitation of methotrexate and the metabolites 7-hydroxymethotrexate and 2,4-diamino-N$^{10}$-methylpteroic acid within the renal tubules is considered to be the instigating event, which can yield tubular necrosis and renal failure.[3] Ancillary treatments administered with HDMTX to improve drug solubility and lessen renotubular drug exposure are essential for reducing regimen-related renal dysfunction. Alkalinization of the urine pH from 6 to 7 increases the solubility of methotrexate and its metabolites by 5- to 8-fold. In addition, administration of intravenous fluids at a rate of 2.5–3.5 L/m$^2$ per 24 h hastens the transit of methotrexate and its metabolites through the renal tubules.[3]

The logistics required for treatment delivery and patient monitoring with administration of HDMTX and ancillary interventions generally warrants hospitalization. Hospital stay duration is largely determined by the time required for administration of ancillary treatments. Events that can prolong hospitalization include diagnostic testing to assess disease response, central venous line placement for drug delivery, medically significant regimen-related adverse events, or unexpected acute illness. At our institution, the specific method used to provide ancillary hydration and urinary alkalinization for HDMTX administration is oncologist-specific. All of the oncologists initiate intravenous hydration with 5% dextrose solution containing sodium bicarbonate, 100 or 150 mEq/L, to the hospitalized patients in order to attain a urine pH exceeding 7 or 7.5 and urine output exceeding 100 mL/h. Only one oncologist instructs his patients to take oral sodium bicarbonate prior to their admission for single-agent HDMTX. He instructs the patients to ingest oral sodium bicarbonate 1300 mg every 4 h beginning the morning of their scheduled admission.

This report presents findings from a quality improvement project done to analyze the methods used by our medical oncologists for providing urinary alkalinization and hydration to patients with PCNSL undergoing treatment with single-agent HDMTX with respect to the time to achieve the target urine pH values and the number of hospital days per treatment encounter. The project also examined renal and metabolic parameters of patient tolerance.

## Materials and methods

### *Clinical data*

The methodology and findings of our institutional quality project were reviewed by the institutional review board and designated as exempt from full board review according to the Department of Health and Human Services-defined criteria for research.

The project identified adult patients treated with single-agent HDMTX for PCNSL during the calendar years of 2008 and 2009 by way of an electronic medication use inquiry and from the records of the clinical pharmacist for adult oncology. The patient's electronic medical records were reviewed to determine the amount of oral and intravenous sodium bicarbonate administered and the time to achieve urine pH > 7. The amount of bicarbonate in each 650 mg tablet was 7.6 mEq. In addition, the ordered rate of hydration was tallied. Reported values for urine pH and urine output were monitored from the start of the methotrexate infusion until the serum methotrexate level was <0.05 micromolar or the patient was discharged, whichever occurred first. Data for urine output was noted as volume ≤100 mL/h on the first day of hydration and equal to or less than 2400 mL/24 h on subsequent days. The occurrence of serum bicarbonate values exceeding 40 mEq/L was noted for each encounter. A serum bicarbonate value exceeding 40 mEq/L is designated as a critical value by the institutional laboratory. Analysis of urine pH not exceeding 7, serum bicarbonate >40 mEq/L, and urine output <2400 mL/24 h (<100 mL/h) was documented in a plus or minus manner with respect to whether or not the event occurred during each patient encounter.

The method used for calculating the number of hospital days was chosen to provide data that was meaningful for our practitioners and staff, and cleanly quantifiable for retrospective data analysis. The number of hospital days for each interval examined was counted in increments of whole days. As an example, admission at 09:00 or 16:00 on the same day would count as one hospital day for each case. The total number of hospital days per encounter (hospitalization) equals the day of admission and all days through and including the day of discharge. The number of hospital days from admission to start of methotrexate equals the day of admission and all days through and including the day of methotrexate administration. The number of hospital days from the start of methotrexate to discharge equals the day of methotrexate infusion and all days through and including day of discharge.

The frequency and severity of acute kidney injury and elevated serum creatinine values were evaluated using

**Table 1.** Patient encounters

| Bicarbonate administration | | |
|---|---|---|
| Parameter | Oral and intravenous | Intravenous only |
| Number of encounters | 36 | 43 |
| Number of patients | 4 | 6 |
| Patient age/ages | 68, 70, 74, 78 | 56, 58, 60, 60, 74, 75 |
| Male:female (number) | 1:3 | 3:3 |

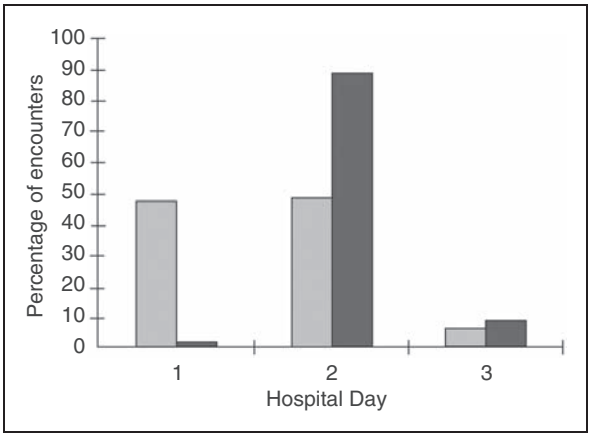


**Figure 1.** Hospital day of methotrexate administration: oral and intravenous bicarbonate (light grey); intravenous bicarbonate only (dark grey).

**Table 2.** Mean (standard deviation) time to urine pH > 7 and mean (standard deviation) number of hospital days per encounter

| Bicarbonate administration | | |
|---|---|---|
| Parameter | Oral and intravenous | Intravenous only |
| Time to urine pH > 7 (hours) | 5.4 (3.9), $p = 0.012$ | 10.8 (8.2) |
| Total number of hospital days | 6.4 (2.4) | 7.1 (3.9) |
| Admission to start of HDMTX (days) | 1.8 (1.2) | 2.4 (2.0) |
| Start of HDMTX to discharge (days) | 5.5 (1.7) | 5.5 (2.9) |

HDMTX: High-dose methotrexate.

the National Cancer Institute Common Terminology Criteria of Adverse Events, version 4.[8]

### *Statistical analysis*

Using the statistical software *R*,[9] a survival analysis model was run for time to urine pH > 7 using oral bicarbonate as a predictor variable and including a frailty term. Cox proportional hazards model was not used to implement survival analyses because our data had multiple observations per individual, which violates the assumption of the Cox model that individuals are independent of each other. To account for this dependence between individuals the Weibull distribution (a parametric model) was utilized. The frailty term, which accounts for the dependence between individuals, was insignificant with a $p$ value of 0.220 and a Chi-square test statistic of 7.82. The test statistic and $p$ value for the oral bicarbonate predictor were given as 6.26 and 0.012, respectively. At the $\alpha = 0.05$ level, this gives evidence that the effect of oral bicarbonate was significant. Observational statistics were performed for other parameters.

## Results

A total of 79 encounters for 10 patients with PCNSL undergoing treatment with single-agent HDMTX were identified for the calendar years of 2008 and 2009 (Table 1). The HDMTX was administered on hospital day 1 or 2 for most encounters (Figure 1). The mean number of total hospital days and the mean number of hospital days between admission and start of HDMTX were shorter by 0.7 days and 0.6 days for the patients receiving oral bicarbonate. However, the mean number of hospital days from start of the HDMTX infusion to patient discharge was similar between the two groups, which implicate an event or events preceding HDMTX administration as the factor/factors influencing length of hospital stay (Table 2). Target urine pH was achieved in less time for patients taking preadmission oral bicarbonate ($p = 0.012$; Table 2). The number of patients receiving HDMTX on the same day as admission was greater for those receiving oral and intravenous bicarbonate in comparison to those receiving intravenous bicarbonate only (Figure 1). One patient receiving intravenous bicarbonate only routinely received a 50 mEq bolus prior to initiation of the continuous intravenous infusion of alkaline hydration. Despite this intervention, his methotrexate was initiated on the second hospital day for 11 of 13 encounters. Chemotherapy administration on the other two encounters was delayed beyond hospital day 2 due to time needed for the initial diagnosis of PCNSL and placement of a peripherally inserted central catheter.

Patients receiving only intravenous bicarbonate were administered more parenteral fluid and a higher daily dose of bicarbonate (Table 3). The mean amount of bicarbonate ordered for administration over a 24 h period and the mean rate of hydration during the same time frame were 1.4-fold and approximately 1.7-fold greater, respectively, for patients receiving

**Table 3.** Urinary alkalinization and urine output

| Bicarbonate administration | | |
|---|---|---|
| Parameter<br>Amount of bicarbonate ordered; mean (standard deviation) | Oral and intravenous | Intravenous only |
| Intravenous bicarbonate per 24 h (mEq) | 407 (96) | 647 (154) |
| Oral and intravenous bicarbonate per 24 h (mEq) | 477 (96) | 647 (154) |
| Rate of hydration (mL/h) | 125–150 | 200–250 |
| Rate of hydration ($L/m^2/24$ h) | 1.4–2 | 2–3.5 |
| Urine pH < 7 per encounter; *N* (%) | 7 (19) | 5 (12) |
| Urine output < 100 mL/h per encounter; *N* (%) | 13 (36) | 5 (12) |

**Table 4.** Regimen related adverse events

| Bicarbonate administration | | | | |
|---|---|---|---|---|
| | Oral and intravenous | | Intravenous only | |
| Adverse event | Per encounter<br>*N* (%) | Per patient<br>*N* (%) | Per encounter<br>*N* (%) | Per patient<br>*N* (%) |
| Serum bicarbonate >40 mEq/L | 7 (19) | 4 (100) | 13 (30) | 4 (67) |
| Acute kidney injury | | | | |
| Grades 1 and 2 | 9 (25) | 4 (100) | 9 (21) | 4 (67) |
| Grades 3 and 4 | 0 | 2 (5) | 2 (33) | |
| Elevated serum creatinine | | | | |
| Grades 1 and 2 | 25 (69) | 4 (100) | 26 (60) | 6 (100) |
| Grades 3 and 4 | 1 (3) | 1 (25) | 2 (5) | 2 (33) |

intravenous alkalinization only, in comparison to those receiving oral and intravenous alkalinization. The rate of one or more urine pH values dipping to less than 7 was similar between the two groups. However, the rate of recorded urine output being less than 2400 mL/24 h on at least 1 day of therapy was noted more frequently in patients receiving oral bicarbonate therapy. Three-fold more encounters of patients receiving oral plus intravenous bicarbonate had at least 1 day during which the recorded urine output was less than 2400 mL/24 h. All patients receiving oral bicarbonate therapy experienced at least 1 day of recorded urine output below 2400 mL/24 h versus one third of patients receiving only intravenous bicarbonate.

Serum bicarbonate values exceeding 40 mEq/L were noted in 1.6-fold more encounters of patients receiving intravenous bicarbonate only (Table 4). However, all patients receiving oral plus intravenous bicarbonate experienced at least one serum bicarbonate value exceeding 40 mEq/L versus two thirds of those receiving only intravenous bicarbonate. Mild-to-moderate acute kidney injury occurred in a similar number of encounters in both patient groups (Table 4). All patients in the oral bicarbonate group experienced mild-to-moderate acute kidney injury versus two thirds of those receiving only intravenous bicarbonate. However, Grades 3 and 4 acute kidney injury occurred in two of 43 encounters (5%) receiving only intravenous alkalinization and no patients receiving oral plus intravenous bicarbonate. One patient was a 60-year-old female, who experienced a doubling of serum creatinine the morning after her first dose of HDMTX that was administered at 11:20 the preceding day. This patient required hemodialysis to manage her acute renal failure. The second case of severe acute kidney injury occurred with the second dose of methotrexate administered to a 75-year-old male, whose admission serum creatinine was the same as his baseline value for cycle one of chemotherapy. This gentleman did experience Grade 1 acute kidney injury and Grade 2 changes in serum creatinine with cycle one of HDMTX. Urine pH values were consistently >7 for both encounters with Grades 3 and 4 acute kidney injury. The rate of Grades 1–4 changes in serum creatinine were similar for both groups, when analyzed by encounter and per patient.

## Discussion

High-dose methotrexate is included in various chemotherapy regimens for lymphomas, leukemias, and osteosarcoma.[10–14] This analysis was limited to patients receiving single-agent HDMTX for the treatment of PCNSL, in order to examine a similar group of patients receiving the same therapy without the confounding influence of additional concurrent or recent chemotherapy agent administrations. The nature and severity of adverse events attributed to administration of HDMTX and ancillary treatments were as expected for this type of therapy. The frequency of acute kidney injury was within the rate reported in the medical literature (18–81% of patients).[4–7] Episodes of markedly elevated serum bicarbonate were handled appropriately on a case-by-case basis, and there were no clinical adverse events in our patients attributable to systemic alkalosis. One key aspect of ancillary treatments for reducing methotrexate-related renal impairment is that the targeted amounts for urine pH and output are readily measureable by standard clinical monitoring. A particular regimen for hydration and urinary alkalinization may offer cost and convenience benefits; however, the critical element for reducing the nephrotoxicity of treatment with HDMTX is provision of adequate hydration and urinary alkalinization.[3]

The data was harvested retrospectively as part of an institutional quality project. The initial intent of the quality project was to ascertain whether patients treated with single-agent HDMTX at our medical center consistently received adequate urinary alkalinization and hydration for this therapy. Analysis of the retrospectively collected data identified the divergent methods for urinary alkalinization and the impact on hospital stay. A limitation to this work is that the data was harvested from an institutional quality project instead of a prospectively controlled clinical study. The manner in which hospital days were tallied does not delineate differences that may have arisen from patient arrival on the nursing unit in the morning versus late in the afternoon. This is why statistical analysis was limited to the documented element of time from start of ancillary hydration to measurement of urine $pH > 7$. The time frame from initiation of alkaline hydration to urine $pH > 7$ provides an objective measure directly related to sodium bicarbonate administration, which the time to administration of HDMTX is contingent upon. Moreover, detailed analysis of concurrent medication therapy and comorbidities was not performed as part of the quality project. Standard practice at our medical center includes pharmacist evaluation of medication therapy to identify and address any concurrent medications that can alter the pharmacokinetics or safety of HDMTX. Albeit this was not documented for inclusion in the quality project and the institutional review board exemption covering publication of this material did not support extraction of additional data from patient medical records.

One weakness of the methodology for this report is that the self-administered dose of oral sodium bicarbonate was not quantified for each patient. This was not feasible with retrospective chart review because the amount of sodium bicarbonate taken prior to admission was not routinely noted in the patient's medical record. Moreover, for cases where this information was documented, the validity of the data was limited by the uncertain reliability of self-reporting. Another caveat to the findings of this project is that the retrospective data collection was based on a chronologic time interval so not all encounters for all patients were included in the analysis. A more stringent investigation would have been provided by analysis of all encounters for all patients. For most patients, the first hospitalization for their PCNSL encompasses the greatest number of hospital days because it entails admission for management of symptomatology that culminates in the subsequent cancer diagnosis. All such first encounters were captured for all patients included in this analysis.

The mean time to achieve urine $pH > 7$ was two-fold longer for patients receiving only intravenous alkaline hydration beginning at the time of admission in comparison to those beginning oral bicarbonate the day of admission prior to their hospitalization (Table 2). It is evident from examination of data in Tables 2 and 3 that the cumulative and hourly amounts of prescribed bicarbonate (oral and intravenous) from the initiation of intravenous hydration to the time of urine $pH > 7$ were approximately 2.7- and 1.4-fold greater for patients receiving intravenous alkalinization only (291 mEq over 10.8 h) in comparison to those receiving intravenous and oral bicarbonate (109 mEq over 5.5 h). So, in addition to the amount of bicarbonate administered, the rate of intravenous hydration likely impacted the time to urinary alkalinization. Data in Tables 2 and 3 also demonstrate that the cumulative volume and hourly rates of hydration from the initiation of intravenous hydration to the time of urine $pH > 7$ were approximately 3-fold greater and 1.4- to 1.8-fold greater for patients receiving intravenous alkalinization only (2160–2700 mL over 10.8 h; 83–146 mL/$m^2$/h) in comparison to those receiving intravenous and oral bicarbonate (688–825 mL over 5.5 h; 60–83 mL/$m^2$/h). Reduced fluid intake with oral bicarbonate self-administration relative to intravenous infusion of alkaline hydration may lead to more rapid equilibration of serum bicarbonate concentration to a value exceeding the renal threshold for this base and underlie the relatively rapid urinary alkalinization noted with this intervention.[15] The dilutional effect of intravenous

hydration may explain why administration of sodium bicarbonate 50 mEq as an intravenous bolus immediately prior to initiation of the continuous alkaline infusion did not facilitate HDMTX administration on the day of hospital admission for a particular patient.

At our institution, the duration of hospitalization was reduced for most patients receiving oral bicarbonate prior to admission for single-agent HDMTX. However, continuation of oral bicarbonate therapy throughout the patient's hospitalization did not provide an advantage to parenteral delivery of daily bicarbonate requirements. In addition, there are advantages to consolidating bicarbonate administration into the intravenous fluid. The systemic exposure to bicarbonate is certain with intravenous administration; whereas, oral administration of bicarbonate yields variable systemic concentrations. Administration of sodium bicarbonate 1300 mg orally every 4 h while awake necessitates the ingestion of 8 to 10 650 mg tablets throughout the course of the day. Presumably, most patients would be pleased to stop this regimen earlier rather than later. Moreover, system workflow is improved by truncating the duration of oral bicarbonate therapy.

## Conclusion

At our institution, the time to achieve urinary alkalinization was reduced for patients receiving preadmission oral bicarbonate in comparison to administration of intravenous bicarbonate only beginning with the patient's arrival on the nursing unit. In addition, patients receiving oral bicarbonate prior to admission were more likely to receive HDMTX on the same day as admission and spend fewer calendar days in the hospital.

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