

## A case of fatal metformin overdose

### 一個致命的二甲雙胍過量個案

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Metformin is a widely used antidiabetic agent that is generally considered safe. Reported here is a fatal case of acute metformin overdose in a 73-year-old male patient. The rapid clinical deterioration is described to illustrate the possible severity of toxicity. It is followed by a literature review on the topics concerning acute metformin intoxication. Pathogenesis and clinical features on metformin-associated lactic acidosis, as well as the current recommendations in management are discussed in details. (*Hong Kong j.emerg.med.* 2009;16: 93-97)

二甲雙胍為廣泛使用的抗糖尿病藥，普遍認為是安全的。這裏報告一名73歲男病人的急性二甲雙胍過量致命個案。描述急速的臨床惡化以作可能有嚴重毒性的例證。隨後為關於急性二甲雙胍中毒題目的文獻審查。詳細討論有關二甲雙胍乳酸中毒的發病機理及臨床徵狀，及時下處理的建議。

**Keywords:** Biguanides, diabetes mellitus, hypoglycaemic agents, lactic acidosis, toxicology

**關鍵詞：**雙胍類口服降血糖藥、糖尿病、降血糖藥劑、乳酸中毒、毒理學

## Introduction

Overdose with antidiabetic drugs can potentially produce major morbidity, with many patients requiring intensive care treatment and prolonged hospital stays.<sup>1</sup> Generally speaking, metformin is considered as a relatively safe oral hypoglycaemic agent although biguanides, the group of antidiabetics in which metformin belongs to, are well known to cause profound lactic acidosis as one of their major side effects.<sup>2</sup> However, there are only limited descriptions of metformin overdose in the literature,<sup>3,4</sup> despite its well-recognised potentially fatal side effect. One case of fatal metformin overdose is described in this case report to illustrate the possible severity of toxicity and rapidity of clinical deterioration. Current

recommendations in the management of acute metformin overdose are also reviewed.

## Case report

A 73-year-old gentleman with known history of hypertension and diabetes mellitus (DM) presented to a local accident and emergency department (ED) in October 2007 for repeated vomiting and abdominal discomfort. He had regular follow up in government out-patient clinic and was treated with gliclazide 120 mg daily, metformin 1 g bd as well as perindopril 4 mg daily. He appeared rather unhappy lately because of disputes in the family. Before his attendance, he had had vomiting and diarrhoea on-and-off for two weeks. Further history taking revealed that he had taken 10 tablets (500 mg/tab) of metformin about four hours prior to his visit, together with an unknown amount of gliclazide and perindopril.

The patient was fully conscious with a full Glasgow Coma Score. He was afebrile. The blood pressure was

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128/63 mmHg and pulse rate was 89 bpm at triage. Physical examination findings were unremarkable except that he was clinically dehydrated. No specific toxidrome was identified. The ECG performed shortly after the initial assessment revealed sinus tachycardia of 110 bpm. Bedside blood test demonstrated significant metabolic acidosis with pH=7.18, PaO<sub>2</sub>=11.6 kPa, PaCO<sub>2</sub>=3.91 kPa, HCO<sub>3</sub><sup>-</sup>=10.8 mmol/L, BE=-18, Na=133 mmol/L, K=4.1 mmol/L (Table 1). Calculation of anion gap was not possible at that juncture because the bedside blood test results did not include chloride value. Bedside haemoglucostix was 19.8 mmol/L. Serum ketone was marginally increased to 0.3 mmol/L whereas urine ketone was not detectable. The low serum and urine ketone levels made the clinical picture not compatible with diabetic ketoacidosis.

Based on the history and the biochemical findings, the provisional diagnosis of metabolic acidosis secondary to acute metformin overdose was made at the ED. Gastrointestinal decontamination was performed with 50 g of activated charcoal at the ED; and 50 ml sodium bicarbonate (NaHCO<sub>3</sub>) was administered intravenously at full rate for the acid base imbalance. The patient was then admitted into the general medical ward for further management. Serum toxicology screening test for paracetamol, ethanol and salicylate

showed negative findings. On the other hand, metformin was the only substance detected in the patient's urine. Serial blood tests showed deranged renal function over a previously normal creatinine reading in the subsequent few hours (Table 1). There was an increased anion gap of 37.1 mmol/L at 1.5 hours after ED attendance (normal anion gap ranges from 8 to 16 mmol/L). Furthermore, serum lactate was markedly elevated to 21.2 mmol/L (Table 1). In summary, there was evidence of a high anion gap metabolic acidosis due to lactate accumulation as a result of acute metformin overdose.

Refractory hypotension developed shortly after hospital admission and a high dose of inotropic support was required. The patient was transferred to the ICU about 4 hours from the ED attendance. He subsequently ran into a rapid downhill course with persistent hypotension and progressively deteriorating metabolic acidosis despite repeated doses of intravenous sodium bicarbonate infusion, vigorous fluid challenge and high dose inotropic support. He developed acute pulmonary oedema and required intubation for mechanical ventilation approximately 6.5 hours after presentation. It was further complicated by disseminated intravascular coagulopathy, evidenced by a drastic drop of haemoglobin and platelet counts, as well as a

Table 1. Laboratory results

	Collection time									
	Baseline 6 months ago		Time from emergency department attendance							
			5 minutes	0.5 hour	1.5 hours	4.5 hours	8.5 hours	11.5 hours		
Inspired O <sub>2</sub>			Room air		Room air		28% O <sub>2</sub>		28% O <sub>2</sub>	
pH			7.18	L	7.09	L	6.78	L	6.74	L
pO <sub>2</sub>			11.6		15.2	H	19.5	L	8.9	L
pCO <sub>2</sub>			3.91	L	3.5	L	5.5		7.8	H
HCO <sub>3</sub> <sup>-</sup>			10.8	L	8	L	6	L	8	L
Base excess			-18	L	-21	L	-25	L	-24	L
Na	133	L	133	L	138		147		148	
K	3.9		4.1		4.1		4.3		2.8	L
Cl	101			95	L	97	L	101	94	L
Urea	4.7			7.3		7.4		6.8	3.9	
Creatinine	99			134	H	149	H	171	H	117
Lactate						21.2	H			

H=high, L=low

profusely deranged clotting profile. The patient eventually succumbed 13.5 hours after his presentation. Haemodialysis and continuous veno-venous haemofiltration were not commenced due to the extremely poor haemodynamic status.

## Discussion

Biguanides were originally developed in the 1920s and they were not used as antihyperglycaemic agents until the 1950s.<sup>2</sup> Of the three biguanides originally produced, phenformin and buformin were withdrawn from the market in the United States in the 1970s because of their notorious major side effects of lactic acidosis.<sup>2,5,6</sup> Metformin remains as the only biguanide still in wide usage nowadays around the globe.<sup>5</sup> Metformin can be used as monotherapy for type II DM patients as well as combination therapy along with other antidiabetic agents for both type I and type II DM patients.<sup>2,5</sup> The mechanism of action of metformin is multifaceted, including reduction of intestinal absorption of glucose, promotion of intestinal glucose utilisation, inhibition of hepatic gluconeogenesis, suppression of fatty acid oxidation and improvement of peripheral insulin sensitivity.<sup>2,5,7</sup>

Although metformin appears far much safer than the other two banned counterparts in the same group, potentially life-threatening side effects are occasionally reported in acute intoxication. The primary problem in acute metformin overdose is the potential risk of metformin-associated lactic acidosis (MALA).<sup>2,5,7</sup> The incident of MALA is not clearly documented. The estimated rate of MALA from previous studies is believed to range somehow between 3 to 9 cases per 100,000 patient-years.<sup>8</sup> Though the incidence of MALA is not particularly high, its mortality is extremely formidable and has been estimated to be >50%.<sup>9</sup> Patients with certain concomitant risk factors are particularly vulnerable to the development of MALA and these include renal failure, hepatic disease, cardiovascular disease, infection and alcoholism.<sup>2,5,6,9</sup> These factors increase blood lactate concentrations on their own. The plasma concentration of metformin in these cases is not necessarily skyhigh.<sup>6</sup> It is therefore

crucial to identify these risk factors in diabetic patients and avoid using metformin in such patients to prevent the occurrence of MALA and its associated mortality.

The pathogenesis of MALA is complex and not completely understood.<sup>10,11</sup> There are several postulations concerning the pathogenesis of MALA. First, metformin, which accumulates in the intestine in a much higher concentration than any other tissues, doubles lactate production in the intestine. This naturally increases portal lactate levels and subsequently decreases the pH of liver, resulting in a decrease in lactate metabolism due to suppression of the pyruvate carboxylase. Second, high concentrations of metformin, such as those encountered in acute overdose and renal failure, decrease glucose utilisation and increase lactate production by hepatocytes. As a result, accumulation of excessive amount of circulating lactate occurs. Furthermore, metformin also increases glucose uptake by muscle peripherally in the overdose condition, which may facilitate non-oxidative metabolism and lead to lactate accumulation. Last but not the least, diabetes itself may directly increase the risk of lactic acidosis secondary to abnormal lactate metabolism.<sup>10,11</sup> All these actions contribute cumulatively to the end result of lactate accumulation.

The clinical features of metformin toxicity are mainly gastrointestinal upset and those secondary to lactic acidosis.<sup>2,5</sup> Hypoglycaemia is rarely reported with biguanide exposure.<sup>12,13</sup> Gastrointestinal upset such as abdominal pain, nausea and vomiting are prominent in acute overdose situations.<sup>3,6,12,13</sup> In fact, the patient in this case presented to the ED with distressing gastrointestinal symptoms. The onset of lactic acidosis may take several hours.<sup>13</sup> Lactic acidosis may be profound and the patients usually experience Kussmaul's respiration in the early stage. It is followed by central nervous system involvement that is characterised by confusion, lethargy, coma and seizure.<sup>3,13</sup> Cardiovascular decompensation is evidenced by the presence of hypotension, tachycardia, shock, ventricular arrhythmias and myocardial infarction.<sup>3,13</sup> Death is unavoidable in severe lactic acidosis if the condition is not treated in a timely manner.

The management of acute metformin intoxication is essentially supportive.<sup>1,2,5</sup> The aims are restoration of normal acid-base status, removal of absorbed metformin and support of cardiovascular functions.<sup>5</sup> Unfortunately, there is no specific antidote available.

Basic knowledge in the pharmacokinetics of metformin is essential in formulating the management plan in acute overdose. All biguanides are incompletely absorbed through the gastrointestinal tract. The oral bioavailability is rather low and ranges only between 40-60%, depending on the type of drug and the dose ingested.<sup>7</sup> For metformin, only 80% of an oral dose is normally absorbed.<sup>14</sup> The unabsorbed portion of the drug binds to the intestinal wall and the intestinal transition period may then be prolonged. Understandably, gastrointestinal decontamination forms an important constituent component in the management of acute intoxication. Activated charcoal is capable of binding metformin effectively. It is theoretically useful even for late presenters because a significant portion of the ingested metformin is expected to remain in the gut.<sup>5</sup> However, it should be noted that gastrointestinal upset is extremely common in acute metformin overdose, as previously stated. The gastrointestinal symptoms, especially vomiting, may complicate the administration of activated charcoal. Therefore, activated charcoal should be used cautiously and airway protection is necessary in patients with altered level of consciousness in order to prevent aspiration.

One of the main goals in the management of acute metformin overdose is the correction of acid-base imbalance. Management of lactic acidosis with the use of  $\text{NaHCO}_3$  is well known and yet still controversial.<sup>2,6</sup> It should be emphasized that  $\text{NaHCO}_3$  administration is not able to eliminate the excessive lactate accumulated in acute overdose situation. In a large number of severe cases,  $\text{NaHCO}_3$  alone cannot stop the progress of metabolic acidosis.<sup>5</sup> It only serves as a temporary measure in the early phase of resuscitation to gain time for the arrangement of haemodialysis. On the other hand, theoretical disadvantages of using large doses of intravenous  $\text{NaHCO}_3$  are multiple, including leftward shift of the oxygen dissociation curve, intracellular acidosis, increased lactate production,

rebound metabolic alkalosis, disturbances in serum potassium and calcium, decreased cardiac output and reflex vasodilatation after bolus injection.<sup>2,5,6</sup> Large doses of  $\text{NaHCO}_3$  infusion are therefore not recommended.<sup>2,5,6</sup> A reasonable initial dose is 1-2 mEq/kg of  $\text{NaHCO}_3$ <sup>5</sup> and it aims at increasing the base excess by 4-6 mmol/L.<sup>2</sup> The effort of seeking for definitive treatment should not be delayed in spite of  $\text{NaHCO}_3$  administration.

Pharmacokinetically, metformin is not protein bound and 90% of the absorbed drug is excreted by the kidney.<sup>14</sup> Together with a low volume of distribution, all these properties make metformin a good candidate for haemodialysis in acute overdose.<sup>2,5,6</sup> Clinical experience suggests that haemodialysis plays a crucial role in the management of acute metformin overdose and is therefore recommended in severe cases of MALA.<sup>5</sup> It is effective in the removal of both metformin and the circulating lactate, restoring acid-base balance, as well as normalisation of potassium, sodium and fluid balance.<sup>2,5,6</sup> When the patient's haemodynamic status is too unstable to undergo haemodialysis, continuous veno-venous haemofiltration is a recommended alternative.<sup>3,15</sup>

## Conclusion

Acute metformin overdose is potentially life threatening and the patients may have rapid clinical deterioration. In the presence of clinical suspicion of MALA, patients should be treated promptly and aggressively before clinical deterioration occurs. In view of the high mortality rate, early haemodialysis and intensive care should be considered in such patients.

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