Metformin Intentional Overdose and its Association with Metabolic Acidosis and Elevated Lactate—As reported by Toxicologists

Fernández D,1 Nelson LS,1 Repplinger DJ,1 Smith SW,1 on behalf of the Toxicology Investigators Consortium

1Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, New York University School of Medicine, New York, New York USA

Background:

- Metformin is the most commonly prescribed anti-hyperglycemic agent in the US.
- A Cochrane review concluded that metformin associated metabolic acidosis and hyperlactatemia do not occur.1
  - Fraught by significant methodological limitations.
- A systematic review reached contradictory conclusions (i.e., acute metformin overdose was associated with elevated serum lactate and low pH).2

Hypothesis:

- We hypothesize that metabolic acidosis with hyperlactatemia is a significant risk in patients with acute metformin overdose.

Methods:

- We retrospectively analyzed Toxicology Investigators Consortium (ToxIC) registry data collected from January 1, 2010 to September 30, 2015.
- We searched for all patients with metformin toxicity.
- We included cases with metformin listed as “primary agent, most consequential.”
  - We focused on cases of acute, intentional overdose and noted if metabolic acidosis (pH<7.2) and lactate concentrations were reported.
  - We reviewed demographics, laboratory analyses, co-exposures, treatments, and survival.

Results:

- There were 77 cases with metformin listed as “primary agent, most consequential” available for analysis.
- “Intent” was reported as intentional overdose (n=65), unintentional (n=9), adverse drug reaction (n=2), and drug abuse (n=1).
- Of 65 intentional ingestions, all of which were acute, the dose was reported in 12 (range, 4-100 grams).
  - Co-exposures were present in 47 (72.3%).
  - Twelve (18.5%) cases reported no sequelae.
  - Ten (15%) experienced a blood glucose < 50 mg/dL.
- There were 77 cases with metformin listed as “primary agent, most consequential.” available for analysis.
- We were surprised by the number of patients with reported acidosis (pH<7.2) and lactate concentrations were reported.
- In patients coded with metabolic acidosis or anion gap > 20 (n=7), the mean serum lactate was 7.1 mmol/L (range, 4.16-11.1 mmol/L).
- Table 1 presents the individual data.

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<th>Case</th>
<th>Metabolic Acidosis (pH&lt;7.2)</th>
<th>Anion Gap &gt;20</th>
<th>Bicarbonate Conc. (mEq/L)</th>
<th>Lactate Conc. (mmol/L)</th>
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*Not reported in the ToxIC Database, ✓ noted in the ToxIC Database

Results (continued):

- Twenty patients (31%) had a reported pH<7.2.
- Six (9.2%) had an anion gap (AG)>20.
- Lactate was reported in 17 cases of metformin exposure (mean, 6.9 mmol/L; range 1.58-36.04 mmol/L; normal, <2.20 mmol/L).
  - In patients coded with metabolic acidosis or anion gap > 20 (n=7), the mean serum lactate was 7.1 mmol/L (range, 4.16-11.1 mmol/L).
  - Table 1 presents the individual data.

Discussion:

- In ToxIC, the majority of patients with metformin exposures had acute, intentional overdoses.
- Approximately 40% of the patients with metformin overdoses in ToxIC had metabolic acidosis (pH<7.2 or AG>20).
- Our analysis of lactate was limited, as it was not specifically included in ToxIC until 2015.
- Renal insufficiency was reported in 13.8% of patients.
- We were surprised by the number of patients with reported hypoglycemia (N = 10).
  - This could be explained by co-ingestions (insulin or sulfonylureas, N = 5) in 50% of cases.
  - However, the cause of hypoglycemia in the other 50% remains unclear.

Limitations:

- ToxIC Data is voluntarily reported.
- This study had a significant amount of missing data (e.g., values not entered into ToxIC or questions left unanswered).
- Analysis was limited to the clinical factors included in the ToxIC data entry form.

Conclusion:

- Metabolic acidosis was present in a significant number of patients with acute metformin exposures.
- Providers should be cognizant of this significant association.

References: