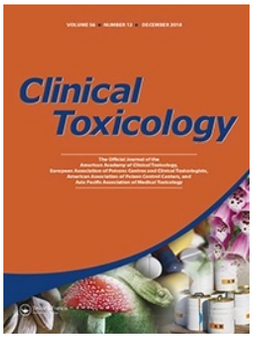

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POISON CENTRE RESEARCH

Time to development of metformin-associated lactic acidosis

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ABSTRACT

Objective: Metformin-associated lactic acidosis (MALA) is a complication of metformin overdose. Recommendations for observation time after an acute ingestion to monitor for MALA vary. The aim of this study was to characterize the time to development of MALA after an acute metformin overdose.

Methods: Utilizing Crystal Reports (Version 11.0), all metformin cases reported to the Illinois Poison Center (IPC) with a National Poison Data System (NPDS) clinical effects code of "acidosis" or "anion gap" were retrospectively queried over a 14-year period (2001–2014). Demographic data, time to MALA, co-ingestants, therapeutic modality use, and case outcome were extracted. Interrater reliability was assessed using kappa analysis.

Results: A total of 88 cases were identified of which 44 met criteria for MALA; 40 were acute, acute on chronic, or unknown ingestions. The remaining four were chronic ingestions which were excluded. The mean age was 41 years (range 19–79 years). Most were female (55.0%) and over half (62.5%) were acute on chronic ingestions. Hypoglycemia was seen in three ingestions of metformin only. Of the 40 MALA cases, 18 developed MALA less than or equal to 6 h after ingestion, 9 between 6–12 h, 3 after 12 h, and 10 patients had an unknown time to MALA. The only death in the cohort had MALA detected beyond the typical 6-h observation period. Of the exposures when time to MALA was known, 40% (12/30) developed MALA greater than 6 h post ingestion.

Conclusion: A 6-h observation period after a single acute ingestion of metformin may be inadequate, as a significant portion of exposures developed MALA beyond this time. We recommend a minimum of 12 h of observation following an acute overdose. Further study defining prospectively the time to development of MALA may improve management of this population.

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Introduction

Metformin is the only available biguanide in the United States and was first available to be prescribed in 1995. Since then it has become one of the most widely prescribed oral hypoglycemics being used routinely to treat both type 2 diabetes mellitus, as well as polycystic ovarian syndrome. In the 2017 annual report of the American Association of Poison Centers (AAPCC) there were 9402 cases of biguanide exposures, 21 deaths and 58 patients experiencing major adverse outcomes [1].

In overdose, metformin can cause a range of symptoms including gastrointestinal upset, dizziness, and lethargy [2,3]. While significant controversy exists as to whether metformin can cause a lactic acidosis in chronic therapeutic use in patients with normal renal function, it is well accepted that lactic acidosis can occur following an acute metformin overdose [4]. Lactic acidosis occurs secondary to inhibition of mitochondrial glycerophosphate dehydrogenase which leads to elevated lactate levels due to decreased conversion to pyruvate [5,6].

Given the potential morbidity and mortality associated with development of metformin associated lactic acidosis (MALA), it is crucial to observe a patient for a time period that is expected to detect the development of MALA. Based on a review of toxicology resources, there does not seem to be a well-defined observation period following an acute metformin overdose [7–9]. Some do not suggest an observation period or when suggested, recommend 4–6 h post ingestion of an immediate release preparation and vary widely in recommendations regarding extended release preparations. Therefore, we undertook a retrospective review of poison center cases over a 14-year period to determine the time to development of metformin-associated lactic acidosis (MALA) after an acute or acute on chronic metformin overdose.

Materials and methods

This was a retrospective review of metformin exposure cases reported to the Illinois Poison Center from January 2001 to December of 2014 that had a National Poison Database System (NPDS) clinical effects code of "acidosis" or "anion gap". Utilizing crystal reports (version 11.0), data was extracted by two independent reviewers (NC, JT). The information abstracted included demographic data (age, sex), time to MALA, co-ingestants, use of therapeutic modalities

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such as hemodialysis, dextrose or bicarbonate, and death. Whether the ingestion was acute, acute on chronic or chronic was determined. An acute ingestion was defined as an acute ingestion of someone else's medication. Acute on chronic was an acute ingestion of a medication that was the patient's medication. Chronic cases were identified as cases with no known acute ingestion in someone prescribed metformin. Cases where it was not documented if the metformin belonged to the patient were coded as unknown. Inter-rater reliability was assessed using kappa analysis.

MALA was defined as an elevated lactate (>5 mmol/L) with acidemia (bicarb < 20 mmol/L or pH < 7.35). If neither bicarbonate nor pH was documented, then an isolated elevated lactate (>5 mmol/L) was used to categorize a case as MALA. Cases were not considered MALA and excluded if there was absence of elevated lactate or if a lactate was not documented even in the presence of a bicarb < 20 and/or pH <7.35. Time to MALA was determined based on reported ingestion time. Cases that developed MALA 6 h or greater after reported ingestion were categorized as delayed MALA. In cases where it could be confirmed that MALA was truly delayed vs appearing delayed due to late presentation to the hospital, additional case details were extracted. These cases had blood work not meeting MALA criteria on hospital presentation, but later met criteria for MALA. The additional case details that were extracted included formulation of metformin, amount ingested, all co-ingestants, initial laboratory blood work, labs at the time of MALA, highest lactic acid, the time to peak lactic acid, all treatments, and complications.

To evaluate for other potential causes of elevated lactate level, hypotension on presentation to the emergency department was documented. Hypotension was defined as a documented blood pressure less than 90/60 mmHg. If the patient was not hypotensive on arrival to the hospital but later developed it during the hospital course, it was documented as "later". Cases with hypoglycemia (blood glucose < 70 mg/dL) on presentation were also noted.

Results

From 2001 to 2014 the Illinois Poison Center had an annual exposure case volume between 73,000 and 88,000. During this time, there were 2693 metformin exposures reported and 88 cases were identified that included the clinical effects codes of "acidosis" or "anion gap". Of the 88 metformin cases that were coded as acidosis or elevated anion gap, 44 of those were found to meet the defined criteria for MALA. Four of the 44 MALA cases were chronic ingestions therefore not included in the final analysis, leaving a total of 40 cases or 1.6% of total metformin exposures. All 40 cases were treated at a health care facility. There were eight cases that were acute ingestions, however it was not documented if the metformin was the patient's medication or not and therefore these were defined as "unknown". There were three cases that only had a lactate documented initially that was > 5 mmol/L without an associated bicarbonate or pH. Two of these cases later were shown to be acidemic with a bicarbonate < 20 or a pH < 7.35. The remaining case only had serial lactates documented. These cases were counted as MALA based on the criteria described above. Of the 40 cases, the age range was (19–79) with a female predominance (55.0%). Only three cases meeting criteria for MALA were hypoglycemic, all of which ingested only metformin.

To evaluate for other potential causes of elevated lactate, the incidence of hypotension was extracted. No cases with MALA were found to be hypotensive on presentation. Later in the course of the hospital stay, seven patients became hypotensive. Treatments for all cases consisted of hemodialysis (HD), dextrose infusion or bolus, and bicarbonate infusion or bolus. Most cases were cared for in the intensive care unit (ICU) and one case ultimately resulted in death. These data and the frequency of cases is given in Table 1.

Time to development of MALA was determined for the 40 MALA cases (Table 2). There were 10 cases where the time of ingestion was not documented or unknown and these were labeled as unknown times. Of the cases where the ingestion time was known, 12 out of 30 developed MALA more than

Table 1. Patient characteristics of metformin cases with 'acidosis' and 'anion gap' codes meeting criteria for MALA.

Characteristic	Cases with MALA ($n = 40$)	Cases with delayed MALA ($n = 9$)
Age, median (range), years	41 (19–79)	47 (24–65)
Under 18	0	0
Over 18	39	9
Not documented	1	0
Sex, female (%)	22 (55.0%)	4 (44.4%)
History of diabetes		
Yes	24	6
No	13	2
Not documented	3	1
Type of ingestion		
Acute	7	1
Acute on chronic	25	5
Unknown	8	3
Cases with any co-ingestants (%)	37 (67.5%)	6 (66.7%)
Cases with hypoglycemic co-ingestants*	7	2
Sulfonylurea	3	1
Thiazolidinediones	0	0
Meglitinides	0	0
Insulin	4	1
Hypoglycemia on presentation		
Yes, metformin only	3	1
Yes, metformin + hypoglycemic co-ingestant reported	0	0
No	37	8
Not documented	0	0
Hypotension on presentation		
Yes	0	2
No	30	6
Later	7	1
Unknown	3	0
Treatments		
Bicarbonate	13 (32.5%)	5 (55.6%)
Dextrose	11 (27.5%)	2 (22.2%)
Hemodialysis performed	9	4
Disposition		
ICU	37	9
Step-down unit	1	0
Medical floor	2	0
ED observation	0	0
Unknown	0	0
Survival	39 (97.5%)	8 (88.9%)

Hypoglycemia was a blood sugar less than 70 mg/dL and hypotension was a blood pressure < 90/60. *Some cases had more than one hypoglycemic co-ingestant.

Table 2. Time to MALA for cases that were not chronic toxicity (acute, acute on chronic, or unknown ingestions) with labs meeting criteria for MALA ($n = 40$).

Post ingestion time	Number of MALA cases	Number of confirmed delayed MALA cases
<or = 6 h	18	–
6–12 h	9	5
>12 h	3	1
Unknown	10	3

The time to development of MALA for cases that developed MALA greater than 6 h post-ingestion and had labs not meeting criteria for MALA on emergency department (ED) presentation ($n = 9$).

6 h post-ingestion while 18 developed it under 6 h. Of the 12 cases that met criteria for delayed MALA, 9 could be confirmed. Confirmed cases had labs that did not meet criteria for MALA on hospital presentation, then later developed MALA greater than 6 h after presentation. Details of the confirmed delayed cases are described in Table 3. We did not include the additional three cases where MALA was delayed based on the patient's reported ingestion time as we could not be certain the delay was not due to delayed hospital presentation. The confirmed delayed MALA cases had an age range of 24–65. No cases were hypotensive on arrival although 4 (44.4%) later developed hypotension. A higher percentage of patients in the delayed MALA group received bicarbonate and HD treatments than patients with early-developing MALA. There were three cases complicated by hyperkalemia all of which were given sodium polystyrene sulfonate but did not undergo hemodialysis. The highest documented creatinine levels were 2.1 mg/dL, 2.5 mg/dL and 2.6 mg/dL, however only HD was performed for the case with a creatinine of 2.1 mg/dL. There was one death that occurred on hospital day 20.

We attempted to examine the time to peak lactic acid. However, because the timing of lab draws varied greatly among patients, comparisons between cases was difficult. We were able to abstract peak lactate for delayed MALA cases and the corresponding time was recorded (Table 3). No correlation between the magnitude of the peak lactic acid and the duration of time could be determined.

Discussion

MALA is a relatively rare development following metformin exposure. Previous poison center studies have shown that approximately 1% of all metformin exposures develop MALA and this number may be higher in health care facility cases [3,4]. During the time frame of this study there were 2693 metformin exposures reported, and the cases meeting MALA criteria were 1.6% of these cases.

A significant finding in our study was the number of cases that developed MALA in a delayed fashion. Twelve of the 40 MALA cases developed MALA beyond 6 h from the time of reported ingestion and 9 of these cases were confirmed delayed as they did not meet MALA criteria upon ED presentation but later did. Delayed development of MALA has been reported in the past. McNamara et al reported a case series of acute metformin overdoses in which one patient developed MALA 18 h after ingestion. The authors recommended that an acute metformin overdose should be observed for 12 h post-ingestion [10]. In another acute metformin overdose, a patient had an elevated lactate level at 6 h but did not meet criteria for MALA until 12 h after ingestion [11]. However, other case reports have found that severe large ingestions, where a profound lactic acidosis developed, were symptomatic and met criteria for MALA within a few hours of ingestion [12,13].

In comparing the cases that had confirmed delayed development of MALA to the those with early-developing MALA, there was a higher percentage of delayed MALA cases that received HD and bicarbonate infusion. There was also a male predominance in the delayed MALA group compared to all cases with MALA. Given that the number of confirmed MALA cases is small, a larger data set, possibly including multiple poison centers would help to identify specific factors that place patients at risk for delayed development of MALA. The cases that had confirmed delayed MALA all had a lactate greater than 2 on initial labs. Although this study did not compare the cases of delayed MALA to those that did not develop MALA, it would be interesting to see if a lactate greater than 2 could be used as a measure to delineate those who will develop delayed MALA from those who will never develop MALA.

The mechanism for the delay in the development of lactate acidosis following an acute metformin overdose is likely multifactorial. At therapeutic doses, gastrointestinal absorption is complete by 6 h. At doses higher than 1.5 g, overall bioavailability decreases signifying a saturable absorptive process. Because metformin is eliminated renally without metabolism, changes in creatinine clearance can greatly effect levels [14]. In the nine confirmed cases where the development of MALA was delayed, only three patients had documented increased creatinine concentrations indicating that decreased metformin clearance is not the only variable. Another factor that may contribute to the delay in the development of MALA is metformin's two-compartment distribution model where the initial distribution is to a central compartment, then secondarily to a deep compartment. Elimination half-life is also much longer from the deep compartment compared to the central (12–14 h vs 2 h) [14]. Furthermore, a misalignment between the time for production and accumulation of lactate and the time to lactate clearance is likely involved. Co-ingestants can play a role in tipping the balance to lactate accumulation, however, in about one-third of our cases there were no reported co-ingestants. These toxicokinetic factors complicated by toxicodynamic factors likely contribute to a delayed development of MALA, however the exact mechanism has not been elucidated.

Another interesting finding in our study was that hypoglycemia occurred more frequently than expected and was seen in 7.5% (3/40) of the cases with MALA had hypoglycemia. Of these three cases with hypoglycemia in our MALA cohort, none were exposed to other hypoglycemics medications. Although hypoglycemia occurs less frequently following a

Table 3. Details of cases where delayed development of MALA could be confirmed.

Age sex	Type of ingestion	Metformin ingested amount (formulation)	Co-ingestants	Initial labs	Labs at time of MALA	Hours after ingestion to MALA	Hours post ED presentation to MALA	Highest lactic acid	Hours to peak lactic acid from ingestion	Hypoglycemic (<70 mg/dL)	Hypotension	Treatments	Complications	Outcome
42 M	Acute on chronic Intentional	15–20g (500 mg)	Insulin	LA 6.3 Bicarb 26	LA 13 pH 6.9	19.5	17	20.3	21	No	Later	Antibiotics Bicarb Drip HD Intubation PEG tube Tracheostomy Vasopressors	Rhabdomyolysis Sepsis Hyperthermia CT head: diffuse hypoattenuation and global ischemia EEG: consistent with encephalopathy	Became hypotensive and febrile just prior to death on Hospital Day 20
39 M	Acute on chronic Intentional	15 g (500 mg)	None	LA 3.6 Bicarb/pH not documented	LA 9.1 pH 7.27 Bicarb 19	11	8	9.1	11	No	No	Sodium polystyrene sulfonate	Hyperkalemia	LA normalized on hospital day 3, case closed
62 M	Acute on chronic	Handfuls (850 mg)	None	LA 3.6 Bicarb 26	LA 5.0 Bicarb/pH not documented	10	9	6.3	10	No	No	Bicarb Drip Calcium Insulin/D50 Sodium polystyrene sulfonate	Hyperkalemia	Labs normalized on hospital Day 4, cased closed
65 F	Acute Intentional	14 g (1000 mg)	Glipizide Carvedilol Simvastatin Finasteride Tamsulosin Potassium chloride Omeprazole Donepezil B12	LA 3.4 pH 7.67 Bicarb 20	LA 5.7 pH 7.3 Bicarb 18	12	10	5.7	20	No	No	None	None	Transferred to inpatient psych on hospital day 2
41 F	Unknown	10 tabs (unknown mg)	Unknown	Initial BMP "normal" No LA documented	LA 17.4 pH 6.8	Unknown	11.5	6.5	24	Yes (34)	Later	Bicarb Drip D50 D5/45 Drip HD Vasopressors	None	Transferred to the floor on hospital day 3
24 M	Acute on chronic Intentional	Unknown amount or formulation	Emtricitabine tenofovir disoproxil fumarate darunavir	LA 3.9 Bicarb 21 pH 7.22	LA 13 pH 7.21	Unknown	12	14	Unknown	No	No	Bicarb Bolus and drip HD Lorazepam/ Haloperidol	Agitation	Labs normalized, transferred to floor on hospital day 3
46 F	Unknown	13 g (500 mg)	Ethanol	LA 2.4 Bicarb 26	LA6.7 pH 7.25 Bicarb 13	11	Unknown	6.4	12.5	No	No	Bicarb drip	None	Labs normalized on hospital day 1, case closed
44 M	Unknown Intentional	10 g (500 mg)	Lisinopril clonidine quetiapine	LA 3.6 Bicarb 28	LA 5.7 Bicarb 18	Unknown	6	14.4	20.5	No	Yes	Insulin bolus and drip Sodium polystyrene sulfonate Vasopressors	Hypotension Hyperkalemia Hyperglycemia	Labs normalized on hospital day 3, weaned off vasopressors and insulin drip, transferred to psychiatry
60 F	Acute on chronic	225 g (500 mg)	Clonazepam Ethanol	LA 6.7 BMP "wnl"	LA 11.5 pH 7.09	8	4	13.2	8	No	No	HD Lorazepam	Agitation	Labs normalized on hospital day 3, case closed

All patients were admitted to the ICU. Lactic acid is expressed in mmol/L and was converted from mg/dL if necessary. LA: lactic acid; HD: hemodialysis; BMP: basic metabolic panel; Bicarb: bicarbonate; D50: dextrose 50%; D5/45: dextrose 5% and 0.45% saline; WNL: within normal limits; PEG: percutaneous endoscopic gastrostomy; EEG: electroencephalography; CT: computed tomography.

metformin overdose than other anti-diabetic medications, it can occur [15]. In a review of pediatric metformin exposures reported to eight poison centers, there were no instances of hypoglycemia however these were primarily unintentional, low dose ingestions [16].

There were several important limitations in our study. This was a retrospective review and case data was not collected prospectively for the purpose of this study. Given the nature of poison center data, there is potential for missing data points or incorrectly reported or recorded data points. It was assumed that if a lactate was greater than 5 and a bicarbonate or pH was not documented that the patient was likely acidemic. There were three cases included in the MALA group that had only lactate with no associated bicarbonate or pH documented. Our cases of confirmed delayed MALA may have had abnormal labs consistent with MALA earlier in their hospital stay and this data was either not collected by the poison center or the blood work was not done frequently enough in the course of their exposure. This would overestimate the number of delayed MALA cases. It is also possible that cases with missing data, that were not categorized as MALA, would have satisfied the criteria had the data been provided to the poison center or blood was drawn at a later time post ingestion. This would likely underestimate the number of cases that developed delayed MALA. Nevertheless, we limited the delayed cases to those that we were certain had normal initial labs and then later developed MALA.

Another limitation of the study is not definitively knowing whether the formulation of metformin ingested was immediate release (IR) or extended release (ER) for delayed MALA cases. While this specific data point was not always collected by the poison center, we were able to make some extrapolations based on what was collected. Both metformin ER and IR come in the dosage form of 500 mg and 1000 mg tablets. However, only metformin IR comes in the 850 mg dosage form. Of the nine delayed MALA cases in Table 3, one was reportedto have ingested the 850 mg dosage form and therefore was the metformin IR formulation. In 2010, metformin IR was the 58th most prescribed medication in the United States and metformin ER was 168th [17]. We cannot say for certain that the metformin ingested was IR in the other eight delayed MALA cases however based on prescribing patterns we would expect a higher number of IR formulation ingestions than ER.

Many of the limitations of our study could be overcome by a future prospective study. This would allow for further clarification of the time course to development of MALA and address the role of metformin formulation in the time of MALA development. Additionally, with a larger more robust database it may be possible to determine if initial lactic acid levels correlate with developing delayed MALA which can aide in risk stratifying patients after an acute metformin exposure.

Conclusions

MALA is a severe outcome following a metformin overdose. Delayed development of MALA can occur and in our case series, was confirmed in nine cases. An extended observation period of 12 h post-ingestion, should be considered in patients reporting a significant metformin overdose. The results of this study call for further, prospective, and precise research into the optimal period of observation after the ingestion of this very common and readily available medication.

Disclosure statement

No potential conflict of interest was reported by the authors.

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