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Fatal Metformin Poisoning: Adolescent Case Report

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Abstract

Metformin is a biguanide oral hypoglycemic agent used for non-insulin dependent diabetes mellitus. Lactic acidosis still the most important and dangerous side effect of acute and chronic metformin use, its mortality can reach up 50%. Metformin poisoning in children remains rare and is very rarely reported in the literature. The curative treatment is based on early extrarenal purification by haemodialysis or haemodiafiltration. However, the prognosis of high doses of metformin can be fatal. We are reporting the case of a 14-year-old female patient who intentionally overdosed on metformin, resulting in lactic acidosis and death.

Keywords: *Metformin; Poisoning; Lactic: Acidosis; Haemodialysis.*

Introduction

Metformin is a biguanide oral hypoglycemic agent used for non-insulin dependent diabetes mellitus (NIDDM)**[**1**]**. It is arguably the most commonly prescribed oral hypoglycemic agent **[**2**]**. In the absence of overdose or intoxication, the side effects of metformin are usually minor, consisting of digestive disorders: dyspepsia, nausea, vomiting. Exceptional cases of pancreatitis and rhabdomyolysis have been reported**[**3**]**. Lactic acidosis still the most important and dangerous side effect of acute and chronic metformin use, its mortality can reach up 50%**[**4,5**]**. The mechanisms that can explain metformin-induced lactic acidosis are not clear. Several effects of metformin can lead to lactate accumulation.

Metformin poisoning in children remains rare and is very rarely reported in the literature. In this case report, we describe a 14-year-old female patient who intentionally overdosed on metformin, resulting in lactic acidosis and death. Our goal is to analyze the clinical, prognostic, and therapeutic aspects of metformin-induced lactic acidosis in intentional overdose cases, as well as compare the prognosis of intentional metformin overdose to that of accidental overdoses.

Case Report

A.R, a 14-year-old female patient with no notable medical history, was admitted to the emergency department due to an acute onset of altered mental status, without fever or history of trauma, and preceded by intractable vomiting 24 hours before admission. Despite receiving symptomatic treatment, there was no improvement in her condition. Upon interviewing the family, it was discovered that the

patient had voluntarily ingested 8 tablets of metformin 1000mg, totalling 8g, and belonging to her grandfather who was being treated for type 2 diabetes. However, the time of ingestion was uncertain. The suspicion of metformin overdose arose due to the number of missing tablets from the grandfather's medication and a search of the patient's home excluded the presence of other drugs or toxins. This was likely an isolated case of intentional metformin overdose for suicidal purposes due to the presence of family conflict.

Upon initial examination at the emergency department, the patient was found unconscious with a Glasgow Coma Scale score of 8/15, reactive miosis, capillary blood glucose level of 0.19, and residual vomitus. She received IV glucose 10% and a nasogastric tube was placed immediately to protect airways. The patient had a heart rate of 150 beats per minute, systolic blood pressure of 110 mmHg, cold extremities, prolonged capillary refill time, and a respiratory rate of 30 cycles per minute without signs of respiratory distress or abnormalities on cardiac and pulmonary auscultation. Oxygen saturation (SpO2) was 94%. The patient received initial treatment including oxygenation, intravenous access, nasogastric tube placement (without gastric lavage), urinary catheterization, IV glucose with close monitoring of blood sugar levels, and vascular filling with 20 ml/kg of 0.9% saline solution. Toxicological samples were collected from three biological fluids (urine, blood, and gastric fluid), blood tests including beta-hCG and infection screening. Arterial blood gas analysis revealed high anion gap and metabolic acidosis, suggestive of organic metabolic acidosis.

At the intensive care unit an hour later, the patient had a GCS of 11/15 with left upper limb monoparesis, semi-mydriasis, and reactive pupils. Her capillary blood glucose level was measured at 1.03g/dl. Her systolic blood pressure was 125 mmHg, with some wheezes on pulmonary auscultation. The arterial blood gas analysis showed severe metabolic acidosis; pH=6.96, PaCO2=17mmgh, HCO3-=3.6, Anion gap=47, and lactate levels> 5mmol/L. Immediate alkalization was initiated using sodium bicarbonate serum. However, the patient's condition rapidly deteriorated, leading to cardiovascular collapse and neurological deterioration, Hemodynamic optimization was achieved using vascular filling with 0.9% saline and high doses of norepinephrine (>2µg/kg/min).

On the biological level, there is evidence of renal failure with a creatinine level of 35.3 mg/L, coupled with a low prothrombin time (PT) at 37%, a thrombocytopenia at 136,000, negative inflammatory markers, and a SOFA score of 12. Toxicology tests were negative. The patient underwent intermittent hemodialysis to facilitate renal clearance of metformin and improve plasma pH, with a total duration of twenty hours spread over five sessions.

The patient's condition progressed to multi-organ failure, with renal and hepatic failure, disseminated intravascular coagulation, and persistent shock. The patient died on the 6th day of hospitalization. A metformin assay performed on day 3 of admission confirmed metformin poisoning, with a plasma metformin level of 8.5 mg/L.

	Day1		Day2		Day3		Day4	
	1st Hour	2nd Hour	Pre-dialysis	Post-dialysis	Pre-dialysis	Post-dialysis	Pre-dialysis	Post-dialysis
pH	7.33	6.96	7.18	7.20	7.27	7.47	7.20	7.42
$HCO3^-$ (mEq/l)	6.2	3.6	14.6	12.5	11.8	15	12.5	15.5
$PaCO_2$ (mmgh)	12	17	40	33	26	21	33	28
Base excess (mEq/l)	-16.9	-26.9	-13.1	-14.3	-13.6	-6.7	-14	-5.1

Table 1: Arterial blood gas monitoring of the patient during her stay in the intensive care unit.

	Day1	*Day2*	*Day3*	*Day4*	*Day5*
Urea (g/l)	0.43	0.64	0.97	0.82	0.87
Creatinine (mg/l)	35.3	33.4	42.7	41.9	40.7
Potassium (mEq/l)	5.8	4.5	6.8	6.2	>7
Chloride (mEq/l)	89	86	89	96	97
HCO3- (mEq/l)	<5	16	10	14	13
Lactate (mmol/l)	>5	>5	>5	>5	>5
AST (U/l)	58	984	883	580	988
ALT (U/l)	48	270	360	343	313
Albumin (g/l)	48	27	36	25	18
PT (%)	37	42	19	62	20
APTT (sec)	69.1	54	45	73	60
FV activity (%)	45	35	20	93	50
Platelets count x103 /ml	136	50	16	25	20

Table 2: Biological monitoring of the patient during her stay in intensive care.

Discussion

Severe metformin poisoning often presents with a profound lactic acidosis followed by collapse of the cardiovascular system[6]. Symptoms of metformin poisoning are diffuse with abdominal pain, nausea, vomiting, hypothermia, decreased level of consciousness, and circulatory instability leading to multiorgan failure. The circulatory instability is due to peripheral vasoplegia as described in many case reports where low systemic vascular resistance was measured [7].

Metformin poisoning in the paediatric population is rare and not widely reported in the literature. Of the 55 patients collected for ingestion of less than 1700mg of metformin, Spiller et al. reported no patients with signs of lactic acidosis [8].

22 children admitted to the paediatric intensive care unit due to metformin intoxication between 2013 and 2019 in Ankara and were evaluated retrospectively[9]. Mean age of the patients was 13.04±5.46 years (1-18 years), 18 were female. Ingested metformin dose ranged from 1.7 gr to 85 gr (mean 19±22.6 gr, median 10 gr), with coingestants taken in 12 patients. Nausea and/or vomiting were present in 16 (72.7%) of the patients. Hyperlactatemia (lactate > 2mmol/L) was present in 13 (59%) of the patients. Mean peak lactate level was 5.1±5.7 mmol/L (0.9-21 mmol/L). Acidosis was present in 12 (54.5%) of the patients. Mean lowest pH level was 7.28±0.16 (6.9-7.45). There was a positive correlation between lactate level and ingested dose ($r = 0.816$; $p < 0.001$) while pH was inversely related to dose ($r = -0.873$; $p < 0.001$). Six (27%) patients required renal replacement therapy because of profound lactic acidosis despite the intravenous fluid support. Haemodialysis was applied to 5 patients and high dose continuous venovenous hemodiafiltration was applied to 2 patients. 16 years old female patient who ingested 85 g metformin died despite prolonged haemodialysis.

The half-life of metformin exhibits two peaks on concentration time curves. First curve coincides with 2 hours after ingestion; second peak is at 16 hours as a result of accumulated metformin in tissues. Because of this pharmacokinetic property of metformin, patients with acute metformin intoxication who develop MALA usually required prolonged and repetitive HD sessions [10].

Raising the pH and lowering the lactatemia should not be therapeutic objectives in themselves. In fact, there is no recent clinical data confirming the deleterious effects of such measures, no recent clinical data confirm the deleterious effects, particularly cardiovascular, of organic metabolic acidosis.

Some experimental studies even show that that acidosis can have beneficial effects [11]. Furthermore clinical studies show no benefit either from alkalinisation of lactic acidosis lactic acidosis [12].

Metformin, a molecule with exclusively renal elimination, is dialysable. Thus, extrarenal renal replacement therapy (ERT) is the first-line treatment for lactic acidosis associated with

Metformin. This has two main objectives: to supplement renal insufficiency which is often present and to allow elimination of metformin **[**13**]**.

It seems preferable to use the purification technique over a long It seems preferable to use the purification technique over a long period of time because of its lesser haemodynamic impact and its greater efficiency in purifying the cellular compartment without plasma rebound **[**14**]**.

The rest of the treatment is purely symptomatic and does not present any particularity. It consists of the replacement of haemodynamic and respiratory failures which may occur during the course of this pathology.

Conclusion

Metformin intoxication associated lactic acidosis is a potentially fatal condition. The mechanism of metformin-induced hyperlactatemia is complex and multifactorial, but essentially secondary to disruption of hepatic mitochondrial respiration.

The curative treatment is based on early extrarenal purification by haemodialysis or haemodiafiltration, which allows elimination of the drug and correction of the acidosis. The pharmacokinetic data pharmacokinetic data justify a prolonged duration of purification.

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