Outcome of Metformin-associated Lactic Acidosis in Type 2 Diabetic Patients

Chih-Neng Hsu[1], Chung-Hao Chang[1], Jeng-Haw Lin[2], and Yen-Kuang Tai[3]

[1]Intensive Care Unit; [2]Division of Nephrology; [3]Division of Endocrinology and Metabolism;
Department of Internal Medicine,
Yuan's General Hospital, Kaohsiung, Taiwan

Abstract

Lactic acidosis is a rare but life-threatening complication of metformin treatment. The current contraindications to metformin use have been defined for prevention of this adverse event; renal dysfunction is among the most important ones. This study aimed to explore the factors associated with unfavorable outcome of metformin-associated lactic acidosis (MALA) and assess the impact of previous chronic kidney disease (CKD). We conducted a retrospective analysis of patients admitted in ICU with MALA during a five-year period. The premorbid conditions, clinical presentations, biological data, therapeutic strategies and outcomes were recorded. A total of 17 patients with MALA were identified. All of them were accompanied by acute kidney injury and associated with a mortality rate of 35.3%. The factors associated with a fatal outcome were high APACHE (acute physiology and chronic health evaluation) II score (p=0.002), the presence of shock (p=0.028), the requirement for mechanical ventilation (p=0.002) and vasopressors (p=0.035). Compared with non-survivors, the survivors stayed longer in the ICU (p=0.014). There were no significant differences on illness severity and mortality rate between patients with or without previous CKD. In conclusion, the prognosis of MALA is mainly determined by the severity of underlying conditions. Previous stage 3 CKD has no negative influence on the outcome following acute kidney injury.

Key Words: Lactic acidosis, Metformin, Metformin-associated lactic acidosis, Diabetes mellitus, Chronic kidney disease, Acute kidney injury

Introduction

Since the benefit on reducing the cardiovascular disease was shown by the UK Prospective Diabetes Study, metformin has become the recommended first-line treatment for patients with type 2 diabetes[1,2]. The increasing use of metformin, therefore, might result in more drug-related adverse effects encountered in clinical practice. Lactic acidosis, a rare but life-threatening complication related to metformin use, is a great concern of clinicians[3]. There is an ongoing debate on the pathogenesis of metformin-associated lactic acidosis (MALA). In the meta-analysis of comparative trials, Salpeter et al. concluded that metformin was not associated with an increased risk of lactic acidosis

Reprint requests and Correspondence：Dr. Yen-Kuang Tai
Address：Department of Internal Medicine, Yuan's General Hospital, 162, Cheng-gong 1st Road, Kaohsiung, Taiwan

under study conditions[4]. However, in real-life practice, MALA solely following drug accumulation continued to be reported[5-7]. Furthermore, intentional metformin intoxication when taken in very large doses does highlight metformin's intrinsic ability to cause lactic acidosis[8].

MALA has been reported with a mortality rate of up to 50%[9,10]. However, the prognostic study of MALA in Asian patients was limited[11]. On the other hand, metformin was traditionally contraindicated in patients with chronic kidney disease (CKD)[2,3], but it is not known whether following the prescription guideline may have a favorable outcome.

This study aimed to describe our experience of MALA over a 5-year period and highlight the factors correlated with unfavorable outcome and the impact of previous CKD.

Materials and Methods

Between January 2007 and December 2011, the medical records of all patients admitted to the ICU were retrospectively reviewed. Patients were defined as having MALA if : (i) they had lactic acidosis (plasma lactate level > 5 mmol/L), acidemia (pH < 7.35) and arterial bicarbonate level < 22 mmol/L; and (ii) they had been prescribed metformin therapy before ICU admission. This study was approved by the Institutional Review Board of Yuan's General Hospital.

Patient data, abstracted into predefined forms, included demographic data, metformin prescription, presenting symptoms and signs, documented premorbid conditions likely to be associated with MALA (hypertension, dyslipidemia, stroke, ischemic heart disease, and chronic kidney disease), APACHE (acute Physiology and chronic health evaluation) II score, biological parameters (arterial blood gas analysis, lactate, creatinine, and prothrombin time) and therapeutic strategies (vasopressors, mechanical ventilation and dialysis requirement).

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Patients were stratified based on the NKF-KDOQI criteria for CKD stages according to their previous serum creatinine: normal eGFR ($\geqq$ 60 ml/min/1.73m^2) and CKD (< 60 ml/min/1.73m^2), and those with CKD in stage 3a (eGFR between 45 and 59 ml/min/1.73m^2) and 3b (30-44 ml/min/1.73m^2). Acute kidney injury was defined according to the RIFLE (acronym indicating Risk of renal dysfunction; Injury to the kidney; Failure of kidney function, Loss of kidney function and End-stage kidney disease) criteria.

The patients were divided according to their 28-day outcome to investigate if there were differences in relation to the studied parameters. In addition, based on the presence or not of previous CKD, the patients were classified to assess the influence of previous renal dysfunction on the outcome.

Results were expressed as median (range) for quantitative variables. Comparisons between groups were performed with a Fisher's exact test or Mann-Whitney U test when appropriate. Statistical analyses were conducted using the SPSS (version 14.1) and a two-tailed $p<0.05$ was considered significant.

Results

Seventeen patients (10 women and 7 men), of median age 70 (range, 44-89) years, were admitted to ICU with final diagnosis of MALA during the study period. Fourteen patients had at least one documented vascular comorbidity; the remaining 3 patients had chronic liver disease. All of them were type 2 diabetic patients taking metformin as their usual treatment; none presented with deliberate metformin overdose. The median dose of metformin that patients were taking at presentation was 1500 (range, 1000-3000) mg/day (Table 1).

Table 1. Comparison of patient characteristics on admission according to the outcome

	Total	Survivors (n=11)	Non-survivors (n=6)	p
Age (yrs)	70 (44-89)	70 (44-84)	71 (54-89)	0.880
Male/female	7/10 (41/59)	4/7	3/3	0.644
Hypertension (%)	76.5	90.9	50	0.099
Dyslipidemia (%)	47.1	54.5	33.3	0.620
Stroke (%)	17.6	27.3	0	0.515
Ischemic heart disease (%)	11.8	9.1	16.7	1.000
Metformin (mg/day)	1500 (1000-3000)	2000 (1000-3000)	1000 (1000-2000)	0.052
APACHE II score	25 (8-46)	20 (8-34)	40 (24-46)	0.002
Hemoglobin A1c (%)	7.5 (5.5-12.9)	7.9 (6.6-12.9)	7.1 (5.5-10.7)	0.143
Glucose (mg/dL)	117 (20-753)	69 (23-269)	225 (20-753)	0.129
pH	6.977 (6.692-7.26)	7.028 (6.692-7.26)	6.849 (6.778-7.1)	0.119
Bicarbonate (mmol/L)	6.2 (3-12.7)	5.7 (3-12.7)	7.5 (4-12.7)	0.392
Creatinine (mg/dL)	4.6 (1.1-10.6)	7.6 (1.1-10.6)	4.8 (1.4-6.6)	0.315
Lactate (mmol/L)	20.1 (6.3-35.4)	19.8 (6.3-35.4)	23.4 (10.4-26.6)	0.421
Prothrombin time (sec)	12.8 (10.1-40.6)	11.6 (10.1-22.8)	16.6 (12.5-40.6)	0.257
Hypoglycemia (%)	35.3	45.5	16.7	0.330
Shock (%)	29.4	9.1	66.7	0.028
Hemodialysis (%)	47.1	63.6	16.7	0.131
Vasopressors (%)	58.8	36.4	100	0.035
Mechanical ventilation (%)	47.1	18.2	100	0.002
Length of ICU stay (days)	3 (1-17)	5 (3-17)	2 (1-6)	0.014

Data are expressed as median (range). APACHE = acute physiology and chronic health evaluation.

Based on the RIFLE criteria, 12 patients had kidney failure, 4 patients had kidney injury and one patient had risk of renal dysfunction. Eight patients received emergent renal replacement therapy, but no patient required dialysis after discharge from the ICU. Six patients died in the ICU but none died between ICU discharge and hospital discharge. The 28-day mortality rate was 35.3% in this study. By univariate analysis, significant differences were found between survivors and non-survivors as for APACHE II score (p=0.002), the presence of shock (p=0.028), the need for vasopressors (p=0.035), the need for mechanical ventilation (p=0.002) and the length of stay in the ICU (p=0.014).

As shown in Table 2, 9 out of 17 patients had pre-existing stage 3 CKD (4 stage 3a and 5 stage 3b). Although patients with previous CKD had worse renal function on admission, as compared with patients without CKD, there was no significant difference between the two groups in most parameters assessing illness severity and outcome.

Discussion

Mortality of lactic acidosis is generally correlated with lactate levels[12,13]; however, data are less clear for MALA. In our study, the risk factors associated with a fatal outcome included shock on admission, high APACHE II score, and the requirement for mechanical ventilation or vasopressors, which all reflected the severity

of underlying condition and were in agreement with previous studies. Laulau and Race[12], in their retrospective study, pointed out that neither lactate nor metformin levels were of prognostic value in MALA. They supposed that other hypoxic disease or underlying illness determined the outcome. Seidowsky et al.[9] showed that the vital prognosis was mainly influenced by the occurrence of multiple organ dysfunctions as assessed by the need for inotropic agents and mechanical ventilation. Similarly, Yeung et al.[11] and Peters et al.[14] demonstrated that the presence of shock on admission was associated with poor prognosis. In contrast, a correlation between nadir pH value, lactate and metformin level, and outcome were demonstrated in a recently published review[15]. In recent years, there is increasing evidence to support the association of liver dysfunction with an unfavorable outcome[9,14]. The fact that prothrombin time was related to survival may either reflect the importance of liver function in the pathophysiology of MALA or just be a consequence of shock. However, probably due to small sample size, our study could not reproduce the prognostic value of prothrombin time. On the other hand, the length of ICU stay in our study was found to be shorter in nonsurvivor group than that of survivor group. This may be explained by the high severity of illness in patients with a fatal outcome.

We observed a trend towards larger metformin dosage in survivors (p= 0.052). Although metformin concentration was not measured in our study, a combination of higher metformin dosage and worse renal function in survivor group might be expected to result in a higher serum metformin concentration. This finding was in accordance with previous studies in France and Netherlands[12,16]. In their studies, survivors had a higher serum metformin concentration than nonsurvivors. Based on the protective effects of metformin on glucose metabolism and macrovascular complications in early studies[1], it had been hypothesized that the higher metformin concentration in survivors might reflect a beneficial effect of metformin in type 2

Table 2. Comparison of patient characteristics on admission according to the pre-morbid renal function

	eGFR < 60 (n=9)	eGFR ≧ 60 (n=8)	p
Age (yrs)	70 (60-84)	71 (44-89)	0.470
Male/female	4/5	3/5	1.000
Metformin (mg/day)	1500 (1000-3000)	1500 (1000-3000)	0.841
APACHE II score	22 (14-46)	33 (8-45)	0.300
pH	7.028 (6.692-7.22)	6.882 (6.802-7.26)	0.556
Bicarbonate (mmol/L)	4.8 (3.2-12.7)	7.4 (3-12.7)	0.098
Lactate (mmol/L)	17.6 (10.4-35.4)	22.7 (6.3-26.6)	0.248
Acute renal failure (%)*	72.7	66.7	1.000
Creatinine (mg/dL)	8.5 (2-10.6)	2.9 (1.1-6.6)	0.005
K (mmol/L)	5.7 (4-7.2)	4.3 (3.3-6)	0.075
Hemodialysis (%)	66.7	25	0.153
Vasopressors (%)	44.4	75	0.335
Mechanical ventilation (%)	33.3	62.5	0.347
Mortality rate (%)	22.2	50	0.335

Data are expressed as median (range). APACHE = acute physiology and chronic health evaluation. *Defined by RIFLE criteria: rise of serum creatinine to 3 times the baseline level, or serum creatinine >4 mg/dL accompanied by an acute rise in serum creatinine of at least 0.5 mg/dL.

diabetic patients. However, the hemoglobin A1c and incidence of macrovascular comorbidities, such as stroke and ischemic heart disease, did not differ between the two groups in our study. As the underlying conditions were different between survivors and nonsurvivors in our study, we might explain the observation by less severe underlying illness in patients who survived MALA. Nevertheless, we did not find any significant association between metformin dosage and the severity of underlying illness as assessed by APACHE II score, the presence of shock, the requirement for vasopressors and mechanical ventilation. Therefore, the mechanism underlying this observation warrants further investigation.

In contrast to patients with lactic acidosis of other origin, MALA patients had a favorable outcome with more severe acid-base imbalance. For lactic acidosis in general, a mortality of 74% to 83% has been reported[10,13]; for MALA, a mortality of up to 50% has been reported[9,10]. The mortality rate of 35.3% observed in our study is lower than some recently reported series. Seidowsky et al. reported 29 MALA patients with a mortality rate of 48.3%. Their patients were more acidotic but with lower lactate levels than ours. Friesecke et al. presented 10 MALA patients with a 50% mortality rate. Their pH values were much lower than ours, though their lactate levels were comparable to ours. However, a case series of 10 Taiwanese patients with MALA, after exclusion of subjects with severe sepsis, shock or hypoxia of any cause, demonstrated a substantially low mortality rate of 10%[7]. Obviously, the mortality rate depends mainly on the severity of underlying conditions in studied subjects.

Metformin is rapidly excreted unchanged via the kidney with 90% excreted in the first 12 hours[17]. Pharmacokinetic studies have demonstrated that metformin accumulation is only significant in patients with eGFR of less than 60 ml/min/1.73m^2. In our study, all patients suffered from acute kidney injury with resultant eGFR of less than 60 ml/min/1.73m^2 on admission, supporting the role of metformin accumulation in the pathogenesis of MALA. Previous renal dysfunction has been considered as an important risk factor for MALA. Either the manufacturer's instructions or most prescribing guidelines support CKD as a contraindication to metformin use. While CKD stages 4-5 (eGFR below 30 ml/min/1.73m^2) are universally accepted as an absolute contraindication, the information about moderate CKD (eGFR between 30-59 ml/min/1.73m^2) is more controversial[18]. It is established as an absolute contraindication in the technical information of the drug, but other guidelines of scientific societies, such as the American Diabetes Association, permit its use in patients with an eGFR $\geqq$ 30 ml/min/1.73m^2. In the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines[19] suggest metformin could be used safely in patients with eGFR $\geqq$ 45 ml/min/1.73m^2, but should be used with dose reduction in patients with eGFR of 30-44 ml/min/1.73m^2. Nevertheless, lactic acidosis developed in all our patients accompanied by acute kidney injury even though they followed the guidelines. This seemed to suggest that restricting metformin use in CKD might not be enough. Precautions should also be considered to prevent acute kidney injury.

By univariate analysis, our patients with previous stage 3 CKD had worse renal function but did not correlate with a higher risk of acute renal failure on admission. Moreover, previous CKD was neither associated with a more severe illness nor did it imply a higher mortality. In fact, MALA patients with previous moderate renal impairment (stage 3 CKD) had favorable outcomes as assessed by APACHE II score, the requirement for vasopressors and mechanical ventilation as well as mortality rate, though they were not statistically significant.

Several limitations of this study should

be acknowledged. First, the small size of our series did not allow us to conduct multivariate analysis. Actually, it was difficult to collect larger population due to the low incidence rate of MALA. Furthermore, as shown in Table 2, the lack of significant difference in mortality rate (22.2% vs. 50%, p=0.335) between the two groups may result from the underpowering secondary to small sample size. Second, the current study was retrospective and therefore we could not exclude the possibility of selection bias by clinicians. Finally, in some situations (e.g. shock, severe sepsis or hypoxic states), the exact role and contribution of metformin in the production of lactic acidosis could not be definitely ascertained as these conditions per se may be associated with hyperlactatemia.

In conclusion, we describe the largest series of patients with MALA in Taiwan and suggest the severity of underlying conditions on admission, not metformin itself, determines the prognosis. Our study also shows that previous stage 3 CKD has no negative influence on the outcome of MALA. However, larger and prospectively designed studies are clearly needed to elucidate the independent prognostic factors of MALA.

References

1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metfromin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-65.
2. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32: 193-203.
3. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med 2002; 137: 25-33.
4. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med 2003; 163: 2594-602.
5. Runge S, Mayerle J, Warnke C, et al. Metformin-associated lactic acidosis in patients with renal impairment solely due to drug accumulation? Diabetes Obes Metab 2008; 10: 91-3.
6. Velzen A, Riel A, Vries I, Meulenbelt J. The dangers of metformin: fatal lactic acidosis with therapeutic use due to renal failure. Toxicol Lett 2008; 180: S142-S143.
7. Wen Y-K. Impact of acute kidney injury on metformin-associated lactic acidosis. Int Urol Nephrol 2009; 41: 967-72.
8. Wills BK, Bryant SM, Buckley P, Seo B. Can acute overdose of metformin lead to lactic acidosis? Am J Emerg Med. 2010; 28: 857-61.
9. Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: a prognostic and therapeutic study. Crit Care Med 2009; 37: 2191-6.
10. Friesecke S, Abel P, Roser M, Felix SB, Runge S. Outcome of severe lactic acidosis associated with metformin accumulation. Crit Care 2010; 14: R226.
11. Yeung CW, Chung HY, Fong BM, et al. Metformin-associated lactic acidosis in Chinese patients with type II diabetes. Pharmacology 2011; 88: 260-5.
12. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. Drug Safety 1999; 20: 377-84.
13. Smith I, Kumar P, Molloy S, et al. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med 2001; 27: 74-83.
14. Peters N, Jay N, Barraud D, et al. Metformin associated lactic acidosis in an intensive care unit. Crit Care 2008; 12: R149.
15. Dell'Aglio DM, Perino LJ, Kazzi Z, Abramson J, Schwartz MD, Morgan BW. Acute metformin overdose: examining serum pH, lactate level, and metformin concentrations in survivors versus nonsurvivors: a systematic review of the literature. Ann Emerg Med 2009; 54: 818-23.
16. van Berlo-van de Laar IR, Vermeij CG, Doorenbos CJ. Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. J Clin Pharm Ther 2011; 36: 376-82.
17. Bailey CJ, Turner RC. Metformin. New Engl J Med 1996; 334: 574-9.
18. Herrington WG, Levy JB. Metformin: effective and safe in renal disease? Int Urol Nephrol 2008; 40: 411-7.
19. NICE. Type 2 Diabetes: The management of Type 2 Diabetes: NICE Clinical Guideline 87. National Institute for Health and Clinical Excellence, Updated July 2011. http://www.nice.org.uk/nicemedia/live/12165/44320/44320.pdf. (accessed 30 June 2012)

第2型糖尿病患發生metformin相關的乳酸中毒之預後

許智能[1] 張仲豪[1] 林正浩[2] 戴研光[3]

阮綜合醫療社團法人阮綜合醫院
[1]內科部加護病房 [2]腎臟科 [3]內分泌暨新陳代謝科

摘 要

乳酸中毒是與metformin治療相關的一種罕見但可能威脅性命的併發症。目前，使用metformin的禁忌都是爲防範此併發症而建議的，其中，腎功能異常是相當重要的。本研究旨在探討與metformin相關的乳酸中毒其預後的相關因子及發病前的慢性腎臟病對預後的影響。我們收集過去5年內住進本院加護病房且符合metformin相關的乳酸中毒的個案進行回溯性研究，紀錄他們的過去疾病、臨床表徵、生物學資料、治療方式及預後。共收集17位metformin相關的乳酸中毒個案，發現所有案例都合併急性腎損傷，死亡率是35.3%。與死亡相關的危險因子包括：高APACHE II分數(p=0.002)，休克(p=0.028)，需要呼吸器(p=0.002)及升壓劑(p=0.035)；比起死亡個案，存活者住加護病房天數較長(p=0.014)；過去有無慢性腎臟病，並不影響乳酸中毒時的疾病嚴重度及死亡率。本研究顯示metformin相關的乳酸中毒症其主要決定預後的因子是住院時的疾病嚴重度，糖尿病患使用metformin治療時，有無合併第3期慢性腎臟病，並不影響在急性腎損傷之後引發乳酸中毒症之預後。