Fatal Intoxication with Metformin and Gliclazide – "Case Report"

Peter Jackuliak [a], Magdaléna Kovářová [a], Andrea Martonová [b], Viera Žufková [c], Andrea Gažová [d*], Ján Kyselovič [a] and Juraj Payer [a]

[a] *5th Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia.*
[b] *1st Department of Anaesthesiology and Intensive Medicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia.*
[c] *Department of Languages, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia.*
[d] *Faculty of Medicine, Institute of Pharmacology and Clinical Pharmacology, Comenius University, Bratislava, Slovakia.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Case Study

ABSTRACT

Introduction: Biguanides (metformin) and sulfonylurea molecule (gliclazide) are oral antihyperglycemic drugs. Metformin can make lactate accumulation in patients with hepatic or renal failure or in patients with a suicide attempt. Gliclazide has very low toxicity, and it can develop acute renal failure in patients with massive ingestion in a suicide attempt.

The Patient's Primary Concerns and Critical Clinical Findings: A 53-year-old patient with a personal history of type 2 diabetes mellitus was treated with metformin 1000 mg twice daily and gliclazide 60 mg twice daily. On December 26th 2018, in the evening hours, he consumed 90 tablets of metformin 1000 mg (total dose 90 grams) and 95 tablets of gliclazide 60 mg (total dose 5.7 grams) for suicide. According to the report, he had been sick all night and suffered from muscle pain, diarrhoea, and vomiting.

The Primary Diagnoses, Interventions, and Outcomes: We concluded the diagnosis as a high anion gap metabolic acidosis. As a consequence of metformin intoxication, lactate level was furthermore elevated (24 mM).

*Corresponding author: E-mail: andrea.gazova@fmed.uniba.sk, aandreagazova@gmail.com;

Conclusion: Metformin and gliclazide are commonly using as effective drugs in patients with type 2 diabetes mellitus. Our case report described fatal intoxication with metformin and gliclazide. The aim is to remember the risk of daily used antidiabetic drugs – in high doses, in combinations, they can lead to pancreatitis, renal failure, or so long-known lactic acidosis.

ABBREVIATIONS

T2DM	:	*Type 2 Diabetes Mellitus*
ECTRs	:	*Extracorporeal Treatments*
BP	:	*Blood Pressure*
BPM	:	*Beat per Minute*
BE	:	*Base Excess*
BB	:	*Buffer Base*
ICU	:	*Intensive Care Unit*
CPCR	:	*Cerebral Cardiopulmonary Resuscitation*
DIP	:	*Drug-induced Pancreatitis*

1. INTRODUCTION

Metformin can cause lactate buildup in patients with hepatic or renal failure, as well as those who take a high dose of the medicine (suicide attempt). Metformin toxicity, a difficult clinical condition, is linked to a 30% fatality rate. Metformin poisoning can result in serious side effects, including death. Extracorporeal therapies (ECTRs), such as hemodialysis and hemofiltration, are among the treatments employed. Metformin poisoning was the most common toxicological indication for ECTR, according to a recent literature study [1]. Metformin poisoning with lactic acidosis appears to be amenable to extracorporeal treatments [2].

Gliclazide is a sulfonylurea chemical that is used to regulate glycemia in people with type 2 diabetes. Gliclazide has been shown to have relatively low toxicity in acute and chronic toxicity assessments in a variety of animal species. The LD50 was calculated to be between 330 and 1300 times higher than the dose given to humans. However, there are also case reports in which a patient developed acute renal failure due to low acute tubular necrosis following massive gliclazide ingestion in a suicide attempt [3]. In the case report [3] 42-year-old male ingested 350 tablets (28 grams) of gliclazide and survived after 20 days of hospitalization.

In our case report, the patient took 9 grams of metformin and 5.7 grams of gliclazide together after three days.

2. CASE PRESENTATION

2.1 Patient Information

A 53-year-old patient with a personal history of type 2 diabetes mellitus (T2DM) was treated with metformin 1000 mg twice daily and gliclazide 60 mg twice daily, otherwise, without a personal history of treating other chronic diseases. He smoked about 40 cigarettes a day and was an occasional alcohol consumer.

2.2 Clinical Findings

On December 26th, 2018, in the evening hours, he consumed 90 tablets of metformin 1000 mg (total dose 90 grams) and 95 tablets of gliclazide 60 mg (total dose 5.7 grams) for suicide. According to the report, he had been sick all night and suffered from muscle pain, diarrhea, and vomiting. On the next (on December 27th 2018), he called the emergency. The patent was hypotensive (blood pressure (BP) 80/60 mmHg), and O_2 saturation was 94% on its arrival. In the clinical picture, tachypnoea and hyperventilation were present - the hospital's personal transported the patient to the emergency room. By admission, the patient was still hypotensive (BP 82/45 mmHg), heart rate was 80 beats per minute (BPM), hypoxemic (saturation O_2 only 85%), and cyanotic. He had tachypnoea (30 breaths per minute) and Kussmaul's breathing. The lab test results depicted hyperglycemia (26 mM), renal insufficiency (urea 9.21 mM, serum creatinine 288.4 mmM), hyperosmolality (340 mOsm/l), and elevated levels of myoglobin (998,0 ug/l). There was present severe metabolic acidosis pH: 6.913, Base excess (BE): -27.6 mM, Buffer base (BB): 20.40 mM, cHCO3-: 4.00 mM, $cHCO_3$ stand.: 5.80 mM. The anion gap was 44.0 mM (corrected to albumin level 45.08 mM), delta ratio 2.3, delta gap 32.0.

2.3 Diagnostic Assessment

All lab tests were completed from 12/27/2018 to 12/29/2018, and all results were on Graph 1 A-H.

2.4 Lab Tests

pCO2 (kPa)

A

pO2

B

BE

C

BB

D

cHCO₃⁻

E

cHCO₃ st.

F

pH

G

CRP

H
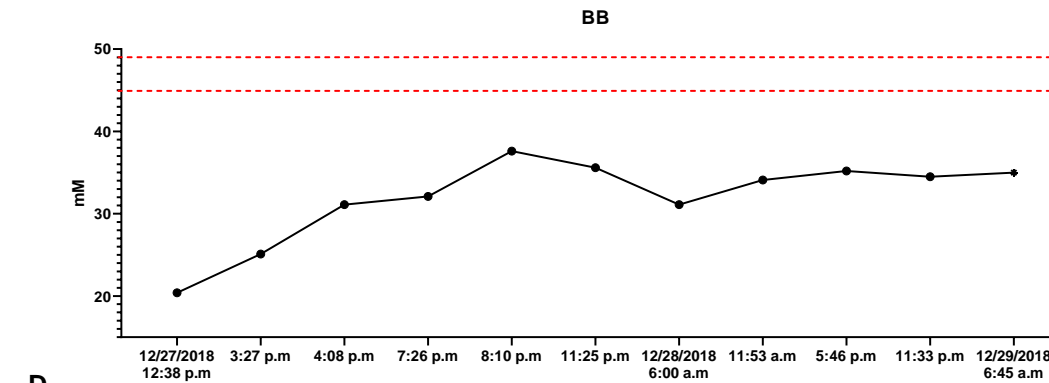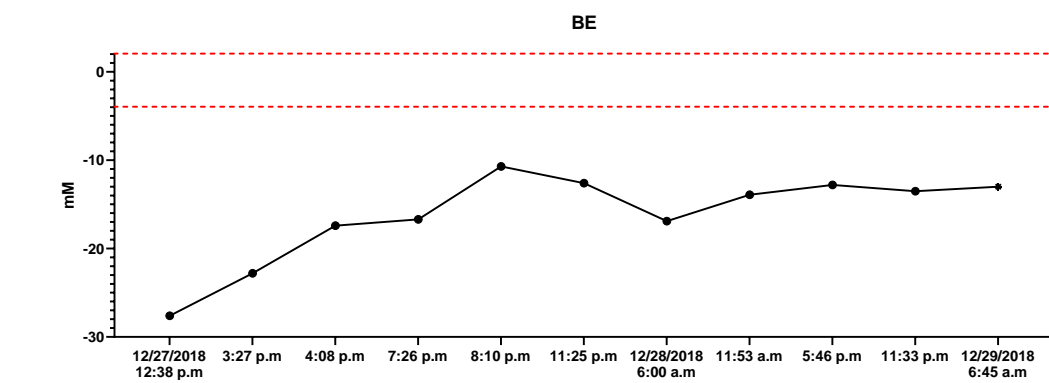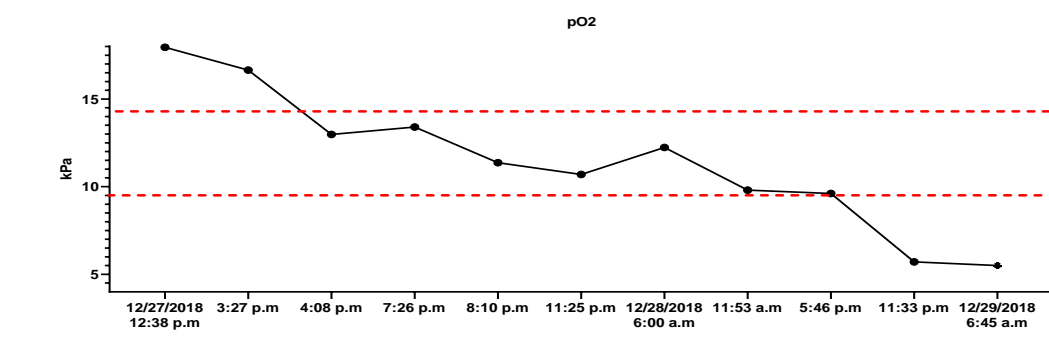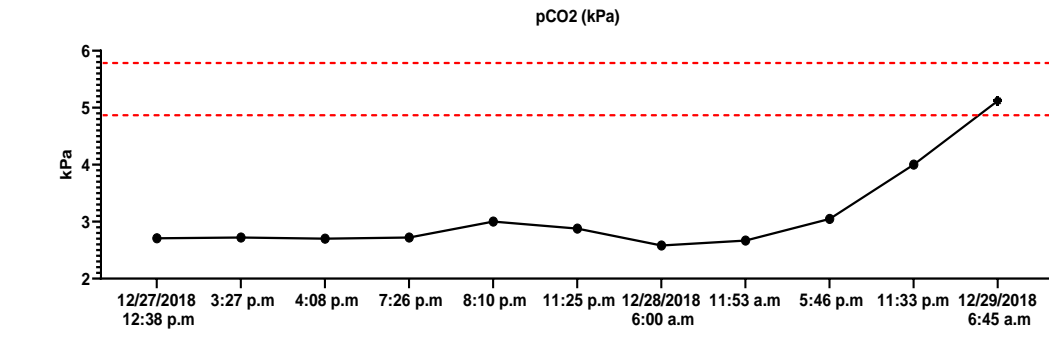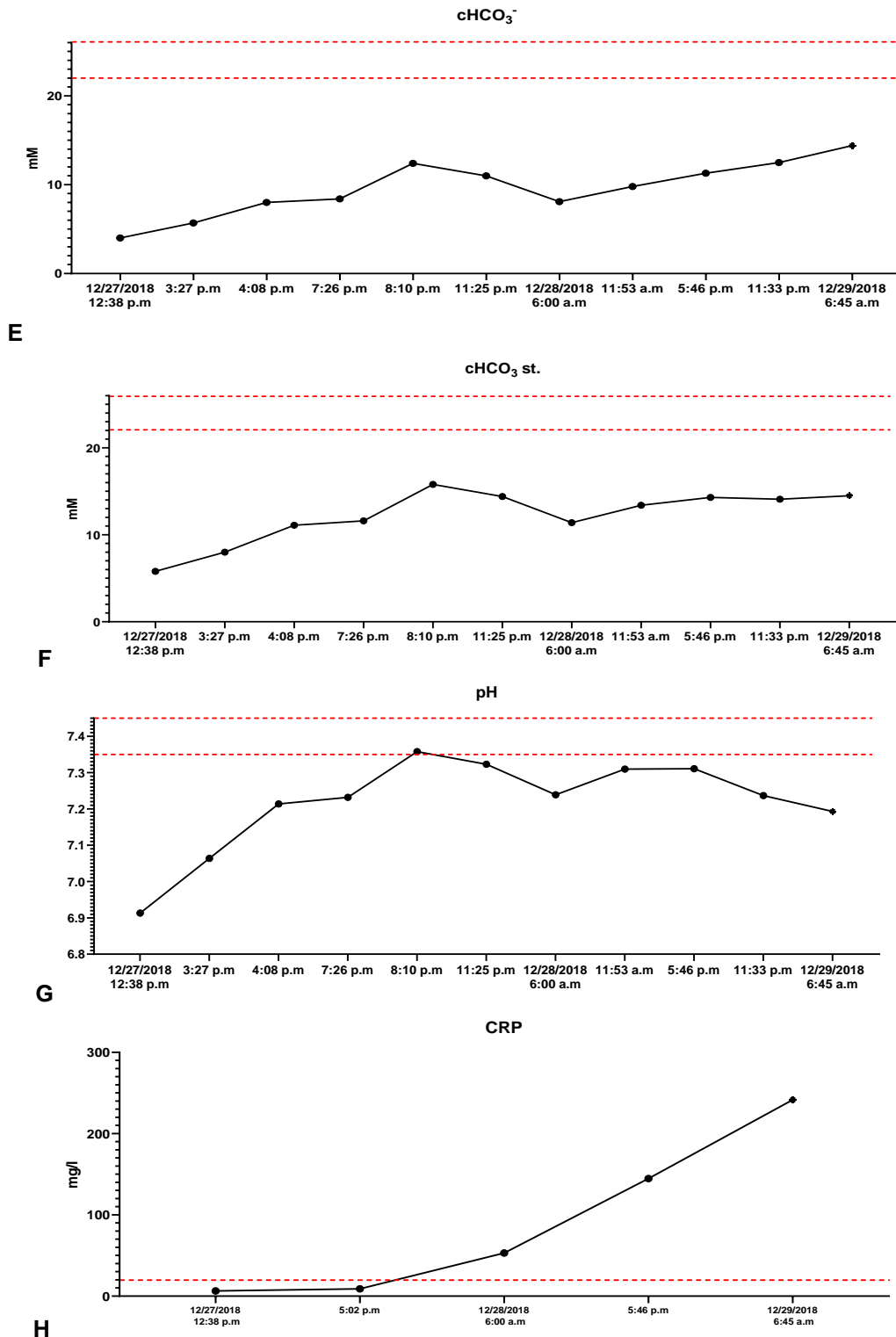
Graph 1. A – Lab tests pCO2 (kPa) [normal values are in the range 4.80 to 5.80]; B - Lab tests pO2 (kPa) [normal values are in the range 9.50-13.90]; C - Lab test – BE (mM) [normal values are in the range -2 to 2]; D - Lab tests – BB (mM) [normal values are in the range 45 to 49]; E - Lab tests – cHCO3 (mM) [normal values are in the range 22.00 to 26.00]; F - Lab tests – cHCO3 st (mM) [normal values are in the range 22.00 to 26.00]; G - Lab tests – pH [normal values are in the range 7.350 to 7.450]; H - Lab tests – CRP (mg/l)

A high anion gap metabolic acidosis was the result of the diagnosis. As a consequence of metformin intoxication, the lactate level elevated (24 mM).

We started the treatment with 500 ml 4.2% bicarbonate infusion, omeprazole 40 mg and metoclopramide IV 10 mg. On account of hypotension, norepinephrine was moreover given, followed by empiric antibiotic treatment (cefotaxime 2 g). The patient was admitted to the Intensive Care Unit (ICU). The therapy continued with rehydration and bicarbonate infusions (1000 ml of 4.2% $NaHCO_3$, 1500 ml of FR 1/1), vasopressor support of norepinephrine.

2.5 The Therapeutic Intervention

Because of the intoxication and severe metabolic acidosis, we indicated urgent hemodialysis. Dialysis has lasted for 8 hours, with ultrafiltration of 400 ml. As a result of the hypotension, the norepinephrine dose (to 0.3 µg/kg/min) was necessary to increase. As the next step, an infusion of 20% glucose was continuously administered intravenously to maintain normoglycemia. Due to the progressing of acute renal failure, another hemodialysis was identified.

On the next day, inflammation markers increased (CRP: from 6.40 to 241.68 mg/L), and also there was an elevation of amylases (39.53 mkat/l) and lipases (60.58 mkat/l). We construed it as drug-induced pancreatitis, which is also described for metformin overdoses.

2.6 Follow-up and Outcomes

On December 29th, 2018, in the morning hours, an asystole occurred. For that reason, cerebral cardiopulmonary resuscitation (CPCR) was initiated. There was only electromechanical dissociation despite twenty-five minutes of effort without a palpable pulse present, and the patient passed away. The patient died 2.5 days after intoxication and 1.5 days after admission to the hospital of multiple organ failure, although we had provided aggressive management, including continuous renal replacement therapy.

3. DISCUSSION

In a large study of metformin-treated patients with lactic acidosis, 55 percent of patients survived, with a median arterial lactate level of 13.1 mM in these individuals. In this group of metformin-treated lactic acidosis patients, neither arterial lactate levels nor plasma metformin concentrations were associated with mortality. Instead, death in these patients appeared to be linked to other hypoxia diseases or underlying health problems [4].

Some other case reports referred to fatal metformin intoxication also despite aggressive treatment together with ECTR [5]. If patients appear with a wide anion gap metabolic acidosis after committing suicide by ingesting medicines, metformin poisoning should be suspected. With other supportive treatment, haemodialysis or continuous renal replacement therapy should be started as soon as possible.

Patients who died from an acute metformin overdose showed lower serum pH nadirs and greater peak serum lactate and metformin concentrations than those who lived [6].

Although our patient's clinical problems combined metformin and gliclazide poisoning, there concluded in anion gap metabolic acidosis, renal failure, and drug-induced pancreatitis. Drug-induced pancreatitis (DIP) is thought to be a rare complication, with incidence rates ranging from 0.1 to 2% of all acute pancreatitis cases [7] and [8]. The true prevalence of DIP, however, remains uncertain. Clinical trials have yielded very little data. The absence or insufficiency of diagnostic criteria for acute pancreatitis, failure to exclude out common etiologies of acute pancreatitis, and lack of a re-challenge test have all reduced the number of cases reported. Metformin is one of the most commonly given oral hypoglycemic medicines, although it has been connected to pancreatitis, either as a result of an overdose or in the case of renal impairment [9,10]. If not used in the context of contraindications such as renal failure, liver illness, alcohol misuse, or congestive heart failure, this medicine is considered safe [11].

In our case, there was present a combination of metformin overdose and renal failure. The exact pathomechanism is unknown, but toxicity is probably secondary to acinar cell injury leading to intercellular leakage of digestive enzymes from ductules [12].

Sulphonylureas, another commonly prescribed medication class, have also been linked to severe pancreatitis. In a French gastrointestinal publication, the majority of case reports and

population-based case-control studies of DIP were potentially connected to glimepiride, with one possibly due to gliclazide [11,13,14].

3.1 Patient Perspective

Our patient took the combination of metformin and gliclazide poisoning, there concluded in anion gap metabolic acidosis, renal failure and drug-induced pancreatitis with fatal results.

4. CONCLUSION

Metformin and gliclazide are effective antidiabetic drugs in patients with type 2 diabetes mellitus. Although antidiabetics are not commonly used for intoxication in suicide attempts, our case report describes fatal intoxication with metformin and gliclazide. The message is to remember the risk of daily used antidiabetic drugs – in high doses, in combinations, they can lead to pancreatitis, renal failure, or so long-known lactic acidosis.

CONSENT

Instruction and informed consent of the patient following § 6 of Act No. 576/2004. The patient obtained written informed consent for publication of this case report and any accompanying images.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mardini J, et al. Case reports of extracorporeal treatments in poisoning: historical trends. Semin Dial. 2014;27(4): 402-6.
2. Calello DP, et al. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. Crit Care Med. 2015;43(8): 1716-30.
3. Barracca A, et al. Acute renal failure after massive ingestion of gliclazide in a suicide attempt. Renal Failure. 1998;20(3):533-537.
4. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. Drug Saf. 1999; 20(4):377-84.
5. Chang CT, et al. High anion gap metabolic acidosis in suicide: Don't forget metformin intoxication--two patients' experiences. Ren Fail. 2002;24(5):671-5.
6. Dell'Aglio DM, et al. 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(6):818-23.
7. Nitsche CJ, et al. Drug-induced pancreatitis. Best Pract Res Clin Gastroenterol. 2010;24(2):143-55.
8. Wolfe D, et al. Methods for the early detection of drug-induced pancreatitis: a systematic review of the literature. BMJ Open. 2019;9(11):e027451.
9. Alsubaie S, Almalki MH. Metformin induced acute pancreatitis. Dermato-Endocrinology. 2013;5(2):317-318.
10. Giorda CB, et al. A systematic review of acute pancreatitis as an adverse event of type 2 diabetes drugs: From hard facts to a balanced position. Diabetes, Obesity and Metabolism. 2014;16(11): 1041-1047.
11. Patrick Nisse, Monique Mathieu-Nolf, Marc Deveaux, Xavier Forceville & Alain Combes. A fatal case of metformin poisoning. Journal of Toxicology: Clinical Toxicology. 2003;41(7):1035-1036. DOI: 10.1081/CLT-120026533

    Mallick S. Metformin induced acute pancreatitis precipitated by renal failure. Postgrad Med J. 2004;80(942):239-40.
12. Krentz AJ, Patel MB, Bailey CJ. New drugs for type 2 diabetes mellitus: What is their place in therapy? Drugs. 2008;68(15): 2131-62.
13. Avcı D, Çetinkaya A, Karahan S, Oğuzhan N, Karagöz H, Başak M, Erden A. Suicide commitment with metformin:

Our experience with five cases. Ren Fail. 2013;35(6):863-5. DOI: 10.3109/0886022X.2013.801299. Epub 2013 Jun 6. PMID: 23742066.

14. Suchard JR, Grotsky TA. Fatal metformin overdose presenting with progressive hyperglycemia. The Western Journal of Emergency Medicine. 2008;9(3):160–164.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/85630