A Paradox: Unintentional Metformin Lactic Acidosis in an End-Stage Renal Disease Patient

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INTRODUCTION

Metformin, a biguanide drug commonly used to treat diabetes mellitus and polycystic ovarian syndrome, is one of the most commonly used antidiabetic agents due to its low incidence of adverse effects. In 2005, there were over 42 million prescriptions written for metformin. [1] However, metformin does have one particular side-effect which is especially-dreaded: metformin-associated lactic acidosis (MALA), which carries an incidence of 3 per 100,000 cases. Due to metformin's clearance from the body by tubular secretion and excretion via the urine, metformin is contraindicated in any patient whose kidney disease has progressed to having a GFR less than 30. In 2006, there were only 300 intentional metformin overdoses reported to poison centers throughout the United States. [2]

What is even more unusual is a patient with end-stage renal disease who suffers from an unintentional metformin overdose. Here, we present such a case, in which an end –stage renal disease patient on hemodialysis was given metformin instead of neurontin by a drug store pharmacist and presented with metformin associated lactic acidosis. This is just one example of how a serious medication error by a community pharmacist affected a patient, but it represents a larger issue that many in the medical field are striving to improve.

PATIENT PRESENTATION

A 72-year old female presented to the emergency department via EMS for shortness of breath. History was significant for end-stage renal disease on hemodialysis, epilepsy, hyperlipidemia, hypertension, and diabetes. The patient revealed that she could not remember the last time she received hemodialysis. The patient was awake and alert but in respiratory distress and appeared to be fluid overloaded, so she was placed on BIPAP. The EKG also revealed peaked T waves *(See Figure 1)* and potassium from the venous blood gas was 6.6, so the following hyperkalemia treatment was given as well: calcium gluconate, sodium bicarbonate, insulin, and dextrose. The VBG also showed a pH of 6.98 and lactic acid was 23. At that time, EMS arrived with more information, including the patient's medication list. Per EMS, the patient was on levetiracetam, carbamazepine, renagel, metoprolol, simvistatin, and metformin. Even though metformin is an absolute contraindication in any patient with a GFR less than 30 ml/min, with this information in addition to the pH of 6.98 (nadir 6.96), the lactate of 23 (peak 25), anion gap of 40, and the fact that the patient was still awake and talking, the working diagnosis became metformin-associated lactic acidosis.

The patient was intubated, central venous access was obtained, and vasopressor agents were initiated. Nephrology was consulted, who agreed with the presumptive diagnosis and strongly recommended checking a metformin level and sending the patient for hemodialysis once the blood pressure was stable. The patient then lost pulses and a rhythm on the cardiac monitor, and one round of epinephrine, sodium bicarbonate, and calcium chloride were given, after which the patient had return of spontaneous circulation. The patient went to the ICU and remained hypotensive overnight while on two vasopressor agents. The patient was finally stable enough for hemodialysis the next day and was able to be dialyzed for 3 hours. The next day the metformin level came back from the laboratory at 60 mcg/ml. The PMD was also contacted the next day, and he revealed that he had never written metformin for the patient, but he did write for neurontin due to some neuropathic pain she was having. It was the pharmacist who unintentionally dispensed metformin instead of neurontin to the patient, which then induced a catastrophic turn of events in this patient. The patient died in the ICU three weeks after initial presentation.

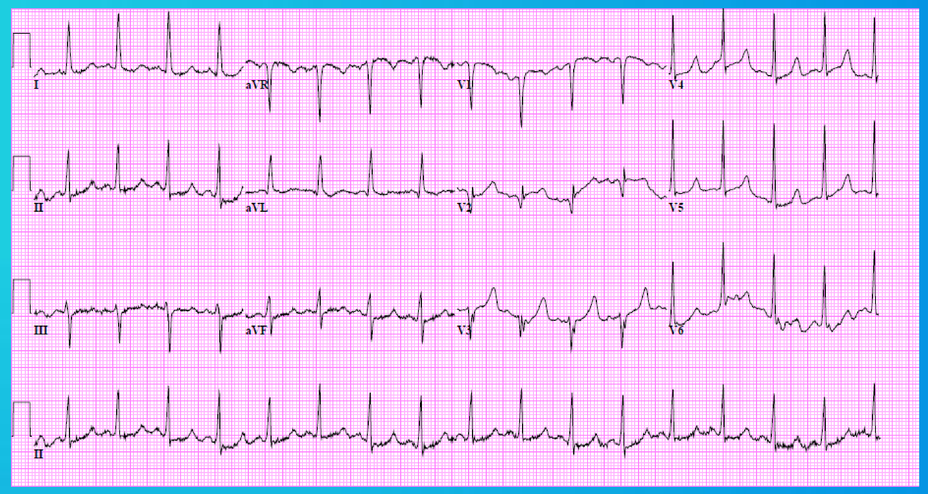

Figure 1: EKG: HR: 100 and signs of hyperkalemia

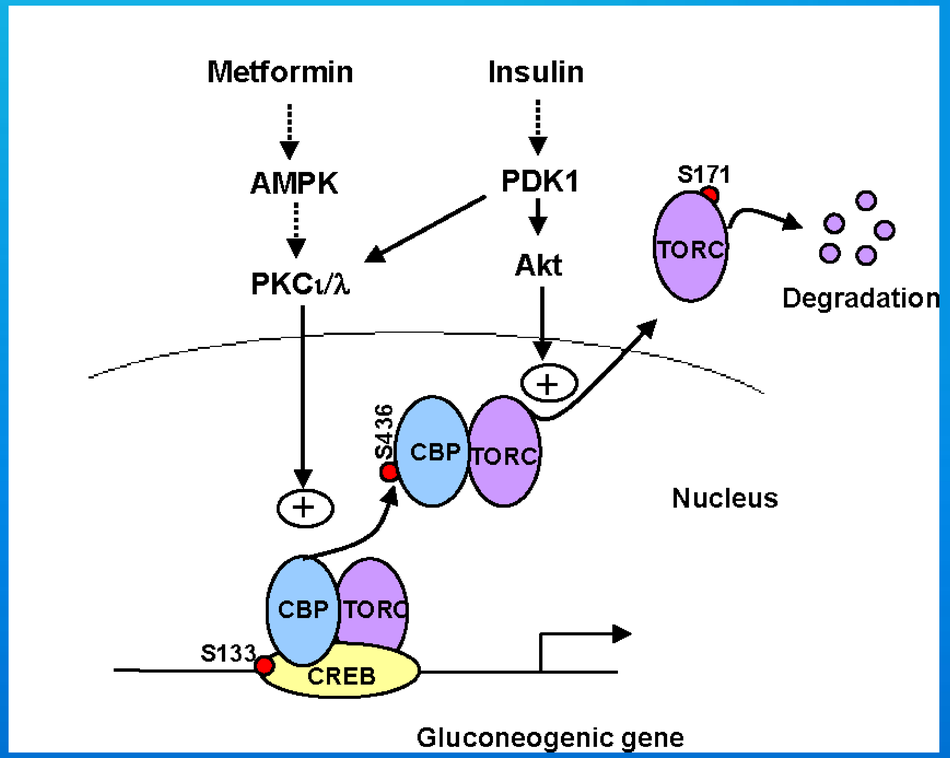

Figure 2: Metformin Suppresses Hepatic Gluconeogenesis by Inhibiting cAMP Signaling Through Phosphorylation of CREB Binding Protein (CBP)[3]

DISCUSSION

An end-stage renal disease patient on hemodialysis with a GFR less than 30 ml/minute should not be prescribed metformin.[4] Our patient's GFR was 4 ml/min. Metformin-associated lactic acidosis typically results from the gradual accumulation of lactic acid in the patient's bloodstream, as the mechanism is thought to be from inhibiting hepatic gluconeogenesis via the phosphorylation of the CREB Binding Protein, which then triggers the dissociation of the CREB-CBP-TORC2 transcription complex. [5] *(See Figure 2)* The gluconeogenic substrates pyruvate and alanine build up, which then causes type B lactic acid to accumulate and fail to clear. [6] [7] This rise in lactate typically occurs insidiously, which is why a patient with a metformin-associated lactic acidosis can possess severe acidosis and be awake and talking on presentation. Therefore, whenever a patient presents awake and talking with a wide anion gap acidosis and high lactate, MALA should be entertained, even if the patient has end-stage renal disease and is on hemodiaysis.

Dell'Aglio, Damon et al. examined acute metformin overdose in 22 patients, where they focused specifically on three levels: serum pH, lactate level, and metformin concentrations in survivors vs nonsurvivors. What is interesting is that our patient's laboratory values were not nearly as profound as the values of the patient study group who died. In this group, the median peak lactate level was 35, the median nadir serum pH was 6.71, and the median metformin level was 110. [8] Our patient's values were not as grave: peak lactate of 24, nadir serum pH 6.95, and metformin level 60. Since our patient's laboratory values were not as profound as those of the deceased group in the study, an appropriate follow-up study would be to examine the relation of GFR to mortality in the setting of end-stage renal disease patients on metformin who present with MALA. MALA has been reported to have a mortality as high as 42% to 50% [9], but the true incidence and mortality of MALA in end-stage renal disease patients is unknown. In 2011, Perrone et al. published a paper with three case reports of MALA, two of whom were ESRD patients. [10] Our cases differs from these in that our patient was unintentionally using metformin, as she thought she was actually taking neurontin. Once diagnosed, treatment for MALA should include aggressive airway management, vasopressor agents as warranted, hemodialysis, and possibly a sodium bicarbonate drip if the serum bicarbonate level is less than 5. [11]

In 2007, Knudsen et al. published a study which focused on the medication errors made by community pharmacists. They followed 40 pharmacies in 2004-2005 and found that 401 medication errors were made, the majority of which were transcription errors. In these transcription errors, the prescriptions were hand-written by the physicians, and the pharmacists misread them and prescribed either wrong medicines, dosages, or strengths. The article then offered a root-cause analysis of this problem, and one of the conclusions they came to was eliminating handwritten prescriptions and using only computer-generated prescriptions. [12]

In 2013, Joosten, Hanneke et al published a study which followed a population in Zwolle, The Netherlands. During their study period, whenever the laboratory found an adult who had a GFR of less than 40 ml/1.73 m^2 , a report was sent the the community pharmacists. Therefore, from that point on, every patient with a GFR less than 40 ml/1.73 m^2 activated an alert warning for "Low GFR." [13]

CONCLUSION

When an end-stage renal disease patient presents with metabolic acidosis, wide anion gap, and high lactate, the "MUDPILES" should not be dropped to "UDPILES" because the patient may intentionally, accidentally, or iatrogenically be taking metformin. Anytime a patient presents with a metabolic acidosis, high lactate, and is still speaking, MALA should be entertained, even if the patient has end-stage renal disease like in this case. Also, efforts should be made to provide patients with computer-generated prescriptions so that community pharmacists are less likely to make errors when filling prescriptions, and once the laboratory determines that a patient has a GFR below 40, it should send a report to the community pharmacies. From that point on, the patient will have a "Low GFR" alert warning in his/her record.

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