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Incidence and risk factors for hyperlactatemia in ED patients with acute metformin overdose

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ABSTRACT

Introduction: The goals of this study are to describe clinical characteristics and risk factors for metabolic acidosis with hyperlactatemia in emergency department (ED) patients with acute metformin overdose.
Methods: This was a secondary analysis of data from a retrospective observational cohort of adult ED patients presenting with acute drug overdose at two tertiary care hospitals over 5 years. The primary outcomes were: (1) hyperlactatemia, defined as a lactate concentration $\geq$ 2 mmol/L at any point during hospital admission and, (2) metformin associated lactic acidosis (MALA), defined as a lactate concentration $\geq$ 5 mmol/L and pH <7.35 at any point during hospital admission.
Results: We screened 3739 acute overdoses; 2872 met eligibility, 56 self-reported metformin overdose (57% female, mean age 55.8). Of these, 39 had measured lactate values. There was a high incidence of hyperlactatemia (56.4%); MALA was less frequent (17.9%). There were no deaths. Low serum bicarbonate was an independent clinical risk factor for hyperlactatemia (adjusted $p < 0.05$). Acetaminophen co-exposure was an independent clinical risk factor for MALA (OR 24.40, 95% CI 1.6–376.4).
Conclusions: In ED patients with acute metformin overdose, initial hyperlactatemia is common but MALA is unusual. Acetaminophen co-exposure is a novel independent risk factor for the occurrence of MALA that deserves further investigation.

1. Introduction

Metformin is an oral antidiabetic biguanide drug used to control blood glucose concentrations in patients with type 2 diabetes mellitus. Unlike other oral antidiabetic medications, metformin generally does not cause hypoglycemia or weight gain [1,2]. Unlike insulin, metformin does not require extensive patient education and training [3]. Additionally, it is usually affordable, contributing to its widespread use [3].

At therapeutic concentrations, metformin improves glycemic control by multiple mechanisms [4-6]. At toxic concentrations, metformin causes metabolic acidosis with hyperlactatemia, more familiarly known as metformin-associated lactic acidosis (MALA), by inducing cellular hypoxia [7]. At toxic concentrations, metformin promotes increased non-oxidative metabolism by inhibition of mitochondrial respiratory chain complex 1. This effect is demonstrated at a concentration of 0.05 mmol/L [8]. Metformin does not reach concentrations capable of causing this effect at therapeutic concentrations [5,9]. This inhibition appears to be dose-dependent, and occurs in extra-hepatic tissues, including cerebral cortex, pancreatic beta cells, neutrophils, oocytes, and endothelial cells [10]. Impaired kidney function is a known risk factor for MALA, as metformin is eliminated by the kidneys. Metformin therapy is currently contraindicated when GFR is <30 mL/min [2].

The reported mortality rate of metformin overdose varies in the literature. The most recent annual report of the American Association of Poison Control Centers' National Poison Data System reports 9393 biguanide exposure cases in 2016. Metformin contributed to 47 fatal overdoses [11]. When caused by chronic use at therapeutic concentrations, MALA has a high mortality rate of 30–50% [12]. The reported mortality rate in acute overdoses varies widely; mortality rates range from zero to 50% [12-16]. Studies conducted at U.S. poison control centers suggest low mortality rates and low rates of major effects (i.e. those that are life threatening or result in major disability), although an Italian study found a mortality rate of 22% [17-19].

Given the otherwise favorable safety profile of metformin, it would be beneficial to understand which patients are at risk for MALA, so that emergency physicians and toxicologists can risk stratify their acute metformin overdose patients. The aims of this study

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were to: 1) describe the incidence of hyperlactatemia in patients with acute metformin overdose; and 2) investigate risk factors for hyperlactatemia and MALA from metformin overdose. Our hypothesis was that in emergency department (ED) patients with acute metformin overdose, demographics and elements of the initial ED evaluation are able to predict adverse clinical outcomes.

2. Methods

2.1. Study type and setting

This was a secondary data analysis of a retrospective observational cohort of ED patients with acute drug overdose who presented to two urban tertiary care hospitals over a five-year period. The initial study was previously described in detail [20,21]. Both EDs had combined annual visits in excess of 150,000 and were staffed 24 h per day with board certified emergency physicians. The study protocol was approved by the Institutional Review Board for all participating institutions with a waiver of informed consent.

2.2. Study population

Patients with suspected acute drug overdose were initially screened for inclusion as previously described [20,21]. Briefly, screening criteria required both of the following: acute presentation (presentation within 24 h of exposure), suspected overdose (i.e. either illicit drug dose sufficient to cause symptoms or any pharmaceutical drug exposure greater than its therapeutic dose). Patients with self-report of metformin overdose were included in this secondary data analysis. Exclusion criteria were the following: alternative diagnosis (per toxicology consultant, e.g. trauma or infection), chronic presentation (i.e. not acute), non-drug overdose (e.g. plant), dermal or inhalational exposures only, age < 18 years, anaphylaxis, and subjects with incomplete data (left against medical advice, transferred to an outside institution, or otherwise eloped from the hospital) or do-not-resuscitate orders.

2.3. Data collection

Data collection from the medical chart occurred in accordance with accepted guidelines for valid medical chart abstraction, including training of abstractors and >90% agreement of a random sampling of ten test charts prior to mass data abstraction [22]. Data included demographics (gender, age), exposure information (timing of exposure, number of exposures, intent, suicidality), drug identification (detail from history of present illness, serum drug concentrations if available), initial mental status (Glasgow Coma Scale rating, agitation, coma), and toxicology screens (urine enzyme-linked immunosorbent assay panel and serum concentration, if any). Blood and urine toxicology screen results sent as routine part of clinical care were recorded in order to help confirm exposure. Serum lactate concentration was measured using Radiometer America reagents (Radiometer America, Brea, CA) on the Radiometer ABL825 Flex analyzer, and the standard cutoff concentration was used (0.5–2.2 mmol/L, detection limit 30 mmol/L). Indications for hemodialysis were interpreted according to the most recent EXtracorporeal TReatment In Poisoning (EXTRIP) recommendations [23]. Data were abstracted to a de-identified electronic database with password protection.

2.4. Study protocol

Subjects were prospectively followed to hospital discharge with data that included electronic medical records, paper medical records, consult records, poison center electronic records, as well as inpatient telemetry monitoring (if any), as described previously [20,21]. The primary outcomes were twofold: (1) hyperlactatemia, defined as an initial lactate concentration $\geq$ 2 mmol/L, and (2) MALA, defined as a lactate concentration $\geq$ 5 mmol/L and pH < 7.35 at any point during hospital admission. Results (from electronic physician notes, laboratory records, radiology results, and discharge summaries) were prospectively available to the study investigators. Patients discharged from the hospital had no further follow-up.

2.5. Definitions

Altered mental status was defined according to charting of any of the following: GCS < 15, "coma", "agitation", or "altered mental status". Suicidal ingestion was defined according to the treating physician's initial impression and confirmed by psychiatry consultation, with disagreements settled by psychiatry consultation note.

2.6. Statistical analysis

Sample size was preset based on enrollment from the parent cohort [20,21]. Data abstractors were blinded to the study hypothesis. Continuous variables were assessed with means, standard error, and the *t*-test. Categorical variables were assessed with proportions, chi-squared, or Fischer exact test when appropriate. Univariate odds ratios were calculated with 95% confidence intervals. Multivariable logistic regression was performed to determine the associations between clinical factors and hyperlactatemia or MALA. The regression models included elements from demographics, initial vital signs, or clinically relevant clinical factors which achieved at least a trend for significance ($p < 0.10$), as well as additional factors by consensus of two board-certified medical toxicologists, up to a maximum of 1 factor for every 2 adverse events. For both models, missing lactate data was dealt with using multiple imputation as follows: subjects without a laboratory evaluation of lactate had this value calculated based on the linear correlation with serum bicarbonate for patients in the study ([lactate in mmol/L] = 27.9–1.0712*[bicarbonate in mmol/L]); when this calculated value was <0, a value of 0 was substituted for analyses. Every patient determined to have MALA had a lactate available for analysis; no lactate values were imputed for this group. Statistics were calculated with SPSS version 22 (IBM Corp., Chicago, IL).

3. Result

3.1. Enrollment

Over the course of the study period there were 3739 acute overdose patients prospectively screened, of whom 2872 patients met eligibility criteria. Fifty-six were self-reported metformin overdoses. Of these 56 patients, 39 had measured lactate concentrations (overall mean 4.2 mmol/L, range = 0.8–23 mmol/L). In patients with measured lactate concentrations, the incidence of hyperlactatemia was 56.4% (N = 22) and MALA was 17.9% (N = 7). No patients had end-stage kidney disease. All patients survived to hospital discharge. Table 1 summarizes baseline descriptive statistics for patients with measured lactates in three groups: all patients without study outcomes, patients with hyperlactatemia, and patients with MALA. >80% of patients with metformin ingestions (all-comers, those with hyperlactatemia, and those with MALA) were prescribed at least one antidiabetic medicine.

Three patients met criteria for hemodialysis by the EXTRIP recommendations, which include lactate concentration > 20 mmol/L, pH $\leq$ 7.0, or failure of standard therapy, including a bicarbonate

Table 1
Baseline characteristics of patients with acute metformin overdose

	Neither hyperlactatemia nor MALA (N = 17)	Hyperlactatemia (N = 22)	MALA (N = 7)
Demographics			
Age, mean (years) [SE]	56.5 [4.3]	57.5 [3.6]	55.4 [5.3]
Sex, female (%)	10 (58.8%)	12 (54.5%)	6 (85.7%)
Race			
White, n (%)	0 (0%)	**5** (**22.7**%)	2 (28.6%)
Black, n (%)	6 (35.3%)	3 (13.6%)	1 (14.3%)
Asian, n (%)	4 (23.5%)	5 (22.7%)	1 (14.3%)
Other, n (%)	7 (41.2%)	9 (40.9%)	3 (42.9%)
Hispanic, n (%)	3 (17.6)	6 (27.3%)	3 (42.9%)
Medical history			
End-stage kidney disease, n (%)	0 (0%)	0 (0%)	0 (0%)
Prescribed ≥1 DM medication including insulin, n (%)	14 (82.4%)	19 (86.4%)	6 (85.7%)
Initial vital signs			
Systolic BP, mean (mm Hg) [SE]	146 [6.9]	128 [7.4]	129 [17.6]
Diastolic BP, mean (mm Hg) [SE]	81 [4.4]	69 [4.5]	73 [12.6]
Heart rate, mean (bpm) [SE]	88 [4.9]	86 [4.8]	83 [11.0]
Respiratory rate, mean (breaths per minute) [SE]	19 [0.4]	19 [0.7]	20 [2.1]
Oxygen saturation, mean	98.8% [0.3]	97.9% [0.4]	**97**% [**0.6**]
Laboratory values			
Creatinine, mean (mg/dL) [SE]	1.0 [0.2]	1.37 [0.2]	2.0 [0.6]
Bicarbonate, mean (mmol/L) [SE]	26.7 [1.2]	**20.8** [**1.7**]	**12.3** [**2.6**]
pH, mean [SE]	7.37 [0.01]	**7.29** [**0.03**]	**7.16** [**0.08**]
Lactate, mean (mmol/L) [SE]	1.3 [0.1]	6.6 [1.4]	13.9 [2.6]

Bold numbers signify univariate $p < 0.05$.
Abbreviations: SE – standard error; DM – diabetes mellitus; BP – blood pressure.

drip [23]. All of these patients required multiple rounds of hemodialysis.

Co-ingestions were reported for 37 patients. The median number of reported exposures in the sample was 3. Thirty-one patients were admitted to an internal medicine service; 4 patients were admitted to psychiatry.

3.2. Regression analysis

Regression models of factors associated with hyperlactatemia and MALA in patients with acute metformin overdose are demonstrated in Tables 2 and 3, respectively. After controlling for confounding using multivariable logistic regression, the only independent predictor of hyperlactatemia was initial serum bicarbonate, and the only independent predictor of MALA was acetaminophen co-ingestion. Seventeen lactate concentrations were added using multiple imputation. Model fit R^2 was 0.36 for hyperlactatemia.

4. Discussion

In this prospectively collected and retrospectively analyzed cohort of ED patients with acute metformin overdose, we found that the incidence of hyperlactatemia was relatively common, while the occurrence of MALA was uncommon. Additionally, there was a good prognosis overall including rare indications for hemodialysis and no deaths in the cohort. This study also ssuggests, for the first time, that co-ingestion of acetaminophen with metformin is associated with over 24-fold increased odds of the occurrence of MALA, compared with metformin ingestion alone.

Other studies have examined acute metformin ingestions, though generally with smaller sample sizes. McNamara et al. examined 36 patients, 25 of whom had lactate concentrations and blood pH measured. Of these 25, hyperlactatemia occurred in 10 patients, and MALA occurred in 5 patients [12]. Studies of patients with MALA and severe MALA (pH < 7.0, lactate concentration > 10 mmol/L) suggest that blood pH and lactate do not prognosticate outcome as well as a patient's triggering factors and comorbidities. While hyperlactatemia in other conditions, such as septic shock, is a poor prognostic sign, the high lactate concentrations and low pH observed in MALA patients often do not predict mortality [13,16]. This data supports our finding that the prognosis of hyperlactatemia and MALA is generally good [13,14]. A Cochrane review performed in 2010 concluded that metformin is not associated with an increased risk of lactic acidosis at all, as compared to other antidiabetic medications. No patients in any of the studies the group analyzed had lactic acidosis. However, because of the stringent inclusion criteria for this analysis, many studies were not evaluated. Examining only patients with diabetes also excludes patients without diabetes who intentionally ingest metformin.

Table 2
Regression model of factors associated with hyperlactatemia in patients with acute metformin overdose

Risk factor	Univariate OR	Adjusted OR[a]	Adjusted 95% CI
Age	1.01	1.006	0.96–1.05
White race	∞	0.97	0.13–7.4
SBP	0.98	0.98	0.96–1.01
Oxygen saturation	0.69	0.69	0.43–1.1
Altered mental status	2.37	2.06	0.52–8.1
Serum bicarbonate concentration	**0.86**	**0.83**	**0.71–0.96**

Abbreviations: CI – confidence interval; OR – odds ratio; SBP – systolic blood pressure.
Bold numbers signify $p < 0.05$.
[a] Adjusted numbers were calculated using multivariable logistic regression.

Table 3
Regression model of factors associated with MALA in patients with acute metformin overdose

Clinical factor	Univariate OR	Adjusted OR[a]	Adjusted 95% CI
Age	0.99	1.01	0.94–1.08
Acetaminophen	6.0	**24.40**	**1.6–376.4**
Oxygen saturation	**0.55**	0.67	0.43–1.03

Abbreviations: MALA – metformin-associated lactic acidosis; OR – odds ratio; CI – confidence interval.
Bold numbers signify $p < 0.05$.
[a] Adjusted numbers were calculated using multivariable logistic regression.

Finally, the Cochrane review only utilized data from randomized controlled trials using metformin to treat DM, so all patients with abnormal creatinine concentrations as well as those with intentional overdose were excluded by study design. These are precisely the patients who are at risk for MALA [24].

If validated, data from the current study may be used for medical decision making in patients with acute metformin overdose. Patients with acute hypoxia, acidosis, or hypotension require a screening blood gas to detect the occurrence of hyperlactatemia. Patients with acetaminophen co-ingestion should be considered at exceptionally high risk for the occurrence of MALA. We recommend consultation with a medical toxicologist or the Poison Control Center for all patients with acute metformin overdose, but particularly for patients with hyperlactatemia, MALA, and for patients with co-ingestion of both metformin and acetaminophen.

4.1. Limitations

This study has several limitations. First, metformin ingestion was self-reported. Metformin confirmation through analytical testing was lacking in these patients, however suspicion of metformin overdose based on history, clinical findings, or ancillary testing was documented by emergency physicians and consulting medical toxicologists. Also, many drugs besides metformin are associated with hyperlactatemia. A recent study showed that in patients for whom lactate was measured after any reported drug overdose, the average lactate concentration was 2.31 mmol/L. Most patients in our sample co-ingested other xenobiotics, which may have contributed to their hyperlactatemia [25]. Furthermore, while missing lactate data may have led to an under-estimation of MALA incidence, it is likely that our method of multiple imputation corrected this limitation. We were unable to evaluate serum bicarbonate in the logistic regression model because this value was used for multiple imputation of missing lactate concentrations. Finally, this study was underpowered for robust modeling or identification of mortality risk factors since there were no deaths in the study population; therefore, mortality factor analysis will require further study.

5. Conclusions

In ED patients with acute metformin overdose, initial hyperlactatemia is common, MALA is unusual, and indications for hemodialysis are uncommon. Additionally, acetaminophen co-exposure appears to be an independent risk factor for the occurrence of MALA.

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Declaration of interest

None.

Previous presentation of data

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