Adverse consequences of low-dose methotrexate medication errors

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Poison, Toxicovigilance and Pharmacovigilance Centre, Lyon (1), Poison and Toxicovigilance Centre, Angers (2), Pharmacovigilance Centre, Marseille (3), Poison and Toxicovigilance Centre, Paris (4), Pharmacovigilance Centre, Bordeaux (5), Poison and Toxicovigilance Centre, Marseille (6), French National Medicine Agency (ANSM) Paris (7) and the French networks of Poison Control and Pharmacovigilance Centers

Background and objectives

✓ Medication errors (ME) associated with low-dose oral methotrexate (MTX) prescribed on a weekly basis can be associated with severe consequences and are continuously reported to the French Networks of Poison Control or Pharmacovigilance centers.

✓ Our objectives were to quantify these errors and to describe their consequences.

Materiel and Methods

All cases involving an oral formulation of low-dose MTX and collected by the French networks of poison control (PCC) or pharmacovigilance (PVC) centres were analysed. Inclusion criteria were the following:

- Cases reported between 1st January 2007 and 31st October 2013
- Intake of more than 2-fold the intended weekly dose or
- Weekly cumulative dose higher than 30 mg or
- Error repeated for more than 7 consecutive days

To carefully evaluate the consequences of the error, a follow-up of at least 4 days after the last MTX dose was required in pharmacovigilance (PVC) centres were analysed. Inclusion criteria were the following:

19 men and 56 women

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Results

75 cases retained among whom 47 (63%) had severity criteria

Source of the data: PCC in 28, PVC in 38 and both sources in 9

Patients and circumstances

- 19 men and 56 women
- Median age: 76 years (44-94)
- Indication: inflammatory rheumatism in 79%
- Type of error (unknown in 1 case)
  - Prescription: 17
  - Administration: 56
  - Self-medication: 1
  - Intake of MTX daily instead of weekly in 88%, single error in 5.3%
- Location of the error
  - At home: 45 (including 2 errors made by the nurse)
  - At hospital: 20
  - In a nursing home: 10

Comparison between severe and asymptomatic or non severe cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Without severity criteria N = 27</th>
<th>With severity criteria N = 47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>21</td>
<td>32</td>
<td>0.37</td>
</tr>
<tr>
<td>Mean age (years ± SD)</td>
<td>66.8 ±12.6</td>
<td>75.6 ±10.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean body mass index (SD)</td>
<td>26.5 ±5.9 (n=14)</td>
<td>24.4 ±5.96 (n=33)</td>
<td>0.27</td>
</tr>
<tr>
<td>Number of patients with creatinine clearance ≤ 60 ml/min before the error</td>
<td>3/18</td>
<td>8/39</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean duration of the error (days ± SD)</td>
<td>7.9 ± 12.6 (n=14)</td>
<td>13.0 ± 13.6 (n=33)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean cumulative dose mistakenly taken (mg ± SD)</td>
<td>68.9 ±45.7</td>
<td>93.0 ± 47.2</td>
<td>0.036</td>
</tr>
<tr>
<td>Mean duration of MTX error after 1st symptoms to overdose (days ± SD)</td>
<td>9.5 ± 4.95 (n=2)</td>
<td>4.1 ± 1.93 (n=13)</td>
<td>0.08</td>
</tr>
<tr>
<td>Chronic folic acid supplementation</td>
<td>8/16</td>
<td>13/36</td>
<td>0.35</td>
</tr>
<tr>
<td>Concomitant treatment with a PPI* drug</td>
<td>3/15</td>
<td>18/39</td>
<td>0.08</td>
</tr>
</tbody>
</table>

(*PPI: proton pump inhibitor)

Characteristics and consequences of the error

- Median duration of the error: 8 days (1-90)
- Ingested dose during the error:
  - Median cumulative ingested dose: 77.5 mg (20-230) or
  - 1,6 to 20-fold the intended dose (median: 5-fold) (calculation only for cases with repeated errors)
- Circumstances of error identification (unknown in 3)
  - Suggestive symptoms of MTX intoxication in 50 cases (67%)
  - Detection of the error in 20
  - Systematic blood cell count in 2
- Consequences of the error
  - Asymptomatic patients: 13 (17.3%)
  - Clinical and/or biological adverse effect occurred in 62 (82.7%) patients within 2 to 90 d after starting the error (median 8 d) with one or more complications. The most common were:
    - Haematological disorders in 47 (grade ≥ 3 in 39)
    - Mucositis in 31 (grade ≥ 3 in 15)
    - Renal disorders in 18 (grade ≥ 3 in 2)
    - Hepatic disorders in 13 (grade ≥ 3 in 7)
    - Digestive symptoms in 9
- Outcome (after standard treatment including antibiotics, folic acid, G-CSF and hydration in most patients):
  - Death in 9 (6 after a ME in hospital and 2 in nursing home)
  - Recovery after a median delay of 10 days (5-45) in 48
  - Unknown in 7

Conclusions

Even very small overdoses due to medical errors involving low-dose oral MTX can be dramatic. As a number of cases occurred in hospitals or health care services, careful attention should be given when dispensing this medication.