Life-Threatening Metformin-Associated Lactic Acidosis: A Case Report

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Metformin is a biguanide oral antihyperglycemic agent used to treat patients with non-insulin dependent diabetes mellitus (NIDDM). This medication is considered safe if not used in the presence of contraindications such as renal failure, liver disease, alcohol abuse, or congestive heart failure. The most significant adverse effect of metformin therapy is the development of lactic acidosis in the susceptible patients. We report a 62-year-old female with NIDDM and end stage renal disease on maintenance hemodialysis but metformin therapy was continued so life-threatening metformin-associated lactic acidosis (MALA) developed. Metformin is an effective and safe oral antihyperglycemic agent useful in the treatment of NIDDM but metformin use should be avoided in patients who have known contraindications to the agent.

Key words: non-insulin dependent diabetes mellitus (NIDDM), metformin-associated lactic acidosis (MALA)

Introduction

Metformin is an oral antihyperglycemic agent approved for management of type 2 diabetes mellitus. It exerts its effects predominantly by reducing hepatic glucose production and also increases insulin sensitivity in peripheral tissues¹. Metformin is the only oral hypoglycemic agent proved to reduce cardiovascular risk and is now recognized as the treatment of choice in overweight patients with type 2 diabetes. There is some evidence suggesting that metformin may have beneficial effects on cardiovascular risk factors such as obesity, dyslipidemia, and hypertension². The efficacy of glycemic control achieved with metformin is similar to that achieved with sulfonylureas, although their modes of action differ. Metformin can be used either alone or in combination with other therapies. The most common adverse effects of metformin are related to the gastrointestinal tract, occurring in 5-30% of patients. The most significant adverse effect of metformin therapy is the potential for the development of metformin-associated lactic acidosis (MALA) in the susceptible patient. The estimated incidence of this complication is reported to be <0.03 per 1000 patient-years³⁴. The patient mortality in reported cases is about 50%⁵⁷. In almost all reported cases, lactic acidosis occurred because of one or more patient associated contraindications for the drug are overlooked. These contraindications include: renal insufficiency, advanced age, cardiac
or respiratory insufficiency, a history of lactic acidosis, infection, surgery, liver dysfunction, alcohol abuse, intravenous radiographic contrast agents, and pregnancy. We present the case of a patient with type 2 diabetes and end stage renal disease (ESRD) on maintenance hemodialysis who developed life-threatening MALA due to continuous metformin therapy.

**Case Report**

A 62-year-old female presented with general malaise and vomiting for 3 days. Her medical history included type 2 diabetes mellitus for 18 years and end stage renal disease (ESRD) on maintenance hemodialysis three times every week for 2 years.

She was brought to the emergency department (ED) where hypoglycemia (finger stick blood sugar: 44 mg/dL) was noted so an intravenous infusion of 50% glucose water 80 ml and 10% glucose water was given then her conscious level improved from the initial Glasgow coma scale E4V1M4 to E4V4M5-6, however, 2.5 hours later, apnea and cardiac arrest developed, immediate laboratory workup showed finger stick blood sugar: 256 mg/dL, potassium 4.24 mEq/L, but the arterial blood gas results were pH 6.643, PO2 245.6 mmHg, PCO2 16.9 mmHg, and bicarbonate 1.8 mmol/L. The lactate concentration was 29 mmol/L. After cardiopulmonary resuscitation and hemodynamic support with total epinephrine 3mg, an intravenous infusion of 1000 ml of sodium chloride solution and a dopamine drip 10ug/kg/min, correction of severe metabolic acidosis and unstable hemodynamic status is a big challenge for clinicians to resolve. The principal fear in management of metabolic acidosis is the risk of impaired myocardial contractility\(^8\). A decrease in cardiac contractility and cardiac output, vasodilation and hypotension, bradycardia and increased susceptibility to ventricular arrhythmias have all been observed but do usually occur until the pH is < 7.2. However, in the intact organism, academia is often accompanied by increased cardiac output\(^9\) due to stimulation of catecholamine release from the adrenals. The primary goal of therapy in metabolic acidosis is to correct the underlying disorders. In fact, we initially had great difficulty to search the underlying disorder responsible for this life-threatening metabolic acidosis until metformin was noted for diabetic treatment of this patient.

**Discussion**

The development of severe metabolic acidosis and unstable hemodynamic status is a big challenge for clinicians to resolve. The principal fear in management of metabolic acidosis is the risk of impaired myocardial contractility\(^8\). A decrease in cardiac contractility and cardiac output, vasodilation and hypotension, bradycardia and increased susceptibility to ventricular arrhythmias have all been observed but do usually occur until the pH is < 7.2. However, in the intact organism, academia is often accompanied by increased cardiac output\(^9\) due to stimulation of catecholamine release from the adrenals. The primary goal of therapy in metabolic acidosis is to correct the underlying disorders. In fact, we initially had great difficulty to search the underlying disorder responsible for this life-threatening metabolic acidosis until metformin was noted for diabetic treatment of this patient.

Metformin is an orally administered antihyperglycemic agent used to patients with non-insulin dependent diabetes mellitus. The drug is used as monotherapy or combination therapy in diabetic patients whose hyperglycemia is not controlled by diet and/or sulfonylurea therapy alone. Metformin therapy improves insulin sensitivity but it is not effective in the absence of insulin. Metformin’s mechanism of action is thought to be by increasing glucose transport into glucose utilizing cells and by decreasing hepatic glucose output.
Biguanide therapy decreases the activity of the enzyme pyruvate dehydrogenase and the transport of mitochondrial reducing agents, and thus enhances anaerobic metabolism\(^{10}\). An inhibition of pyruvate dehydrogenase leads to increased metabolism of pyruvate to lactate and an increase in lactic acid production. Lactic acidosis is a rare but potentially fatal metabolic consequence of metformin therapy. In most patients it occurs because one or more contraindications were overlooked.

Patient-associated risk factors that may directly or indirectly result in increased blood lactate concentrations in patients taking metformin include: renal insufficiency, advanced age, cardiac or respiratory insufficiency, severe infection, surgery, liver dysfunction, alcohol abuse, a history of lactic acidosis, intravenous radiographic contrast agents, and pregnancy. If a metformin-treated patient has a serious illness that is one of the risk factors of lactic acidosis, metformin should be stopped. Unlike our patient had ESRD but metformin therapy was continued so life-threatening MALA occurred. If a patient has lactic acidosis attributable to metformin, he should be aggressively treated with initial bicarbonate therapy and hemodialysis should be considered in patients with severe renal failure for removal of metformin.

In conclusion, metformin is a widely prescribed oral antihyperglycemic agent and health care professionals should be aware of and educated about the contraindications for the drug’s use to avoid doing harm for susceptible patients when prescribing metformin.

References

危及生命的Metformin相關乳酸中毒：病例報告

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Metformin是用來治療非胰島素依賴型糖尿病的口服雙胍類降血糖藥物。在沒有腎衰竭、肝疾病、酒精濫用、心臟衰竭等禁忌下使用這個藥物是安全的。Metformin最嚴重的副作用是使某些病患產生乳酸中毒。本病例報告一位62歲女性，具有非胰島素依賴型糖尿病病史，且接受長期血液透析，但仍持續metformin的治療，因而發生危及生命的metformin相關乳酸中毒。Metformin是用來治療非胰島素依賴型糖尿病的有效且安全口服降血糖藥物，但對於已知有使用禁忌的病患則應避免使用。

關鍵詞：非胰島素依賴型糖尿病，metformin相關的乳酸中毒

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