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Impact of acute kidney injury on metformin-associated lactic acidosis

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Abstract
Objectives Metformin has been shown to reduce diabetic complications in overweight patients, and is increasingly used to treat this condition. However, this agent is associated with a rare but serious risk of lactic acidosis.
Methods From January 2004 to November 2008, 11 cases of metformin-associated lactic acidosis were seen at a medical center in Taiwan. The patients' records were retrospectively reviewed with respect to clinical presentation, biochemical data, therapeutic strategies, and outcomes.
Results Ten out of 11 patients with acute kidney injury were enrolled in this study. From their pre-existing states, these patients would have been considered at low risk of developing lactic acidosis. However, all of them had acute intercurrent conditions that might compromise renal function. Among them, six patients were ventilated and five patients had severe hypotension with vasoactive support. Nine patients received renal replacement therapy to clear the acidosis and treat the renal failure. All but one of our patients survived. Recovery of renal function was the general rule in survivors.
Conclusions Metformin-associated lactic acidosis is commonly accompanied with acute kidney injury. In spite of the severity of their illness, the outcome is favorable with intensive support of the cardiovascular, respiratory, and renal systems.

Keywords Acute kidney injury · Acute renal failure · Lactic acidosis · Metformin · Type 2 diabetes

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Introduction

Metformin is a biguanide that is widely used in the treatment of type 2 diabetes mellitus. The results of the UK Prospective Diabetes Study have provided good evidence of the benefits of metformin for the long-term incidence of diabetic complications in overweight patients [1]. This has resulted in greater use of metformin as the oral hypoglycemic agent of choice for such patients. The increased use of metformin might result in a higher frequency of adverse effects associated with this drug. The most common side-effects are nausea, vomiting, bloating, diarrhea, and loss of appetite. However, the major concern of many physicians remains the possible risk of lactic acidosis. Metformin is considered to be associated with lactic acidosis in patients with renal impairment, advanced age, and conditions associated with tissue hypoxia such as congestive heart failure

and sepsis. The overall incidence of severe life-threatening acidosis is estimated at 1–5 cases per 100,000 patient-years, with a mortality rate up to 50% [2, 3]. Nevertheless, this has been a controversial matter. Because almost all of the reported cases occurred in patients who had risk factors for lactic acidosis, it was difficult to determine to what extent metformin might have contributed to the development of lactic acidosis in any individual case [4, 5]. Salpeter et al. in a meta-analysis of 194 comparative trials found no difference in the incidence of lactic acidosis between diabetics taking and not taking metformin [6]. In contrast to the findings from controlled trials, cases of lactic acidosis continue to be reported in patients taking metformin. Among the first million patients to have received metformin in the USA, there were 47 reports of lactic acidosis registered to the Food and Drug Administration. Of these patients, 43 had renal failure or risk factors for lactic acidosis [3]. Although no causal relationship has been convincingly provided, circumstantial evidence shows that treatment with metformin may be linked to lactic acidosis. Herein, we report our experience in metformin-associated lactic acidosis over a 5-year period and highlight the impact of acute kidney injury.

Methods

A retrospective analysis of all cases defined by hospital discharge with a diagnosis of lactic acidosis related to metformin poisoning between January 2004 and November 2008 was performed. Severe sepsis, shock or tissue hypoxia on admission was ruled out in all of them. Lactic acidosis was accepted on the basis of an arterial blood sample with pH <7.35, bicarbonate levels <22 mmol/l, and circulating lactate values >5 mmol/l. Acute kidney injury was defined and classified by means of the Risk, Injury, Failure, Loss of Kidney Function, End-Stage Kidney Disease (RIFLE) criteria [7]. The standard defines three grades of severity: risk (class R), injury (class I), and failure (class F), and two outcome classes: loss of kidney function and end-stage kidney disease. Class R is considered if there is an increase of serum creatinine $\times 1.5$. Class I is considered if there is an increase of serum creatinine $\times 2$. Class F is considered if there is an increase of serum creatinine $\times 3$, or in patients with serum creatinine >4 mg/dl if there is an acute rise in serum creatinine of at least 0.5 mg/dl. When the baseline serum creatinine is unknown and there is no past history of chronic kidney disease, serum creatinine is calculated using the Modification of Diet in Renal Disease (MDRD) formula for assessment of kidney function, assuming a glomerular filtration rate (GFR) of 75 ml/min/1.73 m^2 [8]. Demographic information, clinical presentation and evolution, biochemical data, risk factors, treatment strategies, and outcomes were obtained by chart review.

Results

Eleven patients were identified as metformin-associated lactic acidosis (nine patients on metformin medication as their usual treatment and two patients of deliberate self-poisoning with metformin). Ten of them fulfilled the RIFLE criteria of acute kidney injury and were included in this study. Patient characteristics are summarized in Table 1. There were six women and four men, all with history of type 2 diabetes mellitus. The age range was 48–79 years. Symptoms and signs on admission included gastrointestinal symptoms (nine out of ten), hypoglycemic coma (seven out of ten), hypothermia (six out of ten), and myalgias (one out of ten). Nine out of ten patients were transferred to the intensive care unit due to respiratory distress or severe hypotension. Six were ventilated and five had severe hypotension with vasoactive support. All patients were treated with bicarbonate infusion first. Nine received renal replacement therapy to clear the acidosis and treat the renal failure. Among them, four received hemodialysis and five hemodynamically unstable patients who were unstable to tolerate hemodialysis received continuous venovenous hemofiltration. Seven had intercurrent infection and received antimicrobial therapy. Length of stay in the intensive care unit ranged from 2 to 7 days. Apart from one patient, who died 48 h after admission, patients' biochemical parameters improved substantially within 24 h, and they were weaned off vasoactive support within 3 days. The period of renal replacement therapy was less than 3 days in all patients, with variable recovery of renal function thereafter (Table 2).

Table 1 Patient details

Case No.	Sex/ age (years)	Premorbid creatinine[a] (mg/dl)	Presentation	Intercurrent conditions or other factors
1	M/79	1.5	Hypoglycemic coma, diarrhea	NSAID
2	F/63	0.7	Hypoglycemic coma, hypothermia, myalgias	Disseminated tuberculosis with liver involvement, NSAID
3	F/76	1.2	Hypoglycemic coma, abdominal pain, vomiting	Pancreatitis, pneumonia
4	F/72	NA	Hypoglycemic coma, hypothermia, vomiting	Urinary tract infection, liver disease gastrointestinal bleeding
5	M/48	1.4	Drug overdose, hypothermia, vomiting	Gastrointestinal bleeding
6	M/76	NA	Hypothermia, vomiting, diarrhea	Urinary tract infection
7	F/65	0.8	Hypoglycemic coma, vomiting, diarrhea	Urinary tract infection, AIIRB
8	F/56	0.9	Hypothermia, anorexia, vomiting	Urinary tract infection, AIIRB
9	M/68	NA	Hypoglycemic coma, vomiting, diarrhea	AIIRB, NSAID
10	F/60	1.0	Hypoglycemic coma, hypothermia, vomiting	Urinary tract infection

[a] Values closest in time to the episode of lactic acidosis, ranging from 1 month to 1 year

NSAID nonsteroidal anti-inflammatory drugs, *AIIRB* angiotensin II receptor blockers, *NA* not available

Discussion

The major toxicity from metformin use is lactic acidosis. The mechanism of metformin-associated lactic acidosis is complex and not well understood. Metformin is known to decrease intracellular pH, which reduces lactic acid utilization by decreasing liver uptake of lactate and suppressing oxidation of the lactate to pyruvate. Metformin may cause a shift in the intracellular redox potential away from aerobic to anaerobic metabolism. Increased hepatocyte anaerobic metabolism increases lactic acid production, resulting in further decrease in lactate uptake. Metformin can also increase intestinal lactate production. Increased production and decreased utilization of lactate predispose patients taking metformin to develop lactic acidosis [9].

Metformin is not metabolized and is mainly excreted by the kidneys. Drug accumulation may occur in patients with renal impairment. Metformin use is currently contraindicated in people with serum creatinine above 1.5 mg/dl in men and above 1.4 mg/dl in women [10]. However, serum creatinine is not a reliable measure of renal impairment. Chronic kidney disease (CKD) is best identified by the estimated GFR, which is easily calculated using the MDRD formula or the Cockcroft-Gault equation. According to National Kidney Foundation Disease Outcomes Quality Initiative CKD staging, three out of ten of our patients (cases 1, 3, and 5) had CKD stage 3 (estimated GFR 30-60 ml/min/1.73 m^2) before presentation despite normal serum creatinine levels. This suggests that identification of patients at risk would improve if CKD staging were incorporated into routine clinical practice. There is no high-level evidence to formulate guidelines, but available data suggest that metformin can be used in patients with mild renal impairment (CKD stage 1–2; GFR 60–90 ml/min) and can probably be safely used in patients with moderate renal impairment (CKD stage 3; GFR 30–60 ml/min), but with some caution. Similarly the evidence for major harm from metformin even at GFR below 30 ml/min is poor, although these patients with severe renal impairment may be more at risk for lactic acidosis and hence this may be a point at which metformin should be discontinued [11].

Previous reports, as well as our series, suggest a high rate of acute kidney injury in patients with metformin-associated lactic acidosis [12, 13]. This highlights the role of metformin accumulation in the

Table 2 Physiological parameters and clinical course

Case No.	Admission creatinine (mg/dl)	RIFLE[a] class	pH	Bicarbonate (mmol/l)	Lactate (mmol/l)	Dialysis support	Ventilator support	Vasoactive support	ICU stay (days)	Discharge creatinine (mg/dl)
1	5.85	F	7.057	3.5	20.67	CVVH × 3 days	Y	Y	7	2.1
2	4.3	F	7.336	11.5	8.07	–	–	–	–	0.83
3	2.38	R	7.067	4.7	17.94	H/D × 1 session	Y	–	7	1.19
4	5.0	F	6.894	2.9	26.34	CVVH × 3 days	Y	Y	5	1.68
5	3.1	I	7.158	4.8	23.64	CVVH × 2 days	Y	Y	Died	
6	6.9	F	6.854	3.7	23.58	H/D × 2 sessions	–	–	3	1.2
7	2.3	I	7.055	5.6	18.35	H/D × 1 session	–	–	2	1.1
8	4.5	F	6.955	4.5	20.56	CVVH × 2 days	Y	Y	6	1.35
9	2.8	I	7.122	6.0	16.85	H/D × 1 session	–	–	3	0.9
10	5.4	F	7.085	5.5	24.55	CVVH × 3 days	Y	6	1.45	

[a] Acute kidney injury classified according to the Risk, Injury, Failure, Loss of Kidney Function, End-Stage Kidney Disease (RIFLE) criteria, which defines three grades of severity: risk (class R), injury (class I), and failure (class F)

CVVH continuous venovenous hemofiltration, *H/D* hemodialysis, *ICU* intensive care unit

pathophysiology of metformin-associated lactic acidosis. However, it is uncertain whether acute kidney injury is primary or secondary to concurrent conditions. Once lactic acidosis has commenced, it can cause or aggravate any organ failure. As a result, metformin-associated lactic acidosis could be not only precipitated by renal failure but could also be further complicated by aggravating kidney injury.

In our series, the majority of the patients had been taking metformin for more than 1 year and had no pre-existing risk factors for developing lactic acidosis. However, all of them had intercurrent conditions that might compromise renal function or promote tissue hypoxia. This shows that it may not be enough to avoid metformin in patients with established contraindications. Most patients had nausea, vomiting, anorexia, decreased appetite or diarrhea. These gastrointestinal symptoms could have deteriorated their previous normal renal function by dehydration. Moreover, intercurrent infection was not uncommon (70%). Other intercurrent conditions included gastrointestinal bleeding (20%), liver disease (20%), and pancreatitis (10%). Furthermore, most patients with type 2 diabetes mellitus are on a number of other therapeutic agents (such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs, and diuretics) that may exacerbate renal function impairment in the state of renal hypoperfusion [14, 15]. Precautions should also be considered when these conditions are anticipated.

We also note a rapidly progressive course of the disease. All patients who were transferred to the intensive care unit (nine out of ten) were in stable condition on admission and developed respiratory distress or severe hypotension within a few hours. This may suggest that only early and aggressive treatment is able to reduce the high morbidity rates in these patients. Another interesting observation from this report is that, despite high grade of severity of the illness, all but one of our patients survived. Moreover, although most patients had severe acute kidney injury (six reached RIFLE class F and three reached class I), recovery of renal function was the general rule in survivors. The 10% mortality rate in our series is lower than previous reported (50% in metformin-associated lactic acidosis) and compared well with a published mortality rate of 11.4% and 26.3% in intensive care unit patients with acute kidney injury RIFLE class I and F, respectively [16]. The reason for this discrepancy is not clear, but early institution of dialysis therapy may have been beneficial in removing the metformin and lactic acidosis, and improving hemodynamic and renal function, leading to rapid recovery.

Hemodialysis has been successfully used in treatment of metformin-associated lactic acidosis when sodium bicarbonate infusion alone fails to reverse severe systemic acidosis [17, 18]. Hemodialysis not only corrects the acidosis but also efficiently removes metformin. In hemodynamically unstable patients who are unstable to tolerate hemodialysis, continuous venovenous hemofiltration or hemodiafiltration achieves the same things more gradually than conventional hemodialysis and could therefore be considered preferable.

In conclusion, metformin-associated lactic acidosis is commonly accompanied with acute kidney injury. It is important to be aware of this complication, identify people at risk, and warn patients to withhold metformin during periods of acute illness which may precipitate metformin intoxication. Because of nonspecific presentations, a high index of vigilance is required to make an early diagnosis. Despite devastating process of the illness, the outcome is favorable with intensive support of the cardiovascular, respiratory, and renal systems.

References

1. UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854–865
2. Stang M, Wysowski DK, Butler-Jones D (1999) Incidence of lactic acidosis in metformin user. Diabetes Care 22: 925–927
3. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA (1998) Lactic acidosis in patients with diabetes treated with metformin. N Engl J Med 338:265–266
4. Brown JB, Pedula K, Barzilay J, Herson MK, Latare P (1998) Lactic acidosis rates in type 2 diabetes. Diabetes Care 21:1659–1663
5. Misbin RI (2004) The phantom of lactic acidosis due to metformin in patients with diabetes. Diabetes Care 27: 1791–1793
6. Salpeter S, Greyber E, Pasternak G, Salpeter E (2006) Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 25:CD002967

7. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P (2004) Acute Dialysis Quality Initiative workgroup. Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:R204–R212
8. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461–470
9. Bell PM, Hadden DR (1997) Metformin. Endocrinol Metab Clin North Am 26:523–537
10. Canadian Pharmacists Association (2001) Compendium of pharmaceuticals and specialties. The Association, Ottawa
11. Herrington WG, Levy JB (2008) Metformin: effective and safe in renal disease? Int Urol Nephrol 40:411–417
12. Chu CK, Chang YT, Lee BJ, Hu SY, Hu WH, Yang DY (2003) Metformin-associated lactic acidosis and acute renal failure in a type 2 diabetic patient. J Chin Med Assoc 66:505–508
13. Almirall J, Bricullé M, Gonzalez-Clemente JM (2008) Metformin-associated lactic acidosis in type 2 diabetes mellitus: incidence and presentation in common clinical practice. Nephrol Dial Transplant 23:2436–2438
14. Gudmundsdottir H, Aksnes H, Heldal K, Krogh A, Froyshov S, Rudberg N, Os I (2006) Metformin and antihypertensive therapy with drugs blocking the renin angiotensin system, a cause of concern? Clin Nephrol 66:380–385
15. Audia P, Feinfeld DA, Dubrow A, Winchester JF (2008) Metformin-induced lactic acidosis and acute pancreatitis precipitated by diuretic, celecoxib, and candesartan-associated acute kidney dysfunction. Clin Toxicol (Phila) 46:164–166
16. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA (2006) RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 10:R73
17. Lalau JD, Andrejak M, Morinière P, Coevoet B, Debussche X, Westeel PF, Fournier A, Quichaud J (1989) Hemodialysis in the treatment of lactic acidosis in diabetics treated by metformin: a study of metformin elimination. Int J Clin Pharmacol Ther Toxicol 27:285–288
18. Heaney D, Majid A, Junor B (1997) Bicarbonate haemodialysis as a treatment of metformin overdose. Nephrol Dial Transplant 12:1046–1047