Case study

Fatal intoxication with metformin and gliclazide – "case report"

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).

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.

Keywords: intoxication, metformin, gliclazide, case report

Introduction

Metformin can accumulate lactate in patients with hepatic or renal failure or in patients who eat a high dosage of drugs (suicide attempt). Metformin toxicity, a challenging clinical entity, is associated with a mortality of 30%. Metformin poisoning can cause severe toxicity, including death. Various treatments are used, in particular extracorporeal treatments (ECTRs) such as hemodialysis and hemofiltration. Indeed, a recent literature review noted that metformin poisoning was the most common toxicological indication for ECTR [1]. Metformin poisoning with lactic acidosis appears to be amenable to extracorporeal treatments. [2]

Gliclazide, a sulfonylurea molecule, is used to control glycemia in patients with diabetes mellitus type II. Acute and chronic toxicity studies with gliclazide, conducted in various animal species, have demonstrated very low toxicity. The LD50 was calculating 330 – 1300 times greater than the dose administered to humans [14]. 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 [6]. In the case report [14] 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.

Case presentation

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.

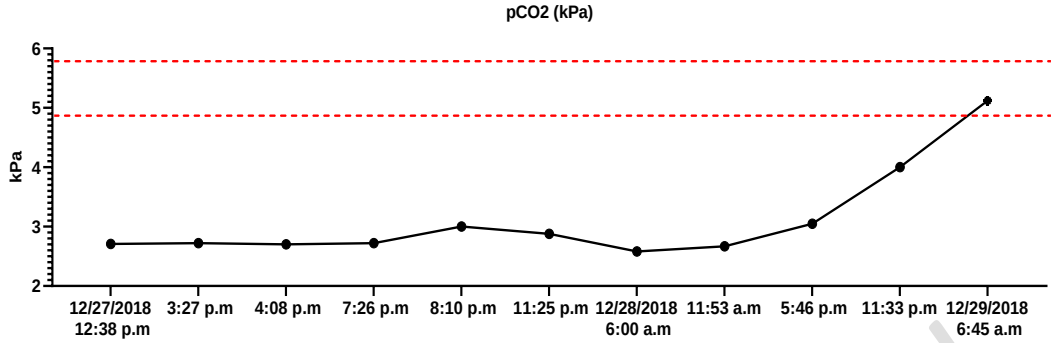
Clinical Findings

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 27th2018), 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.

Diagnostic Assessment

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

Lab tests



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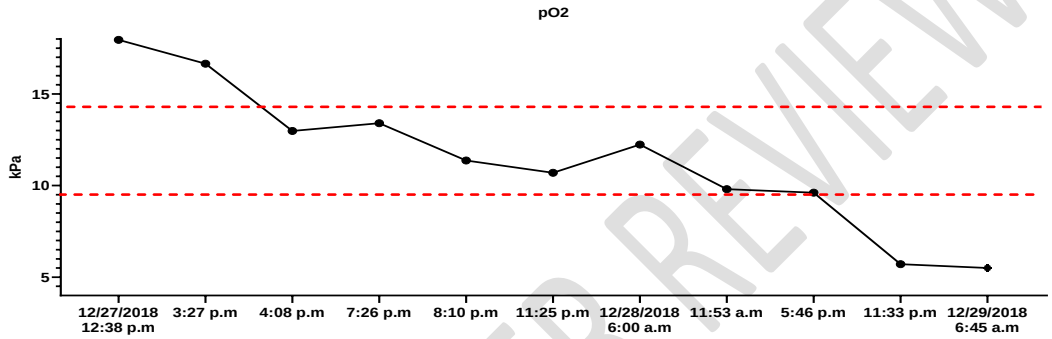

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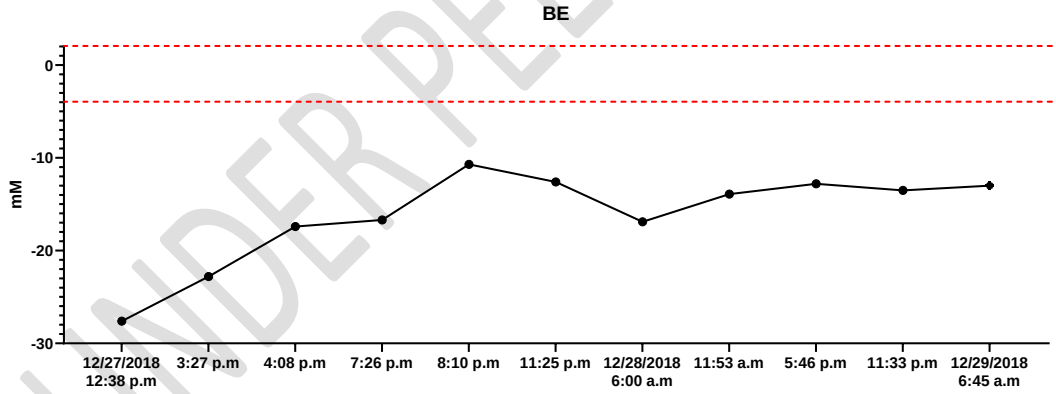

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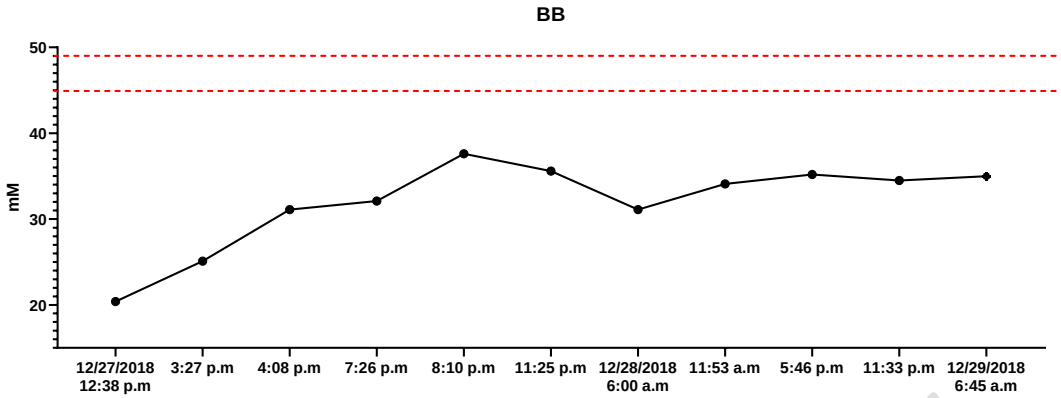

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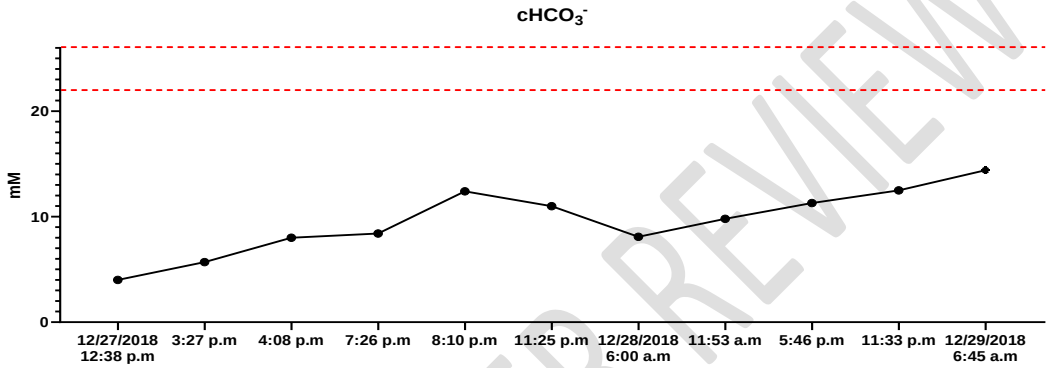

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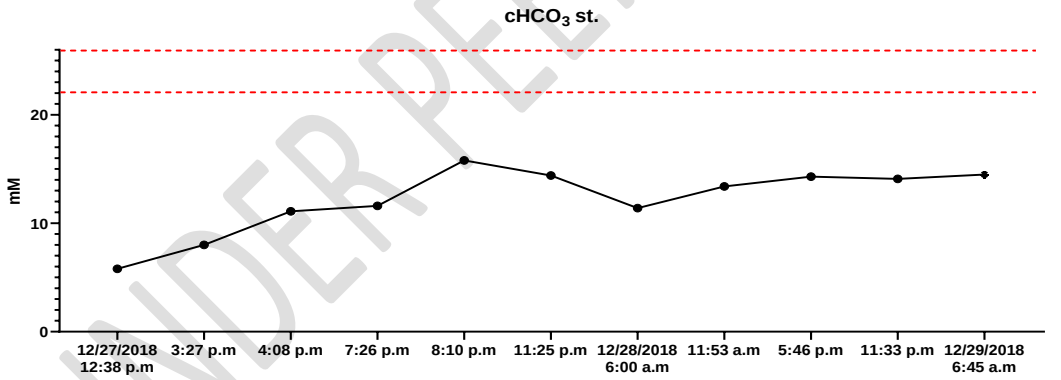

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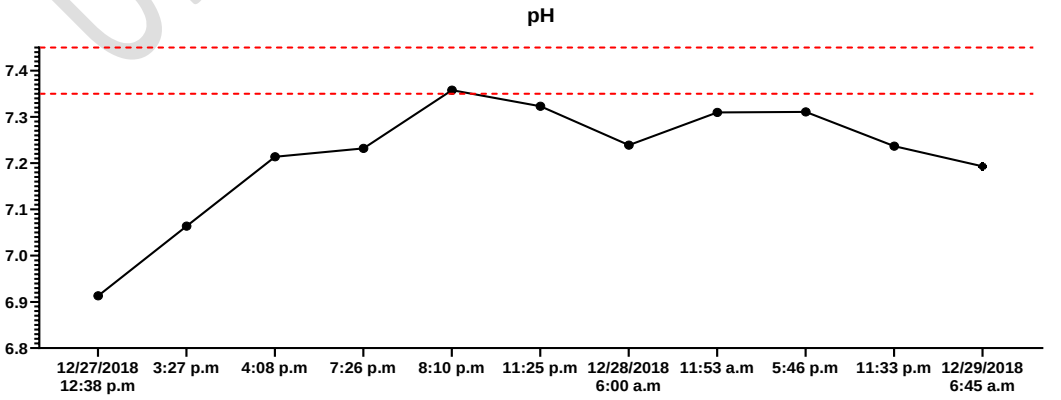

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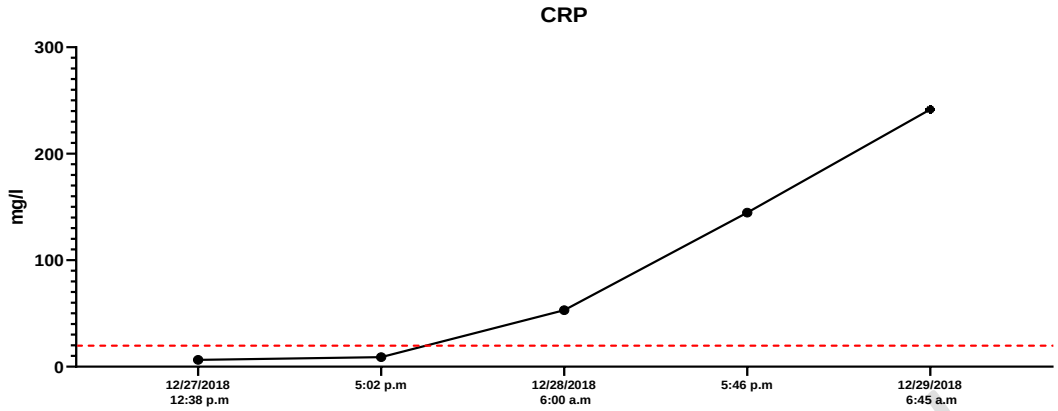

Graph 1: A – Lab tests pCO2 (kPa) [normal values are in the range 4.80 to 5.80]; B - Lab tests pO2 (kPa) [normal values are in the range 9.50-13.90]; C - Lab test – BE (mM) [normal values are in the range -2 to 2]; D - Lab tests – BB (mM) [normal values are in the range 45 to 49]; E - Lab tests – cHCO3 (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.

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.

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.

Discussion

In an extensive series of metformin-treated patients with lactic acidosis reported, 55% of patients survived, and these patients had a median arterial lactate level of 13.1 mM. Neither arterial lactate levels nor plasma metformin concentrations were of prognostic significance concerning mortality in this sample of metformin-treated patients with lactic acidosis. Death in these patients appeared instead to be associated with other hypoxic diseases or underlying ill-health. [3]

Some other case reports referred to fatal metformin intoxication also despite aggressive treatment together with ECTR. [4] Metformin intoxication should be highly suspected if patients have presented with a wide anion gap metabolic acidosis after a suicide by taking drugs. Haemodialysis or continuous renal replacement therapy should be initiated as soon as possible with other supportive care.

Patients with acute metformin overdose who died had much lower serum pH nadirs and much higher peak serum lactate and metformin concentrations than those who survived. [5]

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 assumed to be a relatively rare entity, and its incidence is reported between 0.1 and 2% of acute pancreatitis cases. [7, 8] However, the true incidence of DIP is still unknown. Little evidence has been obtained from clinical trials. Most incidences have been documented as case reports generally limited by the absence or inadequacy of diagnostic criteria for acute pancreatitis, failure to rule out common etiologies of acute pancreatitis, and lack of a re-challenge test.

Metformin is one of the most widely prescribed oral hypoglycemic agents, linked to pancreatitis, secondary to overdose, or in case of impaired renal function. [9, 10] This medication is safe if not used in the presence of contraindications - renal failure, liver disease, alcohol abuse, or congestive heart failure [13].

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. [11]

Also, sulphonylureas, another widely prescribed drug class, has been implicated in causing acute pancreatitis. Most case reports and population-based case-control studies of DIP were possibly related to glimepiride, and another possibly due to gliclazide were published in a French gastroenterology journal. [12]

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.

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.

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

DECLARATION

ETHICS APPROVAL – Not applicable
CONSENT FOR PUBLICATION - 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. A copy of the written permission is available for review by the Editor-in-Chief of this journal.
AVAILABILITY OF DATA AND MATERIAL - Not applicable

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