Case Report

Metformin-dolutegravir interaction leads to metformin-associated lactic acidosis: A case report

Abdullah Zaawari[1], Muralidhar Varma[2], Praveen Kumar Tirlangi[3], Mutthineni Harsha[4], Deepthi Avvaru[1]

From [1]PhD Scholar, Department of Microbiology, [2]Additional Professor, [3]Assistant Professor, [4]Senior Resident, Department of Infectious Diseases, Kasturba Medical College Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

ABSTRACT

Metformin, a biguanide, is considered the standard first-line drug for managing type 2 diabetes mellitus (T2DM) patients owing to its safety profile. Despite having a highly safe profile, it is capable of causing serious adverse effects. Biguanides decrease gluconeogenesis from alanine, pyruvate, and lactate, which may result in lactic acidosis. The risk is high in patients with polypharmacy or comorbidities. This is a case of a 48-year-old Indian female with a known case of human immunodeficiency virus (HIV), T2DM, hypothyroidism, and hypertension who presented to the hospital with progressive right-sided weakness for the past 10 days along with transit loss of vision. The patient was diagnosed with multiple central nervous system tuberculomas, for which antitubercular treatment and dexamethasone were started. The patient was on a tenofovir, lamivudine, and dolutegravir regimen for HIV. The patient was started on metformin for sugar control, which led to metformin-associated lactic acidosis. A drug interaction between dolutegravir and metformin was attributed to this. The patient improved after metformin was replaced with glipizide, and lactate levels returned to normal. Lactic acidosis is a rare side effect of metformin. However, the risk of lactic acidosis is high when another drug interferes with metformin pharmacokinetics. Proper assessment and evaluation of potential drug–drug interactions is crucial to assure safe and effective therapy.

Key words: Dolutegravir, Drug interaction, Lactic acidosis, Metformin, Tuberculoma

Metformin, a biguanide, is considered the standard first-line drug for managing type 2 diabetes mellitus (T2DM) patients owing to its safety profile. Despite having a highly saved profile, it is capable of causing serious adverse effects [1]. Biguanides decrease gluconeogenesis from alanine, pyruvate, and lactate, which may result in lactic acidosis. Lactic acidosis caused by biguanide, also called metformin-associated lactic acidosis (MALA), is rare but serious, with a mortality rate of up to 50% [2,3]. The incidence of MALA increases when the drug is used in patients with conditions that can cause hyperlacticemia. Such conditions include hypoxia, renal failure, heart failure, and sepsis [4]. Another reason is the concomitant use of metformin with other drugs that could potentially increase its blood concentration. The risk of MALA is high with higher drug concentrations [5].

Here, we present a case of metformin-drug interaction leading to MALA. This case highlights the potential of metformin to cause this side effect and the importance of drug interaction review and management.

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CASE REPORT

A 48-year-old Indian female with a known case of human immunodeficiency virus (HIV) disease, T2DM, hypothyroidism, and hypertension presented to the hospital with progressive right-sided weakness for the past 10 days along with transit loss of vision. The patient was diagnosed with multiple central nervous system tuberculomas, for which antitubercular treatment and dexamethasone were started. The patient was on a tenofovir, lamivudine, and dolutegravir regimen for HIV. The patient's blood sugar was uncontrolled (random blood sugar of 252 mg/dL upon admission). Other tests were unremarkable (Table 1).

Given uncontrolled blood sugar, the patient was started on insulin. Later on, it was converted to metformin, following which the patient developed sudden nausea and vomiting with no clear etiology. Upon patient medication review, a potential drug interaction was found between metformin and dolutegravir, which was likely to increase the risk of metformin toxicity and, thus the risk of lactic acidosis. Atrial blood gases confirmed the presence of lactic acidosis with a lactate level of 36.7 mg/dL and a high anion gap of 13.3 mEq/L (Table 2). Metformin was changed to glipizide to avoid drug-drug interactions.

Correspondence to: Abdullah Zaawari, Department of Microbiology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal - 576 014, Karnataka, India. E-mail: abdullahalzawari.aa@gmail.com

Table 1: Day-wise laboratory parameters throughout hospitalization period

Test name	Date						
	30/05	03/06	06/06	09/06	12/06	14/06	18/06
ALT (IU/L)	16.0	7.8	13.0	24.6	35.0	39.0	32.0
Albumin (g/dL)	4.20						3.40
ALP (U/L)	69	55	49	51	53	69	52
AST (IU/L)	11	13	15	27	16	16	14
Creatinine (mg/dL)	0.68	0.63	0.66	0.62	0.63	0.66	0.49
Hemoglobin A1C	7.90						
Calcium (mg/dL)	9.2		9.1				
Magnesium (mg/dL)	2.2		2.6				
Potassium (mmol/L)	4.0	4.4	4.3	4.7	5.2	5.5	6.5
Sodium (mmol/L)	132.0	134.8	130.3	129.9	125.7	122	128
Urea (mg/dL)	8	24	17	32	29	30	24
Haemoglobin (g/dL)	12.8	12.1	13.1	13.1	12.2	12.4	10.9
White blood cells count (×10≥/µL)	9.5	10.5	11.5	11.5	9.4	7.6	6.1
Red blood cells count (×10^6/µL)	4.18	3.91	4.26	4.17	3.93	3.89	3.33
Platelet count (×10≥/µL)	167.0	213.0	320.0	450.0	413.0	387.0	207.0
Lactate (mg/dL)		36.7					

ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate transaminase

Subsequently, the patient's symptoms recovered, and the lactate level was restored to normal. Upon patient follow-up within 2 weeks, the patient's condition was clinically stable.

DISCUSSION

The use of metformin in T2DM is usually safe and effective. The incidence of side effects with metformin is generally low. The common side effects associated with metformin use include nausea, vomiting, constipation, anorexia, diarrhea, and a metallic taste. Hemolytic anemia, reduced vitamin B12 and folic acid absorption, severe hepatitis, and lactic acidosis are less frequent adverse effects. MALA is a rare but serious side effect with a high mortality rate. The risk of its occurrence increases with an increase in metformin serum concentration [6].

In this patient, metformin was used within the therapeutic dose. The occurrence of MALA with dosing is generally rare. However, the concomitant use of dolutegravir with metformin increases the serum concentration of metformin, putting the patient at risk for MALA. The interaction between these two drugs has been reported in the literature and is considered "D" category [7-12]. This is an elimination-mediated interaction. Metformin prescribing information states that because dolutegravir has been shown to inhibit both the organic cation transporter 2 and the multidrug and toxin extrusion protein 1, transporters responsible for metformin elimination, concomitant use may result in increased concentrations of metformin, even in therapeutic doses, and an increased risk for lactic acidosis, which was seen in this patient [13].

A previous report by Umeda *et al*. [10] has shown that MALA is associated with metformin use and might lead to kidney injuries if left untreated. Another case series by Silvestre *et al*. [11] showed that MALA is a rare, preventable, but life-threatening adverse event and should be strongly suspected in patients presenting with high-anion gap metabolic acidosis and high blood lactate concentration. A careful review of drug-drug interactions is crucial, especially for patients receiving polypharmacy. It is vital because drug-drug interactions can result in serious adverse effects and treatment failure.

Table 2: Atrial blood gases

Test name	Date	
	04/06	06/06
Ph	7.37	7.43
$PaCO_2$ (mmHg)	45.00	32.10
PaO_2 (mmHg)	37.40	117.10
SaO_2 (%)	70.10	98.60
HCO_3- (mEq/L)	25.3	20.6
Lactate (mg/dL)	36.7	22.3

CONCLUSION

MALA is uncommon, with metformin use within the normal therapeutic range. However, the concomitant use of some drugs that interfere with metformin pharmacokinetics can lead to metformin toxicity and an increased risk of MALA. Drug-drug interaction review and assessment are essential to ensure safe and effective therapy. This is highly important when a patient is on polypharmacy, elderly, or has specific comorbidities such as sepsis, renal failure, or heart failure.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Institutional review board or ethics approval was not needed for this manuscript. Informed consent for publication was obtained from the patient.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

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