Learning Objective

To understand the risks associated with metformin use in the inpatient acute care setting.

Introduction

- Metformin is considered first-line therapy in the management of type II diabetes mellitus
- Metformin is a biguanide that remains unchanged in the body and undergoes renal excretion
- Clearance of metformin may be diminished in acute kidney injury or chronic kidney disease

Case Description

A 71 year old Russian woman with a history of T2DM, systolic heart failure, and hypertension presented with worsening dyspnea over several months which had progressed to the point where she was having difficulty talking or eating. She noted two pillow orthopnea, occasional paroxysmal nocturnal dyspnea, and edema.

Physical Exam and Labs/Imaging

VS: T35.7C  BP159/61  HR68  RR28  SpO2 95%

Exam: Notable for bibasilar crackles with extensive LE edema with serous drainage.

Imaging: Chest film showed pulmonary edema

Initial labs:
- BNP 2030 pg/mL
- ABG: 6.85/37/110/6
- Chem7: Na 138, K 9.9, Cl 107, CO2 7, BUN 118, Cr 9.98
- AG 24
- Lactate 13.2
- Ethanol, salicylate, acetone, isopropanol and methanol levels within normal limits

Metformin level 65 mcg/mL (therapeutic level 1-2 mcg/mL)

Hospital Course

She was admitted and started on BIPAP for respiratory distress but developed agitation and cardiopulmonary arrest requiring mechanical ventilation. Patient underwent emergent dialysis and was administered sodium bicarbonate, broad spectrum antibiotics, and multiple vasopressors. Eventually, the family decided to withdraw further hemodynamic support. Her lactic acidosis was felt to be secondary to metformin toxicity in the setting of acute kidney injury and cardiorenal syndrome.

Discussion

Lactic acidosis is a rare, but potentially life-threatening adverse effect of treatment with metformin. The FDA estimates the rate of metformin-associated lactic acidosis to be 5 cases per 100,000 persons treated over one year.

Population studies estimate 2 to 9 cases per 100,000 person-years. Metformin is unique because it does not generally cause hypoglycemia or stimulate insulin release, so is considered first-line therapy for treatment of DMII. Metformin is excreted unchanged in the urine and must be dose-adjusted in patients with CKD.

Dose Adjustment of Metformin in CKD

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>eGFR ml/min/1.73 m²</th>
<th>Dose</th>
<th>% max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>≥90</td>
<td>2,500 mg daily</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>≥60</td>
<td>1,000 mg b.i.d.</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>≥45</td>
<td>500 mg b.i.d.</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>≥30</td>
<td>500 mg daily</td>
<td>20</td>
</tr>
<tr>
<td>4–5</td>
<td>&lt;30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

References

1. Frid, Anders MD, et al. Novel Assay of Metformin Levels in Patients with Type 2 Diabetes and Varying Levels of Renal Function. Diabetes Care June 2010 vol. 33 no. 6 1291-1293