Successful Dialysis Treatment of Metformin Associated Lactic Acidosis, Report of Two Cases

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Introduction. Metformin-associated lactic acidosis is rare despite its widespread use. It is often associated with the use of metformin in the presence of chronic kidney disease, but it may also occur in people with normal renal function in the case of acute overdose.
Case Report. 20 years old (patient 1) and 37 years old (patient 2) women without any chronic disease took 40 gram (727 mg/kg) and 60 gram (1200 mg/kg) metformin, respectively; for the suicidal attempt. Deep lactic acidosis was detected in patients. In patient 1, hemodialysis was performed for 4 hours. After the interruption, deep acidosis evolved again and another dialysis session was performed. In patient 2, hemodialysis was performed for 16 hours without any interruption and she did not need any other dialysis session.
Conclusion. Metformin has a large distribution volume. It is not correct to make a final decision as to how long the dialysis will continue when dialysis begins. Dialysis should be continued without interruption until clinical and laboratory targets are achieved.

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INTRODUCTION

Metformin is the preferred biguanide derivative in the treatment of type 2 diabetes.[1] Metformin inhibits mitochondrial respiration in insulin-dependent tissues, activates anaerobic glucose metabolism in intestines. For these reasons, metformin accumulation may lead to lactic acidosis.[2-4] Metformin-associated lactic acidosis (MALA) is rare despite its widespread use. MALA is defined as a venous serum lactate level > 5 mmol/L with serum bicarbonate < 22 mmol/L.[5] It is often associated with the use of metformin in the presence of chronic kidney disease (CKD), but it may also occur in people with normal renal function in the case of acute overdose. Although rare, MALA may be fatal.[6-9] The amount of metformin exposure and concomitant diseases determine mortality. Here we present two cases of metformin poisoning treated with hemodialysis.

CASE PRESENTATION 1

A 20 years old previously healthy woman took 40 gram (727 mg/kg) metformin alone in the home for a suicidal attempt. She was referred to the emergency department of a tertiary hospital. Lactic acidosis detected, then the patient was admitted to the Intensive Care Unit (ICU) of Internal Medicine Clinic. Her vital signs were stable, then conventional hemodialysis was planned. Hemodialysis started at the eighth hour of drug intake. At the beginning of hemodialysis, she was unconscious and had deep metabolic acidosis (Table 1). Hemodialysis was performed with Fresenius 4008 S device, 1.4 m^2 high-flux FX-60 membrane (Fresenius), 300 ml/min blood flow rate, 500 mL/min dialysis fluid rate, 32 mmol/L bicarbonate, without ultrafiltration. Dialysis ceased because laboratory and clinical improvement was observed after 4-hour of hemodialysis. After 8-hours break, hemodialysis started again with the same order because of the deepening of lactic acidosis. After the 4-hours of dialysis treatment, therapy was discontinued. There was no need for dialysis again. During

Case Report

Table 1. Laboratory Values of Patient 1

	Urea (mg/dL)	Cr (mg/dL)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	PH	HCO_3^- (mmol/L)	Lactat (mmol/L)	PCO_2 (mmHg)	AG
Drug Exposure (14:00)										
Hospital Admission (16:00)	36	1.12	138	4.6	104	7.2	10.8	11.4	29	23
Internal Medicine Clinic ICU, 1st HD										
Start (22:00 - 0Time)	17	0.7	138	4.5	103	6.8	4.7	22.2	26	30
2nd hour			134	4.4	96	7.2	11.7	15.7	31.2	26
4th hour			131	3.7	94	7.3	20.5	8	40.5	17
Post-1st HD 2nd hour (04:00)			132	4.2	95	7.3	11.3	10.1	25.6	26
2nd HD										
Start (09:45 – Zero Time)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2nd hour			131	3.8	97	7.4	23.4	1.4	37.1	11
4th hour	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Post-2nd HD, 4 hour			130	3.7	97	7.4	21.9	1.5	35.8	11
Post-2nd HD, 8 hour	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

HCO_3^-, bicarbonate; AG, anion gap; ICU, intensive care unit; HD, hemodialysis; NA, not applicable

dialysis sessions, hypotension developed, but blood pressure normalized with low-dose noradrenaline administration. She discharged on the fourth day of admission.

CASE PRESENTATION 2

A 37 years old previously healthy woman admitted to the emergency department with suspicion of intoxication. The patient reported that she took 60 grams (1200 mg/kg) metformin. Her renal function was normal at baseline and she had a moderate normal anion gap metabolic acidosis (Table 2). Hemodialysis was planned for the patient who developed deep lactic acidosis. Hemodialysis started with Fresenius 4008 S device, 1.8 m^2 high-flux FX-80 membrane (Fresenius), 300 mL/min blood flow rate, 500 mL/min dialysis fluid rate, 32 mmol/L bicarbonate, without ultrafiltration. She was unconscious at the starting of hemodialysis. Her laboratory values and consciousness level did not improve enough in the first 12 hours. Hemodialysis was ceased at the 16th hour. Hypotension developed during dialysis but

Table 2. Laboratory Values of Patient 2

	Urea (mg/dL)	Cr (mg/dL)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	PH	HCO_3^- (mmol/L)	Lactat (mmol/L)	PCO_2 (mmHg)	AG
Drug Exposure (14:30)										
Hospital Admission (17:33)	30	0.9	141	5.1	111	7.3	18.7	2.38	36.7	11
Emergency Service (23:00)	25	1.5	139	4	90	7	3.8	26.9	17.4	45
Internal Medicine Clinic ICU										
HD Start (24:00)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2nd hour	7	0.7	144	3.3	99	7.2	13.9	18.1	38	31
4th hour			143	3.1	95	7.2	16.5	18.3	43.6	32
6th hour			141	3.7	98	7.3	10.8	21.9	24.6	32
8th hour			138	3.8	96	7.2	11.8	21.4	27.9	30
10th hour			139	3.5	100	7.4	12.7	13.4	19.6	26
12th hour			138	3.6	99	7.4	17.7	12.8	30.6	21
14th hour			138	3.4	99	7.4	21	8.3	32.3	18
16th hour			138	3.2	100	7.5	24.6	7.7	35.7	13
Post HD, 2nd hour			135	3.6	98	7.4	22.6	8.3	33.6	14
Post HD, 4th hour			135	3.8	99	7.4	17.4	6.3	26.5	19
Post HD, 8th hour			136	4.1	101	7.4	18.4	4.0	27.7	17
Post HD, 12th hour	38	1.1	133	4	100	7.5	23.2	3.0	33.1	10
Post HD, 24th .hour	30	1.0	137	3.4	106	7.4	25.7	0.8	41.9	5

HCO_3^-, bicarbonate; AG, anion gap; ICU, intensive care unit; HD, hemodialysis; NA, not applicable

corrected with low-dose noradrenaline. The patient, whose consciousness completely recovered and did not describe complaints, was followed conservatively. She discharged on the fourth day of admission.

DISCUSSION

Metformin is dialysable. It circulates without binding to protein and has a very large distribution. Dialysis treatment is the most effective method in terms of both removing the drug and solving the acid-base problem. Dialysis is recommended when PH < 7.0, lactate concentration > 20 mmol/L.[10] Dialysis modality which should be preferred in MALA patients is based on hemodynamic status. Conventional hemodialysis is recommended in patients who are hemodynamically stable. In unstable patients, continuous venovenous hemodiafiltration (CVVHDF) or continuous venovenous hemodialysis (CVVHD) should be preferred.

In the first patient, we applied hemodialysis with 1.4 m^2 high flux dialyzer for 4 hours. At the end of 4 hours, the lactate level decreased from 22.2 mmol/L to 7.9 mmol/L and the bicarbonate increased from 4.7 mmol/L to 20.5 mmol/L. Dialysis discontinued. Her diuresis was good. Two hours later, lactate increased, and bicarbonate decreased. Second hemodialysis session performed after approximately 8 hours. Clinical and laboratory findings improved after the second 4-hour hemodialysis. About a month after the first case, another patient came to the emergency department, taken 60 grams of metformin. The patient had a good clinical picture but a few hours later developed deep acidosis. With the attention of rebound acidosis, exposure to a higher dose in this case, delay on hemodialysis re-starting in the previous case, hemodialysis started with uncertain duration planning. Efficient hemodialysis continued for 16 hours. Dialysis was stopped when PH = 7.45, $HCO3^-$ = 24.6 mmol/L, lactate = 7.7 mmol/L. Two hours after the end of the dialysis, lactate increase was observed (8.25 mmol/L), and at the 4th hour, it decreased to 6.28 mmol/L. It should be kept in mind that while 16 hours of effective hemodialysis seems sufficient in this case, the reasonable recommendation is to continue dialysis until the lactate level is < 3 mmol/L.[10]

Our standard dialysate bicarbonate concentration is 32 mmol/L. In these two cases, we did not want to correct acidosis rapidly then we didn't increase bicarbonate buffer.

CONCLUSION

It is not correct to make a final decision as to how long the dialysis will continue when dialysis begins. Dialysis should be continued without interruption until clinical and laboratory improvement is both achieved.

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