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Drs. Shamir, Kaldas, and Tan report no relationships with proprietary entities producing health care goods and services.

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Metformin-Associated Lactic Acidosis

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Introduction

Metformin is considered first line therapy for newly diagnosed type 2 diabetes mellitus (DM) and is the most prescribed oral anti-hyperglycemic medication in the world.[1] Close to 14 million patients received a prescription containing metformin from U.S. outpatient pharmacies in 2014.[2] While metformin has been a powerful tool in the treatment of DM, it is also known to increase the risk of severe and potentially fatal lactic acidosis, particularly in association with conditions leading to the drug's accumulation, such as kidney and liver disease.[3]

Metformin-associated lactic acidosis (MALA) is estimated to occur at a rate of 0.01 to 0.09 cases per 1,000 patient years.[4] However, given recent proposals to utilize metformin more liberally in patients with mild to moderate chronic kidney disease (CKD),[5,6] it is likely that MALA will become more common. MALA is associated with an extremely high mortality, up to 30% to 50% in affected individuals.[7] Greater appreciation of the risks of metformin and judicious use of this drug will be key to reduce adverse outcomes due to MALA, while a high index of suspicion for its diagnosis coupled with aggressive therapy will improve outcomes among those affected.

Case

A 74-year-old diabetic woman was transferred from an outside hospital with a severe anion gap metabolic acidosis and concerns for ischemic bowel. According to family members, she had originally presented with five days of diarrhea, poor PO intake, and worsening mental status. Her vital signs showed a blood pressure of 154/66, heart rate of 93, and a rectal temperature of 34 degrees Celsius. Physical exam revealed a patient who was awake but confused. She demonstrated no guarding or peritoneal signs. Urine output was decreased. Other aspects of the exam were unremarkable. Laboratory data revealed a white blood cell count of 23.8 x 10^9/L, hemoglobin of 11 g/dL, and platelets of 353 x 10^9/L. In mmol/L, she had a sodium 141, potassium 5.3, chloride 97, and carbon dioxide 5. In mg/dL her blood urea nitrogen was 77, creatinine was 7.4, glucose was 135, calcium was 9.1, magnesium 2, and phosphorus 14.7. An arterial blood gas showed a pH less than 6.79, PCO_2 of 15, PO_2 of 194, and HCO_3 that was less than 7. Lactate was elevated at 21 mmol/L, with a serum osmolar gap of 30. The remainder of laboratory data, including liver function tests, lipase, troponin, and a toxicology screen, were unremarkable. An abdominal CT scan also was negative. The surgical team did not believe she had an acute abdomen requiring any intervention. At that time, it was confirmed with the family that the patient takes metformin.

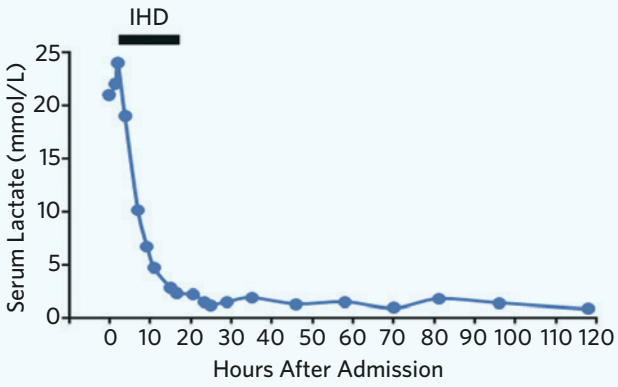

FIGURE 1. Lactate levels of the patient presented in the case. Thirteen hours of continuous high-efficiency dialysis was delivered during the time period indicated, resulting in a rapid lowering of the lactate. Since metformin levels are not widely available, the lactate is used as a surrogate for adequate clearance of this drug.

The patient was started on bicarbonate-containing intravenous fluids and intubated for airway protection. Subsequent hypotension was treated with norepinephrine and vasopressin. Due to a high suspicion for metformin intoxication/MALA, nephrology was consulted, and an extended session of high flow intermittent hemodialysis was initiated. A total of nearly 13 hours of dialysis was delivered in a continuous session and was terminated when her lactate was less than 3 mmol/L (Figure 1). Fortunately, her lactate remained suppressed for the remainder of her hospitalization. Her hemodynamics, mental status, and renal function improved, and she did not require permanent hemodialysis, although her final creatinine was 2.6 mg/dL (unknown baseline). She was discharged six days after her transfer. A metformin level obtained prior to hemodialysis was sent to a processing lab and was reported several weeks later to be 58 mcg/mL (therapeutic level: 1-2 mcg/mL).

Differential Diagnosis of Lactic Acidosis

Lactate is synthesized by liver, small bowel, and peripheral tissues during glycolysis and can accumulate during hypoxia.[8] The liver, kidney, heart, and skeletal muscle are the main sites for lactate metabolism, while the liver and kidney account for approximately 60% and 30% of lactate clearance, respectively.[9,10] Lactate can either be oxidized for energy, or be converted back to glucose (via gluconeogenesis) in the liver.[11]

Lactic acidosis is defined as a high anion gap metabolic acidosis associated with an arterial lactate concentration greater than 5 mmol/L. It is considered the most common cause of metabolic acidosis.[12] An accompanying osmolar gap may also occur, due to the release of osmotically active substances from hypoxic tissue.[13] There are two types of lactic acidosis, denoted Type A or Type B.[14] Type A lactic acidosis is the most common clinical situation and is caused by impaired oxygen delivery or hypoperfusion, sometimes coupled with an increase in glycolysis. This leads to increased anaerobic respiration and the accumulation of lactate. Type B lactic acidosis occurs in the absence of hypoxia, and instead is caused by defects in oxidative phosphorylation and/or suppression of gluconeogenesis in the liver. This, too, will ultimately lead to lactate accumulation and can be caused by a variety of drugs and toxins, including metformin and other biguanides, nucleoside reverse-transcriptase inhibitors, salicylate, cyanide, and toxic alcohols.

Sepsis, liver failure, and some malignancies also are risk factors for lactic acidosis. Any factor that increases glycolysis will lead to an increase in lactate production. Lactic acidosis also can present in up to 10% of patients with diabetic ketoacidosis. This may be due to hypoxia but may also occur without it.[15]

The differential diagnoses of lactic acidosis in our case would include septic shock, ischemic bowel or limb, severe hepatic dysfunction, coexisting diabetic ketoacidosis, or drug/toxin exposure. The patient's baseline renal function was unknown, but it appeared that she had acute kidney injury on presentation, likely related to severe volume depletion in the setting of diarrhea and vomiting, which would predispose her to metformin accumulation. Coupled with normal glucose and liver function tests, a normal toxicology screen, benign abdominal imaging and exam, and the knowledge that she was taking metformin for diabetes, the most likely explanation was metformin intoxication/MALA.

Historical Context

The biguanides, the drug class to which metformin belongs, were initially designed in the 1950s as a treatment for hyperglycemia. The mechanism of action is via reduction of gluconeogenesis in the liver. It does this through effects on insulin sensitivity and through reduction in hepatic uptake of lactate, a substrate for gluconeogenesis.[16,17]

One of the earliest available biguanides, phenformin, was eventually withdrawn from the market due to an association with severe lactic acidosis. This led to extremely cautious use of metformin, at least initially. Europe was the first to adopt its use in the 1980s, followed by the United States in 1994. Since metformin is renally eliminated, the U.S. Food and Drug Administration required labeling stating that use was contraindicated at serum creatinine measurements greater than 1.5 mg/dL in men and 1.4 mg/dL in women.[5,6] This warning label has not been updated until recently, meaning that for more than 20 years there was no cutoff specified for estimated glomerular filtration rate (eGFR), which would be a more accurate determination of renal function compared to serum creatinine alone.

Recognizing the potential benefit of metformin to hyperglycemic patients, as well as the arbitrary nature of the serum creatinine cutoff, a number of endocrine societies have made recommendations that would encourage greater use in mild to moderate chronic kidney disease (CKD). A consensus statement, made jointly by the American Diabetes Association and the European Association for the Study of Diabetes, judged that "recent studies have suggested that metformin is safe" unless the eGFR was < 30 mL/min per 1.73 m^2.[18] In the United Kingdom, the National Institute for Health and Clinical Excellence recommended caution at an eGFR < 45 ml/min, or a serum creatinine > 1.5 mg/dL, with instructions to stop if GFR drops below 30 mL/min, or if the creatinine rises above 1.7 mg/dL.[5] The Australian Diabetes Society has similar recommendations to the United Kingdom. Meanwhile the Canadian Diabetes Association recommends caution with eGFR < 60 mL/min, with contraindication being < 30mL/min.[5] Regardless of the exact wording and cutoffs specified, it does appear that several workgroups are encouraging greater use of metformin in patients with CKD.

Metformin-Associated Lactic Acidosis (MALA)

MALA is a lactic acidosis that exists in the setting of exposure to metformin.[19] With this definition, MALA could indicate any lactic acidosis in which metformin could play a role. MALA rarely develops in patients without comorbidities such as renal or liver failure.[20] This is in contrast to a subset of MALA, referred to as metformin-induced lactic acidosis (MILA), in which metformin is the only cause of the acidosis, such as in acute overdoses.[21]

Metformin enters cells and directly acts on mitochondria to uncouple oxidative phosphorylation through inhibition of complex I-mediated respiration. It also inhibits the citric acid cycle (i.e., the TCA or "Krebs" cycle), which is important in generating the substrate for oxidative phosphorylation. The cellular response is to increase glycolysis, which ultimately leads to lactate accumulation.[22-24]

In animals[25] and humans,[26,27] biguanide administration is associated with hyperlactatemia. Metformin also elevates plasma lactate levels during exercise.[28,29] The hyperlactatemia associated with therapeutic doses of metformin is small, usually

less than 2 mmol/L, although higher levels may occur.[30-33] The small magnitude of the increase may explain why not all studies report high lactate levels.[34]

The clinical manifestations of MALA are nonspecific. Gastrointestinal symptoms predominate, including nausea, vomiting, diarrhea, and epigastric pain. Altered mental status, somnolence, hypothermia, and hemodynamic instability also occur, as in the case of our patient.[35,36]

Mortality

MALA is associated with an extremely high mortality rate of 30% to 50%.[4,37-42] Predictors of mortality have been difficult to validate in the literature. Some studies suggest that high metformin levels (greater than 20 to 50 mg/L), higher lactate levels, and lower pH are associated with poor outcomes.[43,44] However, other studies do not find a relationship between lactate or metformin levels with mortality, citing comorbid conditions as having a greater effect.[45]

Treatment of MALA

There is no specific antidote for metformin overdose, although gastrointestinal decontamination can be used in acute overdoses.[19] For the remainder of patients, intensive supportive care is required. A key aspect to this care is extracorporeal treatment (ECTR), which in this case is essentially hemodialysis.

Metformin is a small molecule with a size of 165 Daltons. Its oral bioavailability is approximately 55%, and it has a half-life of approximately 5 hours. Metformin undergoes very little metabolism, and the unchanged drug is excreted in the urine. In fact, the kidney is the major organ for the elimination of this drug. This ability is proportional to overall renal function, explaining why kidney disease is strongly associated with MALA.[46]

Metformin has negligible protein binding which, when coupled with its small size, equates to a high extraction ratio through hemodialyzers.[19] However, metformin can localize to intracellular compartments and can accumulate to high levels in erythrocytes and other cells. This leads to its relatively large volume of distribution of 1 to 5 L/kg.[46] This large distribution, which would limit the efficiency of dialysis, may necessitate prolonged therapy for adequate clearance.

Until recently, there have been no guidelines for the use of ECTR in the treatment of MALA. In 2015, the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup published guidelines to aid in the treatment of MALA.[19] In publishing these guidelines, EXTRIP did note that available high quality evidence was limited, and that recommendations were based on consensus opinion, using a scale of strength of recommendation from 1 (strong) to 2 (weak) to 3 (neutral) based on levels of evidence ranging from A (high level of evidence) to D (very low level of evidence).

EXTRIP recommends ECTR in severe metformin poisoning (level of evidence - 1D). The rationale for the use of ECTR is based on the high mortality of MALA, lack of other effective treatments, and the ability to correct sequelae of the intoxication, including acidosis, electrolyte disorders, and hypothermia, as well as to treat coexisting kidney failure. The recommendations note that improvement in overall patient condition can be dramatic.

The EXTRIP consensus statement suggests that:

ECTR is recommended if:

- Lactate > 20 mmol/L (1D)
- Arterial pH ≤ 7.0 (1D)
- Standard therapy (including supportive care and bicarbonate) fails (1D)

ECTR is suggested if:

- Lactate > 15-20 mmol/L (2D)
- Arterial pH < 7.0-7.1 (2D)

Other factors where ECRT should be considered are shock (1D), impaired kidney function (1D), liver failure (2D), and decreased level of consciousness (2D).

Regarding the modality of ECTR, although there is a paucity of evidence, EXTRIP recommendations are to use intermittent hemodialysis (IHD) (1D) as the first choice. Continuous renal replacement therapy (CRRT) is an acceptable alternative when IHD cannot be performed (2D).[19] IHD is superior for the removal of metformin and lactate, as well as for correction of metabolic acidosis.[47] Extracorporeal clearance of metformin can reach > 200 ml/min with IHD[6,48-51] but only up to 50 ml/min with CRRT.[52-54] Even in the setting of hypotension, IHD may still be the preferred option since removal of the metformin

may stabilize the patient. On the other hand, CRRT has in case series been used successfully in MALA, and so is a reasonable second choice.[55]

EXTRIP recommends stopping ECTR when lactate levels are less than 3 mmol/L and pH > 7.35 (1D). Metformin levels have a poor correlation with outcome and hence should not routinely be followed for efficacy.[19] Further, metformin levels are not widely available and may not be useful in actual practice. The attainment of the recommended lactate and pH goals may require prolonged treatment, sometimes greater than 24 hours of "intermittent" dialysis.

It is important to note that metformin levels may rise or "rebound" after conclusion of hemodialysis. This is caused by redistribution of the drug out of compartments that were not affected by dialysis. For this reason, EXTRIP recommends close monitoring and repeat sessions of dialysis if needed.

Due to the limited protein binding of metformin, hemoperfusion or plasma exchange were not deemed as useful as hemodialysis.[19,56,57] Peritoneal dialysis also would not be expected to achieve good metformin clearance in severe cases,[58-60] but its use has been described.[61]

Prevention of MALA

As MALA is in many cases an iatrogenic entity, recognition of the most susceptible patients is key to its prevention. Judicious use of metformin, with reduction in dosing for chronic kidney disease, and discontinuation at lower eGFR levels is necessary to prevent MALA occurrences. Patients who might be at risk for developing acute kidney injury should also be cautiously prescribed this medication.

In April 2016, the U.S. Food and Drug Administration distributed the following guidelines for use:

- Obtain eGFR in patients before starting metformin.
- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2.
- Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m^2.
- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.[62]

These guidelines should provide much needed clarity for the prescribing of metformin in general practice.

Conclusions

MALA is a form of lactic acidosis caused by metformin intoxication and is associated with a high mortality. Prevention through dose reduction and/or discontinuation in susceptible patients is vitally important. In addition, a high index of suspicion is required to make the diagnosis during presentation and to initiate aggressive therapy. If metformin overdose is severe, extracorporeal therapy consisting of high-efficiency hemodialysis should be initiated and maintained until lactate levels are normalized.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012; 35(6):1364-79.
2. IMS Health, Total Patient Tracker. 2014.
3. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of Fatal and Nonfatal Lactic Acidosis With Metformin Use in Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis. *Arch Intern Med.* 2003; 163(21):2594-602.
4. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of Lactic Acidosis or Elevated Lactate Concentrations in Metformin Users With Renal Impairment: A Population-based Cohort Study. *Diabetes Care.* 2014; 37(8):2218-24.
5. Lipska KJ, Bailey CJ, Inzucchi SE. Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency. *Diabetes Care.* 2011; 34(6):1431-7.
6. Duong JK, Roberts DM, Furlong TJ, Kumar SS, Greenfield JR, Kirkpatrick CM, Graham GG, Williams KM, Day RO. Metformin Therapy in Patients With Chronic Kidney Disease. *Diabetes Obes Metab.* 2012; 14(10):963-5.
7. Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach the COSMIC Approach Study. *Diabetes Care.* 2005; 28(3):539-43.
8. Phypers B, Pierce JT. Lactate Physiology in Health and Disease. Continuing Education in Anaesthesia. *Critical Care & Pain.* 2006; 6(3):128-32.
9. Stacpoole PW. Lactic Acidosis. *Endocrinol Metab Clin North Am.* 1993; 22(2):221-45.
10. Bellomo R. Bench-to-Bedside Review: Lactate and the Kidney. *Crit Care.* 2002; 6(4):322-6.
11. Chen YJ, Mahieu NG, Huang X, et al. Lactate Metabolism is Associated With Mammalian Mitochondria. *Nat Chem Biol.* 2016. Sept. 12. Epub ahead of print.
12. Kamber N, Davis WA, Bruce DG, Davis TM. Metformin and Lactic Acidosis in an Australian Community Setting: The Fremantle Diabetes Study. *Med J Aust.* 2008; 188(8):446-9.
13. Kraut JA, Madias NE. Lactic Acidosis. *N Engl J Med.* 2014; 371(24):2309-19.
14. Cohen R WHICR, HF Woods, Editors. Clinical and Biochemical Aspects of Lactic Acidosis. In: Acidosis. Tcpacol, editor. Boston (MA): Blackwell Scientific Publications; 1976. p. 40–52.
15. Seheult J, Fitzpatrick G, Boran G. Lactic Acidosis: An Update. *Clin Chem Lab.* Med 2016.
16. Krentz AJ, Bailey CJ. Oral Antidiabetic Agents: Current Role in Type 2 Diabetes Mellitus. *Drugs.* 2005; 65(3):385-411.
17. Madiraju AK, Erion DM, Rahimi Y, et al. Metformin Suppresses Gluconeogenesis By Inhibiting Mitochondrial Glycerophosphate Dehydrogenase. *Nature.* 2014; 510.
18. Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. A Consensus Statement of the American Diabetes Association and the European Association for the Study of Diabetes. 2009; 32(1):193-203.
19. Calello DP, Liu KD, Wiegand TJ, et al. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. *Crit Care Med.* 2015; 43(8):1716-30.
20. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of Fatal and Nonfatal Lactic Acidosis With Metformin Use In Type 2 Diabetes Mellitus. *Cochrane Database Syst Rev.* 2006; (1):CD002967.
21. Vecchio S, Protti A. Metformin-induced Lactic Acidosis: No One Left Behind. *Crit Care.* 2011; 15(1):107.
22. Andrzejewski S, Gravel SP, Pollak M, St-Pierre J. Metformin Directly Acts on Mitochondria To Alter Cellular Bioenergetics. *Cancer Metab.* 2014; 2:12.
23. El-Mir MY, Nogueira V, Fontaine E, Averet N, Rigoulet M, Leverve X. Dimethylbiguanide Inhibits Cell Respiration Via an Indirect Effect Targeted on the Respiratory Chain Complex I. *J Biol Chem.* 2000; 275.
24. Owen MR, Doran E, Halestrap AP. Evidence that Metformin Exerts Its Anti-diabetic Effects Through Inhibition of Complex 1 of the Mitochondrial Respiratory Chain. *Biochem J.* 2000; 348.
25. Madiraju AK, Erion DM, Rahimi Y, et al. Metformin Suppresses Gluconeogenesis by Inhibiting Mitochondrial Glycerophosphate Dehydrogenase. *Nature.* 2014; 510(7506):542-6.
26. Hong Y, Rohatagi S, Habtemariam B, Walker JR, Schwartz SL, Mager DE. Population Exposure-response Modeling of Metformin in Patients With Type 2 Diabetes Mellitus. *J Clin Pharmacol.* 2008; 48(6):696-707.
27. Lalau JD, Lacroix C, Compagnon P, et al. Role of Metformin Accumulation in Metformin-Associated Lactic Acidosis. *Diabetes Care.* 1995; 18(6):779-84.
28. Boule NG, Robert C, Bell GJ, et al. Metformin and Exercise in Type 2 Diabetes: Examining Treatment Modality Interactions. *Diabetes Care.* 2011; 34(7):1469-74.
29. Cunha MR, Silva ME, Machado HA, et al. Cardiovascular, Metabolic and Hormonal Responses to the Progressive Exercise Performed to Exhaustion in Patients With Type 2 Diabetes Treated With Metformin or Glyburide. *Diabetes Obes Metab.* 2008; 10(3):238-45.
30. Bailey CJ, Turner RC. Metformin. *N Engl J Med.* 1996; 334(9):574-9.
31. Marchetti P, Benzi L, Cecchetti P, et al. Plasma Biguanide Levels are Correlated With Metabolic Effects in Diabetic Patients. *Clin Pharmacol Ther.* 1987; 41(4):450-4.
32. Scarpello JH. Review: Optimal Dosing Strategies for Maximising the Clinical Response to Metformin in Type 2 Diabetes. *The British Journal of Diabetes & Vascular Disease.* 2001; 1(1):1-28.

33. Davis TM, Jackson D, Davis WA, Bruce DG, Chubb P. The Relationship Between Metformin Therapy and the Fasting Plasma Lactate in Type 2 Diabetes: The Fremantle Diabetes Study. *Br J Clin Pharmacol.* 2001; 52(2):137-44.

34. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic Effects of Metformin in Non-insulin-dependent Diabetes Mellitus. *N Engl J Med.* 1995; 333(9):550-4.

35. Teale KF, Devine A, Stewart H, Harper NJ. The Management of Metformin Overdose. *Anaesthesia.* 1998; 53(7):698-701.

36. Gan SC, Barr J, Arieff AI, Pearl RG. Biguanide-associated Lactic Acidosis. Case Report and Review of the Literature. *Arch Intern Med.* 1992; 152(11):2333-6.

37. Glucophage (metformin hydrochloride) and Glucophage XR (extended-release) prescribing information. Bristol, NJ: Bristol-Myers Squibb; 2009.

38. Bailey CJ. Biguanides and NIDDM. *Diabetes Care.* 1992; 15(6):755-72.

39. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA. Lactic Acidosis in Patients With Diabetes Treated With Metformin. *N Engl J Med.* 1998; 338(4):265-6.

40. Peters N, Jay N, Barraud D, et al. Metformin-associated Lactic Acidosis in an Intensive Care Unit. *Crit Care.* 2008; 12(6):R149.

41. Richy FF, Sabido-Espin M, Guedes S, Corvino FA, Gottwald-Hostalek U. Incidence of Lactic Acidosis in Patients With Type 2 Diabetes With and Without Renal Impairment Treated With Metformin: A Retrospective Cohort Study. *Diabetes Care.* 2014; 37(8):2291-5.

42. Rocha A, Almeida M, Santos J, Carvalho A. Metformin in Patients With Chronic Kidney Disease: Strengths and Weaknesses. *J Nephrol.* 2013; 26(1):55-60.

43. Dell'Aglio DM, Perino LJ, Kazzi Z, Abramson J, Schwartz MD, Morgan BW. Acute Metformin Overdose: Examining Serum pH, Lactate Level, and Metformin Concentrations In Survivors Versus Nonsurvivors: A Systematic Review of the Literature. *Ann Emerg Med.* 2009; 54(6):818-23.

44. Duong JK, Furlong TJ, Roberts DM, et al. The Role of Metformin in Metformin-Associated Lactic Acidosis (MALA): Case Series and Formulation of a Model of Pathogenesis. *Drug Saf.* 2013; 36(9):733-46.

45. Lalau JD, Race JM. Lactic Acidosis in Metformin-treated Patients. Prognostic Value of Arterial Lactate Levels and Plasma Metformin Concentrations. *Drug Saf.* 1999; 20(4):377-84.

46. Graham GG, Punt J, Arora M, et al. Clinical Pharmacokinetics of Metformin. *Clin Pharmacokinet.* 2011; 50(2):81-98.

47. Lemyze M, Baudry JF, Collet F, Guinard N. Life Threatening Lactic Acidosis. *BMJ.* 2010; 340:c857.

48. Lalau JD, Andrejak M, Moriniere P, et al. Hemodialysis in the Treatment of Lactic Acidosis In Diabetics Treated By Metformin: A Study of Metformin Elimination. *Int J Clin Pharmacol Ther Toxicol.* 1989; 27(6):285-8.

49. Perrot D, Claris O, Guillaume C, Bouffard Y, Delafosse B, Motin J. Metformin and Lactic Acidosis: Value of Initial Plasma Assay of Metformin and Hemodialysis. *Ann Med Interne (Paris).* 1986; 137(2):169-70.

50. Roberts DJ, Ray J. Therapeutic Drug Monitoring of Metformin In a Patient With End Stage Renal Failure on Haemodialysis. *Nephrol Dial Transplant.* 2010; 15:87–8.

51. Walsh S AM, Cannon R. Severe Metformin-associated Lactic Acidosis From Acute Ingestion Without Renal Failure. *Clin Toxicol.* 2010; 48:614.

52. Arroyo AM, Walroth TA, Mowry JB, Kao LW. The MALAdy of Metformin Poisoning: Is CVVH the Cure? *Am J Ther.* 2010; 17(1):96-100.

53. Barrueto F, Meggs WJ, Barchman MJ. Clearance of Metformin By Hemofiltration In Overdose. *J Toxicol Clin Toxicol.* 2002; 40(2):177-80.

54. Huberlant V, Laterre PF, Hantson P. Nearly Fatal Metabolic Acidosis: Septic or Toxic? *Eur J Emerg Med.* 2010; 17(4):243-4.

55. Keller G, Cour M, Hernu R, Illinger J, Robert D, Argaud L. Management of Metformin-associated Lactic Acidosis By Continuous Renal Replacement Therapy. *PLoS One.* 2011; 6(8):e23200.

56. Turkcuer I, Erdur B, Sari I, Yuksel A, Tura P, Yuksel S. Severe Metformin Intoxication Treated With Prolonged Haemodialyses and Plasma Exchange. *Eur J Emerg Med.* 2009; 16(1):11-3.

57. Guo PY, Storsley LJ, Finkle SN. Severe Lactic Acidosis Treated With Prolonged Hemodialysis: Recovery After Massive Overdoses of Metformin. *Semin Dial.* 2006; 19(1):80-3.

58. Ghannoum M, Bouchard J, Nolin TD, Ouellet G, Roberts DM. Hemoperfusion for the Treatment of Poisoning: Technology, Determinants of Poison Clearance, and Application in Clinical Practice. *Semin Dial.* 2014; 27(4):350-61.

59. Bismuth C, Gaultier M, Conso F, Assan R, Heuclin C. Lactic Acidosis Induced By Excessive Ingestion of Metformin. *Eur J Toxicol Environ Hyg.* 1976; 9(1):55-7.

60. Hayat JC. The Treatment of Lactic Acidosis in the Diabetic Patient by Peritoneal Dialysis Using Sodium Acetate. A Report of Two Cases. *Diabetologia.* 1974; 10(5):485-7.

61. Al-Hwiesh AK, Abdul-Rahman IS, El-Deen MA, et al. Metformin in Peritoneal Dialysis: A Pilot Experience. *Perit Dial Int.* 2014; 34(4):368-75.

62. http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm.

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