

Laboratory-Confirmed Metformin-Associated Lactic Acidosis

C. Nestor¹, S. Nasim², N. Coyle³, C. Canavan⁴

1. Specialist Registrar, Irish National Anaesthesia Training Program
2. Senior Registrar, Department of Anaesthesia, Mayo General Hospital
3. Graduate Entry Medicine Student, University of Limerick
4. Consultant Anaesthetist, Department of Anaesthesia, Mayo General Hospital

Abstract

Introduction

Metformin is considered the first line oral hypoglycaemic agent for the treatment of type 2 diabetes. We report three cases of prospectively identified laboratory confirmed metformin-associated lactic acidosis admitted to our intensive care unit.

Case 1

72-year-old female presented with lactic acidosis; pH 6.7, lactate 22.6mmol/L with elevated Metformin levels of 4.9mg/L.

Case 2

56-year-old female presented with lactic acidosis; pH 7.2 and lactate 14.8mmol/L. Metformin levels elevated at 3.9mg/L.

Case 3

72-year-old female presented with lactic acidosis, pH 6.95 and lactate of 27.6mmol/L with elevated Metformin levels of 48.7mg/L.

Results

All three cases were admitted to the intensive care unit to receive supportive care. Despite CVVHD, two patients died.

Discussion

Metformin is considered the first line oral hypoglycaemic agent. Confirmation of this diagnosis often proves difficult due to the scarcity of laboratory testing. Our case series highlights the issues of inappropriate prescription in specific patient populations.

Introduction

Metformin is considered the first line oral hypoglycaemic agent for the treatment of type 2 diabetes in the absence of contraindications¹. Both the European Association for the study of Diabetes and the American Diabetes Association

propose that metformin therapy be initiated, concurrent with lifestyle changes, once a diagnosis of diabetes has been made². Metformin is contraindicated in patients with renal or hepatic insufficiency due to the increased risk of lactic acidosis³. Though metformin-associated lactic acidosis (MALA) is extremely rare (most estimates are ≤ 10 events per 100,000 patient-years of exposure), cases continue to be reported³. MALA is well described in the literature but due to the low prevalence of testing for metformin levels it is usually a presumed diagnosis or one of exclusion. MALA is associated with mortality rates of 30 to 50%⁴. The criteria we use here to define metformin-associated lactic acidosis are those used by Kajbaf et al: arterial pH <7.35 , blood lactate $>5\text{mmol/l}$ and detectable plasma metformin concentration. Their study showed that although 869 cases were reported from 32 countries only 10.4% of cases met all three criteria⁵. Metformin has a therapeutic range of between $0.5\pm 0.4\text{mg/L}$ ⁶. We present 3 cases of laboratory-confirmed metformin-associated lactic acidosis in our intensive care unit.

Case 1

A 72-year-old female was brought in by ambulance with a recent history of increased alcohol intake, diarrhoea, abdominal pain and feeling generally unwell. Her past medical history included hypertension, peripheral vascular disease and non-insulin dependent diabetes. Medications on admission were, metformin (2g per day), amlodipine 10mg, Ramipril 10mg, aspirin 75mg, simvastatin 40mg. Examination revealed agitation, bibasal scattered crepitations and mild abdominal distension. The abdomen was soft and non-tender. Vital signs and significant laboratory results shown in Table 1 and 2 respectively. Blood cultures taken on admission showed no growth after 5 days. The patient was transferred directly to the Intensive care unit (ICU). Central venous access and invasive blood pressure monitoring were established and inotropic support commenced. CT abdomen was performed after surgical consultation and the report concluded previous ischaemic colitis distal to the watershed area. The patient was brought to theatre for laparoscopy which showed distended small bowel with normal serosa and no free fluid. The patient remained intubated post-operatively and was commenced on continuous veno-venous haemodialysis filtration (CVVHDF). After initiation of CVVHDF the lactic acidemia markedly improved to pH 7.2 and lactate 6.6 mmol/L. Metformin levels were elevated at 4.9 mg/L. The patient subsequently died after a prolonged ICU stay of 28 days following commencement of palliative measures

Case 2

A 56-year-old female was brought in by ambulance with a reduced level of consciousness. The patient had fallen the previous day and sustained a right eye and occipital laceration which were attended to by her GP. Her past medical history included non-insulin dependent diabetes, alcohol excess and depression. Her medications on admission were metformin 500mg BD, prothiaden 75mg nocte and esomeprazole 40mg OD. On initial examination the patient was cooperative, chest auscultation revealed bibasal crepitations and abdominal examination was normal. Vitals signs and significant laboratory values shown in Table 1 and 2. Blood cultures taken on admission showed no growth after 5 days. The patient deteriorated, with a significant drop in BP to 59/39 mmHg and she was transferred to the ICU. Inotropic/Vasopressor support, CVVHDF and non-invasive ventilation (NIV) were commenced. The next day the patient failed NIV and required intubation and mechanical ventilation. CT imaging of the thorax/abdomen/pelvis revealed no obvious source of sepsis. Metformin level decreased from 3.9mg/L to 1.15mg/L after CVVHDF. After a protracted ICU course (50 days) the patient was discharged to the ward and later home with no lasting sequela.

Case 3

72-year-old female self-presented to the emergency department with a one day history of diarrhoea and vomiting. Past medical history included non-insulin dependent diabetes, hypertension and hyperlipidaemia. Her medications on admission were metformin 850mg TDS, gliclazide 160mg mane/80mg nocte, simvastatin 20mg OD, amlodipine 10mg OD. On initial exam, the abdomen was soft but tender and bowel sounds were increased, GCS 15/15. Other vital signs and initial significant blood results are shown in Table 1 and 2 respectively. Blood cultures taken on admission showed no growth after 5 days. The patient deteriorated clinically and BP became unrecordable, her GCS fell to 4/15 and body temperature dropped to 31°C. Hypoglycaemia was noted during this episode (blood glucose of 1.8mmol/L) which was treated with intramuscular glucagon. She was immediately transferred to the ICU where she had a cardiac arrest and was successfully resuscitated. Post arrest she remained intubated and ventilated and required increasing amounts of

inotropic support. ABG revealed severe metabolic acidosis with pH 6.95 and lactate 27.6 mmol/l. Metformin levels were grossly elevated at 48.7mg/L and CVVHDF was commenced. She died following a protracted ICU stay of 54 days.

Table 1

Vital Signs			
	Case 1	Case 2	Case 3
Respiratory Rate (breaths/minute)	28	26	16
SpO2 %	100%	99%	96%
Supplemental Oxygen	FiO2 1.0	Room Air	Room Air
Heart Rate (bpm)	57	63	97
Blood Pressure	69/39mmHg	104/56mmHg	143/87mmHg
Temperature	31.7°C	35.8°C	35.9°C

Table 2

Significant Laboratory Results			
	Case 1	Case 2	Case 3
pH	6.7	7.2	
Lactate	22.6	14.8	
WBC	17.3 x10 ⁹ /L	4.3 x10 ⁹ /L	27.2 x10 ⁹ /L
CRP	1.8	191.5	36.5
Urea	11.2mmol/L	21.4mmol/L	16.4mmol/L
Creatinine	134 µmol/L	387 µmol/L	142µmol/L
Estimated GFR	36ml/min/1.73m ²	11ml/min/1.73m ²	34ml/min/1.73m ²
Metformin Levels	4.9mg/L	3.9mg/L	48.7mg/L

Discussion

Metformin is a small molecule of 165kDA which is administered via the oral route. 150 minutes post administration maximum plasma concentrations are reached. The mean fractional oral bioavailability of metformin is 55 ± 16%⁷. The pharmacokinetics of metformin is assumed to be non-linear as its absorption is saturable and incomplete. When used as intended, steady state plasma concentration is reached between 24 to 48 hours and is typically less than 1 mcg/ml. Metformin has negligible plasma protein binding and the mean volume of distribution ranges between 63-276L. Metabolites of metformin have not been identified and excretion of unchanged metformin occurs via the kidneys. Renal clearance of metformin is greater than 400 ml/min thus implying that metformin is eliminated by glomerular filtration plus tubular secretion. The apparent terminal elimination half-life is approximately 5 hours with normal renal function⁸. With impaired renal function clearance of metformin is decreased in proportion to that of creatinine therefore prolonging the elimination half-life and thus increasing plasma levels of metformin⁸. There has been no randomised control trial comparing the use of intermittent and continuous renal replacement therapy in MALA, however, numerous studies have shown continuous renal replacement therapy to be effective⁹. Acute alcohol intoxication and alcoholism are listed as contraindications to metformin therapy. Concomitant use of metformin and alcohol are not recommended as these are both independent risk factors for lactic acidosis¹⁰. Despite this, both Case 1 and Case 2 had previous documented alcohol-related admissions and were continued on Metformin. With the widespread prescribing of metformin in primary care should more onus be placed on general practitioners to educate patients and obtain detailed social history prior to commencement of metformin? Although a relatively rare event we must have a high index of suspicion when patients on metformin present with non-specific signs of muscle cramps, abdominal pain, hypothermia, fatigue and a disproportionate rise in serum lactate as their clinical condition may deteriorate quickly. Confirming the diagnosis with laboratory investigation often proves difficult due to the scarce availability of testing and the turnaround time for results. In these three cases, serum samples for each patient were sent to a laboratory in France by Eurofins Biomnis. The methodology used by the laboratory was high performance liquid chromatography with a turnaround time of two weeks.

Conflicts of Interest Statement:

The author have no conflicts of interest to declare.

Corresponding Author:

Dr. Claire Nestor
Mayo General Hospital,
Westport Road,
Co. Mayo,
Ireland
Email: clairenestor88@gmail.com

References:

1. National Institute for Health and Care Excellence (2015) Type 2 diabetes in adults: Management. NICE guideline (NG28).
2. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centred approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012 Jun;35(6):1364-9.
3. DeFronzo R, Flaming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. *Metab. Clin. Exp.* 2015 Oct; 65:20-29.
4. Eppenga WL, Lalmohamed A, Geerts AF, Derijks HJ, Wensing M, Egberts A, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care* 2014;37:2218–24.
5. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf.* 1999 Apr;20(4):377-84.
6. Kajbaf F, Lalau JD. The criteria for metformin-associated lactic acidosis: the quality of reporting in a large pharmacovigilance database. *Diabet Med.* 2013 Mar;30(3):345-8.
7. Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong JK, Furlong TJ, Greenfield JR, Greenup LC, Kirkpatrick CM, Ray JE, Timmins P, Williams KM. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet.* 2011 Feb;50(2):81-98.
8. Kajbaf F, Bennis Y, Hurtel-Lemaire AS, Andrejak M, Lalau JD. Unexpectedly long half-life of metformin elimination in cases of metformin accumulation. *Diabet Med* 2015. [http:// dx.doi.org/10.1111/dme.12959](http://dx.doi.org/10.1111/dme.12959) [Epub ahead of print].
9. Bethlehem C, van der Voort PHJ. Continuous veno-venous hemofiltration in patient with metformin associated lactic acidosis. *Intensive Care Med Exp.* 2015 Oct;3(Suppl 1):A464.
10. Public Assessment Report: Mutual Recognition procedure [Internet]. Leicester Morningside Healthcare Ltd: Medicines and Healthcare Products Regulatory Agency; 2007. Metformin; [Reviewed 2007 Dec 17; cited 2015 Sep 28]; [26 p.]. Available from: <http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con014461.pdf>