The association between metformin therapy and lactic acidosis

Drug Safety

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## Supplemental Table 1 Adapted WHO-UMC standardised causality assessment [43]

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria</th>
</tr>
</thead>
</table>
| **Certain**    | Event or laboratory test abnormality, with plausible time relationship to drug intake  
- Involves metformin ingestion prior to lactic acidosis  
- Cannot be explained by disease or other drugs  
- Patient presents with no independent comorbidities, concomitant medications or risk factors for lactic acidosis  
- Response to withdrawal plausible (pharmacologically, pathologically)  
- Metformin withdrawal results in resolution of lactic acidosis symptoms  
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)  
  - Diagnosis of lactic acidosis:  
    o Lactate plasma concentration >5 mmol/L  
    o pH <7.35  
- Rechallenge satisfactory, if necessary  
  - Metformin rechallenge results in lactic acidosis  |
| **Probably/Likely** | Event or laboratory test abnormality, with reasonable time relationship to drug intake  
- Involves metformin ingestion prior to lactic acidosis  
- Diagnosis of lactic acidosis:  
  o Lactate plasma concentration >5 mmol/L  
  o pH <7.35  
- Unlikely to be attributed to disease or other drugs  
- Patient presents with independent comorbidities, concomitant medications and other risk factors for lactic acidosis that are unlikely to be a causative agent or none of these  
- Response to withdrawal clinically reasonable  
  - Metformin withdrawal results in resolution of lactic acidosis  
- Rechallenge not required  |
| **Possible** | Event or laboratory test abnormality, with reasonable time relationship to drug intake  
- Involves metformin ingestion prior to lactic acidosis  
- Diagnosis of lactic acidosis:  
  o Lactate plasma concentration >5 mmol/L  
  o pH <7.35  
- Could also be explained by disease or other drugs  
- Patient presents with comorbidities and/or concomitant medications that are risk factors for lactic acidosis and could explain the adverse event  
- Information on drug withdrawal may be lacking or unclear  
  - If available: outcome of metformin withdrawal is unclear or lacking  |
| **Unlikely** | Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not possible)  
- Involves metformin ingestion prior to lactic acidosis  
- Diagnosis of lactic acidosis:  
  o Lactate plasma concentration >5 mmol/L  
  o pH <7.35  
- Disease or other drugs provide plausible explanations  
- Patient presents with comorbidities and/or concomitant medications that are risk factors for lactic acidosis more likely to be the cause than metformin  |
<p>| <strong>Conditional/Unclassified</strong> | Event or laboratory test abnormality |</p>
<table>
<thead>
<tr>
<th>Unassessable/Unclassifiable</th>
<th>Reported suggesting an adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Medical report suggests lactic acidosis diagnosis in patient</em></td>
</tr>
<tr>
<td></td>
<td>Cannot be judged because information is insufficient or contradictory</td>
</tr>
<tr>
<td></td>
<td><em>Insufficient and/or contraindicatory information to diagnose lactic acidosis</em></td>
</tr>
<tr>
<td></td>
<td>Data cannot be supplemented or verified</td>
</tr>
</tbody>
</table>

Annotations of lactic acidosis specific diagnostic criterion are presented in italics. *Risk factors were defined using the list of risk factors for lactic acidosis summarised in Table 1*