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CASE REPORT

Hypoglycemia and severe lactic acidosis in a dog following metformin exposure

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Key Clinical Message

Hypoglycemia and lactic acidosis are rare complications with metformin use in humans. As metformin is not commonly used in veterinary medicine, severe adverse effects secondary to exposure are not known. Awareness of potentially life-threatening complications with metformin exposure is an important addition to the veterinary literature.

Keywords

Acidosis, hypoglycemia, metformin, veterinary.

Introduction

Metformin is used as the first-line agent in humans for the treatment of non-insulin-dependent diabetes mellitus (DM), also known as type 2 DM [1]. There is an expansion of metformin's use to include additional conditions such as polycystic ovarian syndrome, gestational diabetes, and as an adjunct to chemotherapy [2, 3]. Renal disease and hepatic disease have long been considered contraindications for metformin use due to concern for the development of a lactic acidosis, a syndrome previously designated as metformin-associated lactic acidosis (MALA) [4–9]. There is conflicting evidence regarding the significance of metformin in MALA, and recent literature subdivides the condition based on contribution of concurrent disease processes and serum metformin concentration [10–14]. Hypoglycemia is rarely reported as an adverse effect of either acute or chronic metformin use [9, 15–18]. With over 14 million individual prescriptions filled in 2014, companion animals have significant potential for accidental exposure [4]. The incidence and nature of adverse effects in companion animals exposed to metformin are unknown.

Case Report

A 7.5-year-old female spayed, 1.72 kg Yorkshire Terrier was presented to the emergency service for protracted vomiting and seizure activity. Five hours prior to presentation, the patient ingested one metformin hydrochloride extended-release 500 mg tablet, a dose of 290.7 mg/kg. She vomited 15 times prior to presentation and began having seizure activity en route to the hospital. The patient had a previous history of abnormal neurological episodes that were not being managed with medication. She also had a previous history of liver enzymes above the upper limit of the reference interval and abnormal pre- and postprandial bile acids (70.4 μmol/L and 75.7 μmol/L, respectively, reference interval [RI] 0–6.9 μmol/L and 0–14.9 μmol/L). She was being treated

with lactulose 0.29 mL/kg per os (PO) q 8 h and a diet formulated for hepatic disorders (Hill's® Prescription Diet® l/d®, Hill's Pet Nutrition, Topeka, KS). On physical examination, the patient was actively seizuring. She was hypothermic at 36.3°C, bradycardic with a heart rate of 80 beats/min, and had tacky mucous membranes. While intravenous access was obtained, 1 mL of 50% dextrose was applied to her oral mucous membranes. The blood glucose level measured below the level of detection on a point-of-care glucometer (AlphaTrak Blood Glucose Monitoring System, Zoetis, Parsippany, NJ). Once intravenous access was secured, the patient received 50% dextrose (1.7 mL/kg) diluted in an equal volume of sterile saline intravenously (IV), and the seizure activity ceased. A venous blood gas (Stat Profile® pHOx® Ultra, Nova Biomedical Corporation, Waltham, MA) revealed a mixed metabolic and respiratory acidemia with hyperlactatemia (Table 1). The blood glucose was 10.9 mmol/L (RI 4.2–6.8 mmol/L). Packed cell volume (PCV) was 0.54 (RI 0.37–0.55), and total solids (TS) as measured by refractometry were 60 g/L (RI 54–71 g/L). The patient's systolic blood pressure as measured by Doppler was 100 mmHg. The patient received Normosol-R 20 mL/kg bolus IV and was started on Normosol-R with 2.5% dextrose at 111 mL/kg/day. The patient received ondansetron 0.17 mg/kg IV to prevent additional vomiting. A complete blood count, serum chemistry, and citrated prothrombin time were unremarkable.

Two hours after beginning continuous IV fluid therapy and three hours after presentation, the blood glucose had decreased to 2.7 mmol/L. The patient received 50% dextrose 1.2 mL/kg bolus diluted in an equal volume of sterile saline. Continuous dextrose supplementation was increased from 2.5% to 5%. Systolic blood pressure was 120 mmHg. Two hours later, the blood glucose again dropped below the level of detection by glucometer. A repeat venous blood gas revealed progressive hyperlactatemia and metabolic acidemia. Repeat PCV/TS was 0.45 and 46 g/L. Central venous access was obtained using a double lumen catheter in the left jugular vein so that dextrose supplementation could be increased to 7.5%. The rate of crystalloid infusion was increased to 167 mL/kg/day.

Table 1. Sequential venous blood gas values.

Hours after presentation	0	2	13	37
Glucose (mmol/L)	Lo	Lo	14.7	4.8
Lactate (mmol/L)	11.9	12.8	3.9	1.1
pH	7.164	7.099	7.315	7.437
pCO_2 (kPa)	5.85	5.41	5.57	4.58
HCO_3^- (mmol/L)	16	12.7	13.8	23.4
Anion Gap (mmol/L)	24.1	25.9	18.26	
Base Excess (mmol/L)	−12.9	−17.2	−12.6	−1.0

Nine hours after presentation, the blood glucose was 5.2 mmol/L and no changes were made to dextrose supplementation. An abdominal ultrasound showed moderately hyperechoic peripancreatic mesentery. The pancreatic and hepatic parenchymas were unremarkable. No aberrant hepatic vessels were seen. The patient was administered famotidine 0.55 mg/kg IV q12 and maropitant 1.1 mg/kg subcutaneously once. Thirteen hours after presentation, the blood glucose was 14.7 mmol/L and the dextrose supplementation was decreased to 2.5%. Venous blood gas performed at that time revealed a marked improvement in lactate; however, the acidosis persisted. The PCV/TS was 0.46 and 48 g/L. One hour after reducing dextrose supplementation, the blood glucose was 11.2 mmol/L and supplementation was discontinued. Nineteen hours after presentation, the blood glucose was 4.9 mmol/L without supplementation and the patient had started eating. The patient remained normoglycemic and IV fluid therapy was weaned. Thirty-four hours after presentation, the lactate was normalized and there were no acid–base abnormalities. The patient was discharged with directions to continue the previously prescribed lactulose regimen and hepatic diet. On re-evaluation 1 week later, the patient was normoglycemic with a lactate within the reference interval.

Discussion

Metformin (dimethylbiguanide) is an oral antihyperglycemic medication used predominantly as the first choice for treatment of non-insulin-dependent DM in people [1]. There are many proposed mechanisms by which metformin exerts its antihyperglycemic effects including increased peripheral insulin-related glucose uptake, enhanced glycolysis, inhibition of hepatic gluconeogenesis and glycogenolysis, inhibition of glucagon release via incretin stimulation, enhancement of insulin secretion by pancreatic beta cells, and rate reduction of intestinal glucose reabsorption [5, 19–24]. In humans, approximately 50–60% of metformin is absorbed after ingestion and the bioavailability decreases as the dose increases [5]. Unlike older biguanides, metformin is not metabolized in the liver but rather is excreted unchanged by the kidneys via glomerular filtration and tubular secretion [5, 25]. Plasma concentrations peak within one to three hours of ingestion for non-extended-release formulations, and within four to eight hours of ingestion for an extended-release product [26]. With oral doses, approximately 90% of the drug is eliminated within 24 h of ingestion [26].

In recent years, research in human medicine has evaluated metformin for management of polycystic ovarian syndrome, gestational diabetes, and as adjunctive therapy

for cancers and pediatric type 1 DM [2, 3, 27]. The Food and Drug Administration has approved eighteen brand name medications containing metformin and, in 2014, approximately 14.4 million prescriptions for a metformin-containing drug were filled in the United States [4]. The clinical signs associated with metformin overdose in humans are nausea, vomiting, diarrhea, lethargy, and dizziness [9]. Hypoglycemia is a rarely reported complication of metformin ingestion in either therapeutic or overdose situations with an incidence ranging from 0.6 to 12.2% [9, 15–18]. Conditions that may make a patient more susceptible to developing hypoglycemia include malnourishment or insufficient caloric intake, unreported use of additional antidiabetic agents, alcohol consumption, renal or hepatic impairment, and pituitary or adrenal insufficiency [9, 16, 28]. In healthy patients and type 2 diabetics with no comorbidities, it is unclear what makes some susceptible to hypoglycemia while others are not. There is research suggesting that there may be genetic variations that affect the pharmacodynamics, pharmacokinetics, and metabolism of metformin, which may be a contributing factor to the development of hypoglycemia [29].

Antagonism of glucagon activity may be the primary mechanism by which metformin causes hypoglycemia; however, increased glucose consumption during aerobic metabolism may be a concurrent factor [21, 22, 30–32]. In both diabetic and nondiabetic patients, metformin has been shown to independently increase glucagon-like peptide 1 (GLP-1) [22, 33]. GLP-1 enhances glucose-dependent insulin secretion from beta (β) pancreatic cells and inhibits secretion of glucagon from pancreatic alpha (α) cells [34]. Metformin also acts directly on hepatocytes to inhibit the cellular pathways stimulated by glucagon, leading to decreased glycogenolysis, decreased gluconeogenesis, and increased glycogenogenesis [21, 30, 31]. Significant glucagon antagonism is reported when the plasma metformin concentration is greater than the upper limit of the proposed therapeutic metformin plasma concentration of 0.6 ± 0.5 mg/L [21, 30]. In the studies evaluating the effect of metformin on glucagon, the subjects were supplemented with glucose to maintain euglycemia, making it impossible to fully assess the effect of such large doses metformin on blood glucose concentration [21, 30]. Hypoglycemia has been reported in blood and platelet-rich plasma exposed to high concentrations of metformin in a research setting [32, 35]. Although hypoglycemia is not a common side effect with therapeutic use, data suggest it may be more likely in patients with severe metformin accumulation. A recent case report describes a human patient that developed persistent hyperlactatemia and hypoglycemia after acute ingestion of a high dose of metformin [16]. The patient's resulting serum metformin concentration was 267 mg/L [16]. The duration of that patient's hypoglycemia and hyperlactatemia is similar to that of the currently reported patient [16].

Lactic acidosis is defined as a pH < 7.35 and a lactate concentration greater than 5 mmol/L [15, 36, 37]. Anaerobic glycolysis generates pyruvate which is then reduced in the cytosol of highly glycolytic tissues to lactate via lactate dehydrogenase [38]. The lactate is reconverted into pyruvate which is consumed by the mitochondria of the liver (60%), kidneys (30%), and other tissues [37–39]. The hepatic and renal metabolism of lactate into pyruvate via the Cori cycle leads to gluconeogenesis [38]. Additional pathways for pyruvate include the tricarboxylic acid cycle and oxidative phosphorylation to generate adenosine triphosphate (ATP) [38]. Alternatively, lactate can be generated via aerobic glycolysis to create ATP [38]. Clinical signs of lactic acidosis are nonspecific and include anorexia, nausea, vomiting, abdominal pain, lethargy, hyperventilation, and hypotension [5].

Metformin leads to increased lactate concentrations via alterations in mitochondrial oxidative phosphorylation [5, 35, 39]. Metformin inhibits mitochondrial complex I activity leading to an inhibition of the electron transport system and a shift toward anaerobic metabolism [35, 39]. In a study of anesthetized pigs receiving supratherapeutic doses of metformin, there was significantly decreased mitochondrial complex I activity in the liver, heart, kidney, and skeletal muscle when compared to subjects that did not receive metformin [35]. Global oxygen extraction and consumption were significantly decreased, and there was an increase in mixed venous oxygen saturation in the metformin group compared to the placebo group [35]. Administration of metformin to rats in dose ranges used to treat human type 2 diabetic patients resulted in an increase of plasma and hepatic cytosolic redox state and a decrease in mitochondrial redox state [31]. The increase in cytosolic nicotinamide adenine dinucleotide hydrate (NADH) would decrease the conversion of lactate to pyruvate [31]. Lactic acidosis has been considered the most significant adverse effect of biguanides since a possible association was first described in 1959 [5]. The clinical syndrome of MALA was first reported in a retrospective study evaluating patients between 1959 and 1977 with biguanide use and lactic acidosis [5]. Comorbidities in metformin patients with lactic acidosis included renal disorders (85.7%), cardiovascular disease (42.9%), and liver disease (7.1%) [5]. There was no clear relationship between the dose of metformin and the development of lactic acidosis [5]. Since 1988, the reported incidence of MALA is variable throughout the literature ranging from zero to 138 cases per 100,000 patient-years [5, 36, 40]. In 2010, a Cochrane meta-analysis of 347 prospective and observational cohort studies did not identify any cases of

lactic acidosis in 70,490 patient-years of metformin exposure [41]. There was no significant difference in lactate levels between the metformin group and the non-metformin group [41].

Despite the low incidence, MALA is described in numerous case reports and case series. Not all of these publications provide measured metformin concentrations making true association difficult to determine. In addition, a majority of the patients reported have comorbidities that could contribute to hyperlactatemia. Renal impairment is the most common comorbidity reported in cases of MALA [5, 10, 18, 25, 42–44]. This has led to significant research regarding the safety of metformin use in patients with chronic kidney disease. Based on this research, the Food and Drug Administration currently recommends performing an estimated glomerular filtration rate (eGFR) prior to starting metformin [4]. Dose adjustment based on eGFR has been suggested in order to continue metformin use in patients with chronic kidney disease [45]. Patients with decreased renal function accumulate metformin and also have a prolonged elimination of metformin [29, 46, 47]. There is conflicting evidence regarding the relationship between metformin concentration, pH, and lactate concentrations [11–13, 16, 29, 42, 44, 48].

In addition to renal dysfunction, MALA has been associated with concurrent liver disease, alcoholism, cardiac failure, circulatory shock, sepsis, lung failure, cancer, severe dehydration, pancreatitis, and gastrointestinal signs (diarrhea/vomiting) [5, 6, 13, 18, 25, 42]. Liver disease has been considered a contraindication to metformin use; however, the evidence supporting this is weak and based predominantly on case reports [6, 8, 28]. Decreased hepatic lactate uptake has been reported in animals with experimentally reduced hepatic blood flow when perfusion decreased by 50–75% [14]. Reduced hepatic perfusion to that degree would be associated with liver failure, as synthetic failure is not seen until there is a loss of 70% functional mass [49]. One could conclude that although liver disease may not be a contraindication for metformin use, liver failure could be [50].

The mortality rate for patients with MALA is reported as 3–61%, and over the course of 53 years (1960–2013), the mortality rate has decreased from 50% to approximately 25% [11, 15, 18, 40, 42]. The wide variability between studies may be due to type of ingestion (acute overdose vs. chronic treatment), severity of acidosis in reported patients, and improvement in medical therapy. Acute intoxications with metformin as the sole agent have a negligible mortality rate [9, 42]. There is controversy regarding the role of metformin in MALA and conflicting evidence regarding the significance of metformin concentration on patient survival in cases of MALA [10–13]. Additionally, sustained hyperlactatemia is associated with higher mortality among various diseases independent of shock or hypotensive status [38]. To the author's knowledge, there are no studies that evaluate the duration of hyperlactatemia, metformin concentration, and mortality rate. With no clear causative effect of metformin concentration on lactate concentration in clinical practice, the lactic acidosis reported in these patients may not be due to metformin at all. In recent literature, there has been a shift to differentiate the role of metformin in cases previously identified as MALA. When refining the classifications within MALA, Lalau and others take metformin concentration and concurrent disease processes into account [14]. The term metformin-unrelated lactic acidosis (MULA) is used when metformin therapy is considered incidental in the patient's medical history. In these patients, metformin concentrations should be low to only moderately elevated, and they have at least one other condition that predisposes them to lactic acidosis. By contrast, the term metformin-induced lactic acidosis (MILA) is applied to patients with high metformin concentrations and minimal or no concomitant conditions that would contribute to formation of lactic acidosis. MALA is then reserved for patients with elevated metformin concentrations and concurrent disease processes that could cause lactic acidosis. Finally, when metformin concentrations are not available, the appropriate classification for these patients is lactic acidosis in metformin therapy (LAMT) [14]. No such classifications exist for veterinary patients.

Treatment for MALA, or any of the described classifications of lactic acidosis in patients receiving metformin, is predominantly supportive, including decontamination (if appropriate), IV fluid support, and correction of acidosis. Metformin is highly water-soluble and can be removed from the blood using hemodialysis or continuous venovenous hemofiltration [9, 42, 51, 52]. Additionally, renal replacement therapies in metformin toxicosis enhance renal blood flow, restore blood volume, and correct metabolic acidosis [52]. Despite renal replacement therapy, metformin continues to be detected in plasma and erythrocytes up to thirteen days after admission [47]. L-carnitine has also been reported as a potential therapy in MALA [53]. The presumed mechanism is normalization of pyruvate dehydrogenase activity, leading to increased oxidative utilization of pyruvate to glucose instead of converting pyruvate to lactate [53]. Further prospective studies are needed to evaluate the use of L-carnitine for treatment of MALA.

Metformin is not commonly used in the treatment of DM in dogs, as these patients usually require insulin therapy at the time of diagnosis. DM in dogs is most commonly attributed to absent insulin production by pancreatic β-cells, making it more akin to type I DM in

human patients. Evidence of autoimmune destruction of β-cells is reported in up to 50% of canine diabetics [54]. While it is possible that diagnostic evaluation for autoimmunity is not being performed early enough in the disease process, DM may develop secondary to other etiologies causing hyperglycemia and glucotoxicity. In these patients, early detection and regulation of hyperglycemia may prevent the development of insulin-dependent DM [54]. In contrast, cats are more likely to show insulin resistance with subsequent glucose-induced pancreatic β-cell desensitization and β-cell destruction [54–56]. These patients may achieve diabetic remission where euglycemia is maintained without insulin therapy. Patients in whom early and tight glycemic control is achieved are more likely to go into remission, possibly due to the reversal of glucotoxicity and lipotoxicity [56]. There is no definition of prediabetes in either dogs or cats. If there can be a determination of prediabetes in veterinary patients, metformin may become useful to prevent glucotoxicity and progression into insulin-dependent DM.

In 2004, Nelson et al. published a study evaluating the use of metformin in diabetic cats. To achieve a metformin concentration within the therapeutic human concentration range, a dose of 5–10 mg/kg once or twice daily was recommended. Reported adverse effects included intermittent vomiting, lethargy, inappetence, and weight loss. Of five diabetic cats treated with metformin, only one obtained glycemic control. Throughout the study, hyperlactatemia occurred in one subject after receiving metformin for 7 weeks [55]. In a later study of cats with neoplasia, six of nine cats which received metformin doses ranging from 7.5 to 12.5 mg/kg twice daily developed hyperlactatemia. Of these, three had chronic renal insufficiency and may have been predisposed to the development of hyperlactatemia [57]. Hypoglycemia was not reported in either study [55, 57]. There are no studies reporting the use of metformin in dogs for glycemic control; however, an abstract reporting the pharmacokinetics and bioavailability of metformin in dogs was recently published [58].

In cases of accidental veterinary metformin exposure, the clinical signs reported by the American Society for the Prevention of Cruelty to Animals® Animal Poison Control Center (ASPCA® APCC) include vomiting, lethargy, diarrhea, hypothermia, hypotension, pale mucous membranes, nausea, anorexia, diarrhea, and abdominal cramping [26]. In unpublished data from the ASPCA® APCC from 2012 to 2016, 654 dogs were reported to have metformin as a sole toxicant. Of these exposures, 68 dogs were reported to have clinical signs at the time of the call to ASPCA® APCC. The most common clinical signs were vomiting (77.9%), lethargy (22%), and diarrhea (10.3%). An additional four patients (5.9%) reported clinical signs consistent with nausea including retching, hypersalivation, and lip licking. The dose of metformin ingested for vomiting patients ranged from 11.6 to 2057.6 mg/kg. The onset of vomiting has been reported to occur fifteen minutes to eight hours after ingestion [26]. Rare clinical signs include hyperglycemia in one patient and hyperkalemia, cyanosis, collapse, and cardiopulmonary arrest each reported once and in the same patient. Five patients (7.4%) were hypoglycemic, including the patient currently reported. The dose of metformin ingested for hypoglycemic patients ranged from 139 to 294 mg/kg. Six patients (8.8%) were reported to be acidotic. Of these, lactic acidosis was reported in four dogs. The dose of metformin ingested for these acidotic patients ranged from 81 to 263 mg/kg. There were no adverse effects seen in dogs that ingested 5–10 mg/kg of metformin. Unfortunately, the severity of hypoglycemia or acidosis, therapy required, duration of therapy, and outcome of these patients are unknown. As additional clinical signs noted after the initial discussion with ASPCA® APCC may not have been reported, the incidence of adverse effects including hypoglycemia and acidosis may be underrepresented by these data. There are no data reporting the time between ingestion and the phone call to ASPCA® APCC, so the expected time frame for clinical signs to develop is unknown. To the author's knowledge, there are no previously published reports of hypoglycemia or lactic acidosis associated with metformin ingestion in veterinary patients.

In the patient, currently reported extended-release metformin was the sole ingested agent. While this patient required aggressive dextrose supplementation early in the hospitalization, she was able to maintain normoglycemia without supplementation after 37 h of therapy. The patient's hyperlactatemia significantly improved within thirteen hours of presentation, and acidosis resolved within thirty-four hours of presentation. As a serum metformin concentration was not performed, the lactic acidosis for this patient would fall under the LAMT classification as described by Lalau [14]. Potential factors contributing to the lactic acidosis noted in this patient include pancreatitis, profuse vomiting, and seizure activity. Additionally, there is a previous history of liver dysfunction based on a history of abnormal pre- and postprandial bile acids. In the absence of aberrant vessels or hepatic parenchymal changes on abdominal ultrasound, portal vein hypoplasia is the most likely cause of dysfunction in this patient. Yorkshire terriers are a breed with a high incidence of portal vein hypoplasia [59]. Alternatively, the previously abnormal bile acids could have been associated with an acute hepatitis or transient cholestasis. Bile acid levels were not measured at the time of hospitalization, so assessment of the patient's liver function could not be accurately determined. The patient had no evidence of hepatic failure on

presentation based on her physical examination, ultrasonographic examination, or blood work. Vomiting and pancreatitis have both been reported as predisposing factors for the development of lactic acidosis with metformin use and as complications following metformin ingestion [5, 43, 55, 60]. The patient's vomiting and pancreatitis may have contributed to its hyperlactatemia due to altered volume status or systemic inflammation, respectively. Hyperlactatemia can occur in seizure patients secondary to decreased oxygen delivery [38, 61]. The patient's seizure activity on presentation was considered secondary to hypoglycemia, and no additional seizure activity was noted after euglycemia was obtained with supplementation. As the patient's hypoglycemia, hyperlactatemia, and lactic acidosis had a longer duration than would be expected due to any of the concurrent conditions, we conclude that these abnormalities were due to the effect of the ingestion of extended-release metformin.

With the increasing availability of metformin, the likelihood of exposure and adverse effects in companion animals increase. It is unclear how significant metformin intoxication will become in veterinary patients. Aggressive monitoring and therapy is recommended to evaluate for the development of hypoglycemia, lactic acidosis, or any other reported adverse effects.

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Authorship

NB: performed the literature review, wrote the manuscript, obtained patient (client) consent, and organized the table. BE: collected case data, corrected and revised the manuscript, and approved final version of the manuscript. NS: collected case data, performed literature review, wrote part of the manuscript.

Conflict of Interest

None declared.

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