**Introduction**

- Methotrexate (MTX) is used to treat acute lymphoblastic leukemia and solid tumors, such as osteosarcoma, in pediatric oncology patients.
- MTX is primarily eliminated by the kidneys via proximal tubular secretion. As a result of similar clearance mechanisms and potential competitive elimination, there is a possibility that administering beta-lactam antibiotics may decrease the clearance of MTX when given concomitantly.
- Evidence in the literature regarding a potential MTX and beta-lactam interaction is limited to case reports and animal studies.
- Recently at the Alberta Children’s Hospital (ACH; Calgary, Alberta), empiric treatment for febrile patients receiving MTX has changed from piperacillin-tazobactam (pip-tazo) to meropenem to avoid the potential drug interaction with pip-tazo as there is more case report data for pip-tazo and MTX interaction.

**Objectives**

**Primary objective:**
- Determine the change in half-life and time to clearance (TTC) of MTX when administered with a beta-lactam antibiotic

**Secondary objectives:**
- Describe the effect that antibiotic co-administration had on markers of MTX toxicity.
- Changes in leucovorin dosing
- Changes in hydration requirements
- Changes in serum creatinine
- Describe the change in MTX clearance in a subsequent MTX cycle
- Describe the differences in TTC, half-life and other markers of MTX toxicity (as above) between the MTX cycle pre, concurrent and post antibiotic co-administration

**Methods**

**Methodology:**
- Medical records for pediatric patients administered MTX with beta-lactam antibiotics were reviewed retrospectively. Data was collected for the concurrent MTX-antibiotic (interaction) cycle as well as the MTX cycle prior to and after the interaction.
- Data collection included patient demographics, MTX doses and levels, concurrent antibiotic and dose, other concurrent medications, serum creatinine, hydration rates, and leucovorin doses.
- Patients acted as their own control for MTX clearance to limit inter-patient variability

**Inclusion Criteria:**
- Oncology patients (age 1-40) at the ACH who had received MTX at doses ≥ 500 mg/m² for at least one cycle without an antibiotic, at least one cycle concurrently with a beta-lactam antibiotic (pip-tazo, meropenem, amoxicillin, cefepine, ceftriaxone or penicillin). Concurrent administration was defined as receiving one of the above beta-lactam antibiotics any time between the start of MTX infusion and clearance of MTX (serum concentration of ≤0.1 μmol/L).

**Exclusion Criteria:**
- Patients whose MTX levels were not monitored were excluded from the study as MTX clearance could not be calculated.
- Half-life calculated by using slopes of concentrations vs. time as reported in previous literature.
- TTC of MTX was measured from start of infusion until MTX levels were ≤0.1 μmol/L, as per Children’s Oncology Group (COG) protocols.
- COG protocols provided guidance and defined points in time when MTX levels should be drawn.

**Results**

**Figure 1: Patient Recruitment**

- 143 patients, 391 doses of MTX screened
- Excluded MTX administrations based on:
  - MTX cycle without a concurrent beta-lactam antibiotic
  - MTX levels <500 mg/m²
  - MTX interaction cycle with a baseline antibiotic free MTX cycle
- 7 MTX administrations from 7 patients included

**Table 1: Population Data**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (Years)</td>
<td>13; IQR 1.5</td>
</tr>
<tr>
<td>Male (%)</td>
<td>28.6</td>
</tr>
<tr>
<td>Female (%)</td>
<td>71.4</td>
</tr>
<tr>
<td>Median MTX Dose (g)</td>
<td>18; IQR 2.75</td>
</tr>
<tr>
<td>Ant. &amp; MTX Population</td>
<td>Ceftriaxone n=6 85%</td>
</tr>
<tr>
<td></td>
<td>Meropenem n=1 15%</td>
</tr>
<tr>
<td>Antibiotic Dose (mg/kg/day)</td>
<td>46; IQR 12 60</td>
</tr>
</tbody>
</table>

**Figure 2: Median Half-life and Time to Methotrexate Clearance by Cycle**

**Table 2: Methotrexate Clearance and Pharmacokinetic data**

<table>
<thead>
<tr>
<th>Kinetic Parameters</th>
<th>Prior Cycle</th>
<th>Interaction Cycle</th>
<th>Post Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median half-life (h) (25th percentile, 75th percentile)</td>
<td>4.96 (4.72, 5.82)</td>
<td>6.47 (6.14, 6.82)</td>
<td>5.68 (4.88, 6.51)</td>
</tr>
<tr>
<td>Median time to MTX clearance (h) (25th percentile, 75th percentile)</td>
<td>72 (68.67, 84.04)</td>
<td>88.67 (77.75, 93.59)</td>
<td>84 (72, 96.06)</td>
</tr>
</tbody>
</table>

**Table 3: Secondary Endpoints**

<table>
<thead>
<tr>
<th>Kinetic Parameters</th>
<th>Prior Cycle</th>
<th>Interaction Cycle</th>
<th>Post Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median leucovorin dose (mg/m²/day) (25th percentile, 75th percentile)</td>
<td>60 (60, 60)</td>
<td>60 (60, 60)</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Median hydration (mL/m²/hr) (25th percentile, 75th percentile)</td>
<td>200 (143.75, 200)</td>
<td>200 (143.75, 200)</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Median serum creatinine (μmol/L) (25th percentile, 75th percentile)</td>
<td>50 (46.5, 60)</td>
<td>53 (46.5, 58.5)</td>
<td>49.5 (47.25, 59.5)</td>
</tr>
</tbody>
</table>

**Discussion**

**Points:**
- Within ACH, patients do not frequently receive a beta-lactam antibiotic concurrently with MTX administration.
- A total of seven patients were included, 6 receiving ceftriaxone.
- The median MTX half-lives for the prior, interaction and post cycles were 4.96 hours, 6.47 hours and 5.68 hours, respectively.
- Median TTC of MTX for the prior, interaction and post cycles were 72 hours, 88.67 hours and 84 hours, respectively.
- There were minimal differences seen in return close to baseline in the post-cycle.
- The prior cycle of methotrexate had a shorter half-life and TTC than the interaction cycle, and these values return close to baseline in the post-cycle.
- Although sample size was small, this study provides an indication of the rate at which this potential interaction occurs at the ACH.
- COG protocols are used in many institutions in North America, thus the results of this study may be generalizable to other pediatric hospitals also using the same protocols, although further studies would be needed to confirm the results.
- Restricting the inclusion of patients with a pre, interaction and post MTX cycle aids in limiting the inter-patient variability that may be seen with MTX clearance as the patient acts as their own ‘control’. Although this resulted in low patient recruitment.

**Limitations**

- Small sample size
- In this study, we were limited only to the data that was in the physician order system.
- Changes in MTX levels were drawn as defined by COG protocol and thus may not capture the exact time of MTX clearance. MTX serum concentrations may fall below 0.1 μmol/L before the recommended monitoring time as defined by the protocol.
- Therefore, an exact clearance could not be ascertained. Monitoring serum MTX levels hourly in another study would provide more accurate results for clearance times.
- Due to the retrospective nature of the study, other variables that could affect the results could not be controlled. These would include the use of concurrent medications, contrast for imaging studies during the treatment course or physician preference for more hydration in patients they perceived at risk for toxicity. It is not known if any of the above affect MTX clearance.

**Conclusion**

- In following to the prior cycle, increases in half-life and TTC occurred when a beta-lactam was concurrently given with MTX. Values returned close to baseline in the post-cycle.
- Overall this interaction is relatively uncommon when studied over a period of 5.5 years at one pediatric hospital. Caution should be warranted when administering beta-lactam antibiotics to patients receiving high-dose methotrexate.
- Ceftriaxone may marginally increase the half-life and TTC of MTX. However, it is unknown if this would have a clinical relevance or lead to increased toxicities.

**Acknowledgements**

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**References**

References available upon request.

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