

Metformin Associated Lactic Acidosis (MALA) after severe intentional intoxication: Delayed, yet full neurological recovery

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Abstract : Metformin is a widely used drug in the treatment of diabetes mellitus. In case of overdose, metformin can induce lactic acidosis and severe multiple organ failure. Despite very low pH and high lactate levels on admission, patients usually recover within 48 hours when treated with fluids, dialysis, hemodynamic and respiratory support. We present a case of severe lactic acidosis after intentional ingestion of a high dose of metformin leading to seizures and prolonged coma yet finally resulting in full recovery.

Key words : critical care ; intoxication ; lactic acidosis ; metformin ; overdose.

INTRODUCTION

Metformin is a dimethyl-biguanide widely used as an oral anti-hyperglycemic drug in the treatment of diabetes mellitus (1). The mechanisms of action result from a reduction of gluconeogenesis in the liver and glucogenolysis in the muscle cells, an increase in insulin sensitivity of peripheral tissues and stimulation of intracellular glycogen synthesis. Metformin-associated lactic acidosis (MALA) is a rare but serious adverse event. The reported frequency of MALA during treatment is 0.05/1000 patients-years (2, 3). The mechanism by which metformin increases blood lactate concentration is complex, with mitochondrial inhibition of the respiratory chain complex as a likely major factor (4). Accidental overdose during treatment with metformin is frequently caused by an unnoticed decrease in renal function due to illness, and causing dehydration. Usually, there is a striking discrepancy between the very high blood lactate levels on the one hand, and the relatively mild clinical presentation on the other (5, 6). The patients typically fully recover with supportive care within 48 hours. Despite metformin's widespread use, intentional overdose is uncommon (7). Although an increasing dose of metformin is likely to cause more severe multiple organ failure, the ingested dose and resulting severity of clinical syndromes are poorly correlated (5). We herein present a patient with

full recovery of MALA after a suicide attempt, and complicated by extreme laboratory abnormalities, severe multiple organ failure including seizures and prolonged coma.

CASE REPORT

A 49-year old Caucasian male was transferred to the hospital after admitting an intentional overdose with metformin. The exact time and dose of ingestion was unknown but the patient claimed to have taken 40 pills of 1000 mg metformin. The patient's medical history reported late onset diabetes mellitus and a personality disorder with multiple suicide attempts. Upon admission to the Accident & Emergency department, he was obtunded (Glasgow coma score E1M5V2) with isocore light reactive pupils, blood pressure 95/40 mmHg, sinus rhythm 63 bpm, tachypnea 40 breaths/min, oxygen saturation of 99%, body temperature of 32.6 °C and normal urine output. Laboratory tests revealed an extremely high lactate level of > 20 mmol/l with a pH of < 6.8 (Table 1), a blood glucose level of 12.6 mmol/l, normal serum electrolytes, a creatinine level of 195 μ mol/l (normal 45-100 μ mol/l) compared to 69 μ mol/l two months earlier. Metformin level in plasma was 128 mg/l (published therapeutic value 0.5-0.8 mg/l) (8), acetaminophen plasma level was low and no other drugs were detectable.

Shortly after admission to the intensive care unit (ICU) the patient developed generalized tonic clonic seizures lasting for about 30 seconds, confirmed by a consulted neurologist. Because of rapid hemodynamic and respiratory deterioration

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Table 1
Laboratory and clinical data

	12-09	12-09	13-09	13-09	13-09	13-09	13-09	13-09	14-09	14-09	15-09	16-09	17-09	18-09	19-09	20-09	21-09	22-09
	09:50	21:14	02:43	05:48	09:50	17:36	22:05	05:22	16:06	08:00	08:00	08:00	08:00	08:00	16:00	16:00	08:00	
pH	<6.80	6.83	6.90	7.17	6.99	7.13	7.24	7.36	7.40	7.47	7.56	7.57	7.53	7.52	7.51	7.48	7.48	
paCO ₂ (kPa)	2.6	1.8	1.6	1.9	1.7	2.0	2.0	2.7	4.2	4.2	3.5	3.9	4.7	5.0	5.4	5.2	5.6	
paO ₂ (kPa)	18.4	19.2	21.2	19.3	18.8	18.4	17.2	17.5	20.3	14.0	13.3	20.6	9.0	10.6	16.0	12.3	8.6	
Base excess		-30.4	-28.8	-21.3	-26.4	-22.1	-19.0	-12.6	-4.9	-0.1	1.5	4.5	6.1	6.8	8.2	5.1	7.1	
Lactate (mmol/L)	>20	>20	>20	>20	>20	19.5	14.7	6.1	1.7	1.8		1.6						
Glucose (mmol/L)	12.6	6.2	4.7	6.0	8.7	14.7	14.0	14.4	8.9	13.4	5.9	10.0	7.6	7.8	13.6	11.6	15.8	
Creatinine (μmol/L)	195	227	237					231	216	205	277	344	358	311	244	198	174	
Urine output (ml/h)	80	80	41	41	41	41	41	17	17	28	92	172	136	146	130	159	144	
Dialysis		CVVHD	CVVHD	CVVHD	CVVHD	CVVHD	CVVHD	CVVHD	CVVHD	CVVHD								
Ventilation	SV	MV	MV	MV	MV	MV	CPAP	CPAP	CPAP	CPAP	CPAP	CPAP	CPAP	SV	SV	SV	SV	
Blood pressure (mmHg)	84/39	100/49	112/52	97/43	92/43	94/39	112/41	136/48	113/55	142/76	119/71	119/74	134/69	146/73	138/74	158/74	140/85	
Heart rate (beats/min)	70	110	102	98	95	107	115	122	107	88	119	117	103	88	90	98	85	
Norepinephrine (μg/kg/min)		0.95	0.95	0.95	0.95	0.95	0.95	0.80	0.40	0.32	0.20	0.08	0	0	0	0	0	
Temperature (°C)	32.6	36.6	36.2	35.9	35.8	36.3	37.1	37.5	36.7	36.8	38.2	39.1	37.2	37.0	37.4	37.6	37.1	
GCS	E1M5V2	E1M1V1	sedated	sedated	sedated	sedated	sedated	sedated	E2M1Vt	E1M1Vt	E3M1Vt	E2M1Vt	E3M6Vt	E4M6Vt	E4M6V3	E3M6V5	E4M6V5	
	8	3							4	3	5	4	10	11	13	14	15	

Abbreviations : SV = spontaneous ventilation ; MV = mechanically ventilation ; CPAP = Continuous positive airway pressure ; CVVHD = continuous veno-venous hemodiafiltration

the patient was immediately treated with a 5 mg intravenous bolus injection of midazolam and subsequently intubated, ventilated and sedated by a 6 mg/h continuous midazolam infusion. Thereafter, he remained hemodynamically instable requiring high doses of norepinephrine (0.95 μg/kg/min). The severe lactic acidosis persisted for more than 24 hours after admission, with the pH remaining below 7 and lactic acid levels >20 mmol/l despite fluid resuscitation, continuous veno-venous hemodiafiltration (CVVHD) treatment, and buffering with sodium bicarbonate 8.4% (Table 1). During the subsequent two days, the lactic acidosis gradually improved and dialysis and midazolam sedation (in total 44 hours 6 mg/h) could be stopped. Hemodynamics improved with pH normalization, norepinephrine could be rapidly reduced and stopped, and urine output increased in parallel. The patient started to breathe spontaneously and was switched from mechanical ventilation to CPAP mode. Signs of epileptic activity were no longer detectable. Two days after cessation of sedation, the patient was still comatose with a GCS of 3.

A computed tomography of the brain showed no abnormalities. After two additional days, an increase in motor score and improvement of consciousness to a GCS of 10 was observed. On day eight after metformin intoxication, the patient finally became more responsive with a GCS of 14 and his trachea was extubated. Full neurological recovery followed, and the patient was discharged from the ICU on day 16 after admission. After further somatic recovery, he was transferred to an institution for mental support. He was finally discharged 3 months later in a mentally more stable and balanced condition, after having sorted out personal and financial issues and returned to his country of origin where he was lost to follow up.

DISCUSSION

We present a patient with severe lactic acidosis after intentional ingestion of a high dose of metformin, leading to extreme disturbances in the acid-base balance with severe multiple organ failure, including generalized tonic-clonic seizures

and a prolonged coma, yet ultimately resulting in full recovery.

Whereas MALA caused by relative and unintentional overdose is characterized by a striking discrepancy between high lactate serum levels but a relatively mild degree of shock, the ingestion of larger amounts of metformin with suicidal intention causes severe hemodynamic and respiratory failure (5, 6). Metformin overdose of up to 100 g, associated with serum metformin levels of > 400 mg/l and lactate levels of 40 mmol/l with pH 6.59 have previously been reported, with full recovery in the majority of cases and only few lethalties (2, 6, 9-11). Severe acidosis leads to hypotension by decreased catecholamine binding to their respective receptors at low pH, causing significant vasodilatation and decreased myocardial contractility (12). Respiratory failure occurs when the compensatory function of the ventilator system under condition of severe metabolic acidosis reaches its limits. Circulatory failure and exhausted buffer capacity lead to acute renal failure.

Our patient categorizes among the most severe of reported cases regarding the degree of lactic acidosis. The applied blood analysis system in our laboratory has an upper reporting level for lactate of 20 mmol/l and a lower cut-off for pH of 6.8. As lactate was repeatedly measured > 20 mmol/l for more than 24 hours after admission, it can be estimated that the peak value must have been even more anomalous. In addition to the earlier described hemodynamic, respiratory and renal failure in MALA, our case was complicated by generalized tonic-clonic seizures. This finding is less frequently documented in the literature in patients with MALA. Rathnapala et al. described seizures in a case of metformin and kerosene oil intoxication (13). In their patient, the seizures were linked to hypoglycemia, whereas our patient had normal blood glucose levels. The pathophysiologic triggers to develop seizures in our patient could have been directly toxic effects of metformin to the brain (14, 15), extreme lactic acidosis, the compensatory very low pCO₂, and the fulminant hemodynamic shock with hypotension. The seizures were symptomatically treated with benzodiazepines; all metabolic deviations were corrected and normalized within 48 hours. However, the patient remained in a comatose state after cessation of sedation leaving a number of possible explanations. These include persisting seizure activity, a postictal state, prolonged sedative effect of midazolam, and focal or diffuse post-anoxic brain damage after severe hypotension and acidosis. However, there were no clinical

and electroencephalographic signs of persisting epileptic activity. A computed tomography of the brain showed no abnormalities. Treatment and sedation with midazolam could result in a delayed recovery. There are no data available about the midazolam serum levels, kinetics, or benzodiazepine metabolizer cytochrome P450 enzyme activity of the patient. Neurologic improvement occurred only four days after cessation of the sedation, with full recovery not earlier than one week later. This leads to the key clinical message of this case report.

CONCLUSION

Even in the most severe cases of MALA presenting with multi organ failure, supportive therapy results in survival in a majority of cases (11, 16). The herein presented case provides additional evidence that even in patients with seizures and a prolonged coma after MALA, recovery can be complete. Continuation of treatment is therefore warranted.

Consent

Written informed consent was obtained from the patient for publication of this case report.

References

1. King P., Peacock I., Donnelly R., *The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes*, *BR. J. CLIN. PHARMACOL.*, **48** (5), 642-8, 1999.
2. Silvestre J., Carvalho S., Mendes V., Coelho L., Tapadinhas C., Ferreira P. et al., *Metformin-induced lactic acidosis: a case series*, *J. MED. CASE REP.*, **1**, 126, 2007.
3. DeFronzo R., Fleming G. A., Chen K., Bicsak T. A., *Metformin-associated lactic acidosis: Current perspectives on causes and risk*, *METABOLISM.*, **65** (2), 20-9, 2016.
4. Moioli A., Maresca B., Manzione A., Napoletano A. M., Coclite D., Pirozzi N. et al., *Metformin associated lactic acidosis (MALA): clinical profiling and management*, *J. NEPHROL.*, **29** (6), 783-789, 2016.
5. Kajbaf F., Lalau J. D., *The prognostic value of blood pH and lactate and metformin concentrations in severe metformin-associated lactic acidosis*, *B. M. C. PHARMACOL. TOXICOL.*, **14**, 22, 2013.
6. Dell'Aglio D. M., Perino L. J., Todino J. D., Algren D. A., Morgan B.W., *Metformin overdose with a resultant serum pH of 6.59: survival without sequelae*, *J. EMERGENCY MED.*, **39** (1), e77-80, 2010.
7. Spiller H. A., Quadrani D. A., *Toxic effects from metformin exposure*, *ANN. PHARMACOTHER.*, **8** (5), 776-80, 2004.
8. Lalau J. D., Lemaire-Hurtel A. S., Lacroix C., *Establishment of a database of metformin plasma concentrations and erythrocyte levels in normal and emergency situations*, *CLIN. DRUG INVEST.*, **31** (6), 435-8, 2011.
9. Suchard J. R., Grotsky T. A., *Fatal metformin overdose presenting with progressive hyperglycemia*, *WESTERN J. EMERG. MED.*, **9** (3), 160-4, 2008.
10. Ozeki T., Kawato R., Watanabe M., Minatoguchi S., Murai Y., Ryuge A. et al., *A Fatal Case of Metformin-associated Lactic Acidosis*, *INTERN MED.*, **55** (7), 775-8, 2016.

11. Kajbaf F., Lalau J. D., *Mortality rate in so-called «metformin-associated lactic acidosis»: a review of the data since the 1960s*, PHARMACOEPIDEMIOL. DRUG SAF., **23** (11), 1123-7, 2014.
12. Kimmoun A., Novy E., Auchet T., Ducrocq N., Levy B., *Hemodynamic consequences of severe lactic acidosis in shock states: from bench to bedside*, CRIT. CARE, **19**, 175, 2015.
13. Rathnapala A., Matthias T., Jayasinghe S., *Severe lactic acidosis and acute renal failure following ingestion of metformin and kerosene oil: a case report*, J. MED. CASE REP., **6**, 18, 2012.
14. Moreira P. I., *Metformin in the diabetic brain: friend or foe?* ANN. TRANSL. MED., **2** (6), 54, 2014.
15. Takata F., Dohgu S., Matsumoto J., Machida T., Kaneshima S., Matsuo M. et al., *Metformin induces up-regulation of blood-brain barrier functions by activating AMP-activated protein kinase in rat brain microvascular endothelial cells*, BIOCHEM. BIOPHYS. RES. COMM., **433** (4), 586-90, 2013.
16. Timbrell S., Wilbourn G., Harper J., Liddle A., *Lactic acidosis secondary to metformin overdose: a case report*, J. MED. CASE REP., **6**, 230, 2012.