Acute Kidney Injury Associated with Trimethoprim/Sulfamethoxazole

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Abstract:
Introduction. Trimethoprim/sulfamethoxazole (TMP/SMX) effectively treats community-acquired soft-tissue infections and urinary tract infections, both of which occur in patients with risk factors for renal impairment. We systematically studied the adverse renal effects of TMP/SMX in a middle-aged veteran population.

Methods. We reviewed complete electronic records for all patients who, during a three-year period, received ≥ 90 days of treatment with TMP/SMX and for whom a baseline and follow-up determination of serum creatinine and blood urea nitrogen (BUN) were available.

Results. Of 573 patients who met inclusion criteria, 64 (11.2%) had rises in serum creatinine and BUN within one week of completion of therapy (Table 1). TMP/SMX in a middle-aged hospitalized veteran population.

Methods:
- **Patient inclusion**: Consecutive patients (pts) for whom TMP/SMX was prescribed were included if baseline serum creatinine and blood urea nitrogen (BUN) and follow-up within one week of completion of therapy were available.
- **Definitions**: Acute kidney injury (AKI) in pts without CKD: increase in serum creatinine ≥2.0 mg/dL or BUN ≥2.0 mg/dL. [5] AKI in pts with CKD: ≥50% increase in serum creatinine and BUN [5, 6].

Data recorded. Uriminalysis: days of TMP/SMX prior to first documentation of AKI; time to return to baseline after discontinuation of TMP/SMX. Records were reviewed for alternative explanations for AKI (e.g. volume loss, hypotension, diuresis, coadministration of nephrotoxic drugs). The likelihood that AKI was attributable to TMP/SMX was assessed.

Results:
1. Medical records were reviewed for 1,662 patients who received TMP/SMX; 573 met criteria for inclusion.
2. AKI appeared during or immediately after Rx with TMP/SMX in 64 of 573 pts (11.2%).
3. The average duration of Rx in all patients was 7.9 days.
4. Duration of Rx and dose were not related to appearance of AKI.
5. AKI was transient in most cases if therapy was discontinued, with renal function returning to baseline levels within 30 days; 1 pt required dialysis.
6. The frequency of AKI was greater among pts who had preexisting diabetes mellitus, hypertension and CKD (Table 1), especially when diabetes and hypertension were poorly controlled.
7. AKI was clearly attributable to TMP/SMX in 51.6%, possibly due to TMP/SMX; 13 (17.2) patients developed AKI during or immediately after Rx with TMP/SMX in 64 of 573 pts (11.2%).
8. In a similar population of 84 treated for cystitis, AKI was observed in 0% of cases (P < 0.001; data not shown).

Table 1. Characteristics of patients with and without AKI

<table>
<thead>
<tr>
<th>Category</th>
<th>AKI patients</th>
<th>Non-AKI patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 tablets/day?</td>
<td>4 (6.3)</td>
<td>24 (47)</td>
<td>0.59</td>
</tr>
<tr>
<td>&gt;10 days of treatment</td>
<td>23 (35.9)</td>
<td>174 (38.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>36 (56.3)</td>
<td>263 (51.7)</td>
<td>0.49</td>
</tr>
<tr>
<td>Race</td>
<td>White: 32 (50.0)</td>
<td>295 (58.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>Black</td>
<td>23 (35.9)</td>
<td>149 (29.3)</td>
<td>0.51</td>
</tr>
<tr>
<td>Indication</td>
<td>Skin and Soft Tissue: 28 (43.8)</td>
<td>183 (36.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>16 (25)</td>
<td>193 (37.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Diabetes Mellitus (DM)</td>
<td>40 (62.5)</td>
<td>169 (33.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HgbA1c ≥8%</td>
<td>26 (40.6)</td>
<td>131 (25.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>HgbA1c ≥2%</td>
<td>14 (21.9)</td>
<td>38 (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (76.6)</td>
<td>256 (50.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, HgbA1c ≥8%</td>
<td>20 (31.2)</td>
<td>88 (17.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypertension, HgbA1c &lt;8%</td>
<td>11 (17.2)</td>
<td>27 (5.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>22 (34.2)</td>
<td>104 (20.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stage 2</td>
<td>8 (36.4)</td>
<td>47 (45.9)</td>
<td>0.45</td>
</tr>
<tr>
<td>Stage 3</td>
<td>13 (59.1)</td>
<td>54 (51.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>HIV</td>
<td>6 (9.4)</td>
<td>58 (11.4)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Classification of AKI

- **Likely to be caused by TMP/SMX**: 33
- **Possibly caused by TMP/SMX**: 28
- **Medication**: 8
- **Intravenous contrast**: 3
- **Comorbidities**: 3
- **Preeclampsia**: 3
- **Postnatal**: 0
- **Multiple causes**: 10
- **Unlikely to be caused by TMP/SMX**: 3

Discussion and Conclusions:
- *In a largely middle-aged hospitalized veteran population, 11.2% of patients developed AKI during or immediately following TMP/SMX therapy. Immunoassay was transient if therapy was discontinued.
- *Just over one-half of cases, no other factor(s) contributed to AKI was/were identified.*
- *TMP/SMX should be considered an independent risk factor for AKI.*
- *Other risk factors for TMP/SMX-associated AKI include diabetes mellitus, hypertension, and CKD.*
- *Minimal renal impairment rather than interstitial nephritis appears responsible for the great majority of cases.*
- *If renal function does not return to baseline within one month of discontinuation of therapy, the source of the AKI is unlikely to be TMP/SMX.

References:
4. In a middle-aged hospitalized veteran population, 11.2% of patients developed AKI during or immediately following TMP/SMX therapy. Immunoassay was transient if therapy was discontinued.
5. Just over one-half of cases, no other factor(s) contributed to AKI was/were identified.
6. TMP/SMX should be considered an independent risk factor for AKI.
7. Other risk factors for TMP/SMX-associated AKI include diabetes mellitus, hypertension, and CKD.
8. Minimal renal impairment rather than interstitial nephritis appears responsible for the great majority of cases.
9. If renal function does not return to baseline within one month of discontinuation of therapy, the source of the AKI is unlikely to be TMP/SMX.