Case Report **Open Access**

Pancreatitis and Metformin: Case-Report and Review of Literature

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Abstract

Metformin is the most used anti-hyperglycemic agent for the treatment of Type 2 Diabetes Mellitus. It is considered a very good drug, with low risk and high benefit. Metformin intoxication can be due to massive ingestion or to a progressive accumulation due to renal failure. Fatal cases due to metformin intoxication have been described. With regard to that we present a fatal case of a fifty-six-year-old patient with severe metformin intoxication (100 μg/ml) who presented kidney failure, lactic acidosis, hyperglycemia and pancreatitis. He received alkalinization and hemodialysis therapy, afterwards which shortly hereby improved his condition, but the patient deceased after 7 days for a nosocomial pneumonia. Pancreatitis was confirmed by the post-mortem histopathological analysis.

Acute pancreatitis as side effect of metformin is very rare, either in overdose or therapeutic dosage, and it has been attributed to an intrinsic toxicity mechanism. With regard to that, we performed a review of the literature of all cases in which pancreatitis was referred to metformin use in order to evaluate if this complication usually develops in presence of specific predisposing factors, or if it is unpredictable.

From our review, according to the literature, we confirm that acute pancreatitis represents a very rare side effect of metformin, either in therapeutic dosage or overdose. In metformin intoxication, polypharmacy and high doses might be possible risk factors in order to develop pancreatitis.

There is not a specific association of metformin related pancreatitis and hyperglycemia, even if pancreatitis is generally linked to glucose homeostasis alterations. It is possible to assume that the presence of hyperglycemia depends on the extent of pancreatitis that if much extended could lead to a deficit of insulin release and to an increase of blood glucose levels.

Keywords: Metformin; Intoxication; Pancreatitis; Metformin associated lactic acidosis: Hyperglycemia; Acute kidney injury

Introduction

Metformin is the most used anti-hyperglycemic agent for the treatment of Type 2 Diabetes Mellitus. It is considered a very good drug, with low risk and high benefit, if prescribed in the right clinical condition. It allows a good control of diabetes and lowers blood triglycerides of 15% to 20%, without any weight gain and without impairing the glucose level [1]. These effects are the result of inhibition of hepatic gluconeogenesis and fatty acid oxidation, improving peripheral glucose sensitivity, reducing intestinal absorption and appetite too [1-3]. Acute side effects are reported in about 20% of patients: nausea, abdominal discomfort, metals flavor, anorexia [1].

Metformin intoxication can be due to massive ingestion or to a progressive accumulation due to renal failure. Some conditions, such as kidney failure, heart failure or chronic lung disease, represent contraindications for metformin use, because lactic acidosis may occur, both in overdose and with therapeutic dosing. Indeed, the drug increases lactate production from intestinal mucosae while, at the same time, inhibits the hepatic absorption of lactate and the enzyme pyruvate carboxylase, preventing its clearance [2-4]. Metformin-associated lactic acidosis (MALA) is relatively rare (3-9 cases per 100 000/year), but probably it is underestimated [5] and it is potentially fatal (mortality >50%).

The optimal treatment protocol for MALA is controversial. Initial management of MALA is usually supportive and includes supplemental oxygen as well as airways and ventilator support. Intravenous crystalloid should be administered in early phases to resuscitate hypotensive patients. Vasopressors should be given to patients who are unresponsive to fluid administration. Identification and treatment of underlying conditions that may have contributed the development of MALA is of paramount importance. The use of intermittent hemodialysis may be protective, and it is recommended by many intensivists. Some general recommendations to start dialytic treatment areas it follows: 1) lactate concentration greater than 20 mmol/L, 2) pH less than or equal to 7.0, 3) shock, 4) decreased level of consciousness, and 5) failure of other standard supportive care.

Fatal cases due to metformin intoxication have been described. With regard to that we present a peculiar autopsy case of metformin intoxication with ante-mortem laboratory suggestive of pancreatitis. Pancreatitis was moreover confirmed by the post-mortem histopathological analysis. We perform a review of literature about the cases where pancreatitis is related to metformin use, in order to evaluate if this complication usually develops in presence of specific predisposing factors, or if it is unpredictable.

Case Report

On 5th of January 2013 at about 8 AM a fifty-six-year-old prisoner, was found unconscious on his cell-floor. His clothes were soiled with vomit and he had glucose fingerstick level of 140 mg/dl.

He suffered from Type 2 Diabetes Mellitus and some psychiatric diseases; he was treated with metformin, pregabalin, and benzodiazepines as needed. He had a history of prior self-harm attempts.

He was soon taken to the Emergency Department (9:00 AM) where he arrived unconscious (GCS 4), with hypothermia, blood pressure 70/40 mmHg, pulse 50 beats per minute, atrial fibrillation, and normal respiration rate. Blood analysis were performed and showed kidney failure (creatinine 3.2 mg/dl, urea 67.0 mg/dl), severe metabolic acidosis (PH 6.91, lactate>20 mmol/l), acute pancreatitis (amylase 2050 U/L, lipase 114 U/L). Moreover he had a further increase of the level of hyperglycemia (blood glucose from 140 mg/dl to 177 mg/dl). Urine drug test was negative for methadone, opiates, cannabinoids, cocaine, amphetamines, benzodiazepines. The ECG showed atrial fibrillation with low ventricular response and long QT, which was already known on his history. The cranial and cervical CT did not reveal any alteration. Abdominal ultrasound was negative for gallstones.

At 11:00 AM the patient was admitted to the Intensive Care Unite, where he started a dialytic treatment (Continuous Veno-Venous HemoDiafiltration - CVVHDF), bicarbonate infusion, IV hydration (0.9% saline, 150 ml/h) and a continuous infusion of norepinephrine.

Before the beginning of the hemodialysis some blood samples were obtained and stored at -20°C. The CVVHDF temporarily improved the metabolic acidosis, but then the patient's condition got worst and he therefore received endotracheal intubation.

Three Ranson's Criteria (age in years >55; WBC count >16000 cells; serum LDH >350 IU/L) were present at admission; two Ranson's Criteria (Serum calcium <2.0 mmol/L; arterial pO_2<60 mmHg) were present within 48 hours after the admission. According to Ranson's Criteria the estimated mortality was 40%.

On the fourth day, the metabolic and hemodynamic state was still unstable and fever 38.8°C appeared. The sixth day the patient developed dyspnea and several bradycardic and pulseless electrical activity episodes. At first he was resuscitated, but he deceased the next day.

Forensic autopsy was performed 48 hours later. The autopsy revealed red hepatization of lungs and abundant adipose infiltration of the pancreas. Organ and body fluid samples were taken for further histological and toxicological analysis. Specimens from the organs were embedded in paraffin and 4 micrometer thick sections were cut and stained with hematoxylin-eosin. Preparation of samples confirmed the hypothesis of acute pneumonia on both lungs and showed some histological features consistent with pancreatitis (Figure 1). The toxicological analysis showed in the ante-mortem blood (samples taken before dialysis treatment) metformin in concentration of 100 µg/ml and, in the post-mortem blood, traces of metformin. In the pre-dialytic blood pregabalin was found too, but only traces of it. The cause of death was due to an acute pneumonia in a comatose patient, who had arrived at the Emergency Department with severe metformin intoxication.
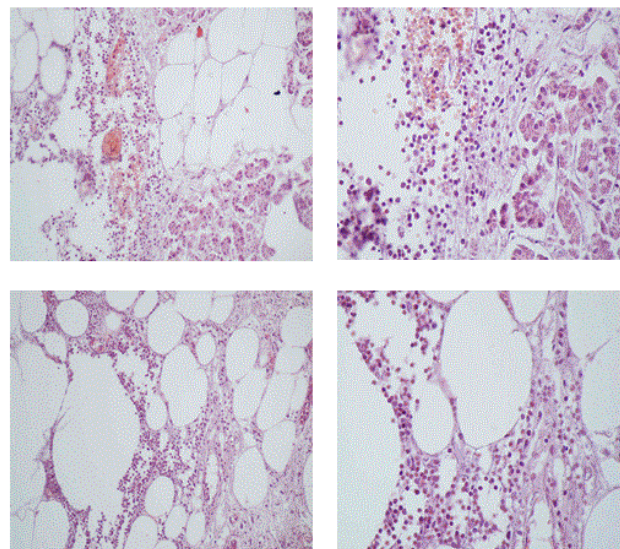

Figure 1: Histological aspects of pancreatitis.

Discussion

Our case presented with severe metformin intoxication (100 µg/ml), kidney failure, pancreatitis lactic acidosis and hyperglycemia.

It was impossible to get an accurate history and to state if the metformin intoxication was due to an acute intake of a large metformin dose (compatible with the history of self-harm) or to a progressive drug accumulation due to a previously unknown renal failure. The same kidney failure was a riddle: it might have caused the metformin accumulation, or the same metformin intoxication might have triggered the organ failure. In fact acute kidney injury (AKI) has been described as consequence of metformin overdose especially due to fluid loss such as in vomiting or diarrhea [6].

Acute pancreatitis typically presents with epigastric pain irradiated to the back, nausea, vomit and increased level of pancreatic serum enzymes (amylase and/or lipase) [7]. Around 80% of cases are caused by alcohol abuse or gallstones; about 2% are due to drugs. Since our patient presented unconscious at the Emergency Department, it was impossible to investigate the typical symptoms, but the pancreatitis was proved by the laboratory analysis and the post-mortem examination. During the stay, the most common etiologies were investigated. When the patient was in jail he did not have access to alcohol; the hypothesis of gallstones was refused thanks to ultrasound examination; there was no evidence of hypercalcemia, hypertriglyceridemia or trauma.

Beside metformin, our patient was taking pregabalin, and benzodiazepines. Benzodiazepines were not identified by the toxicological analysis and pregabalin was identified, but only in traces. Pregabalin was not responsible for pancreatitis because it is not linked to this side effect and moreover it is an effective adjuvant to reduce pain in patients with chronic pancreatitis [8].

The acute pancreatitis relative risk for patients with Type 2 Diabetes Mellitus is two-threefold, because of obesity, hypertriglyceridemia and gall bladder disease [9-11]. These illnesses can hide the role of drugs in cause or contribute to acute pancreatitis [10,12], but a recent study

showed that patients who use metformin, sulfonylureas, thiazolidinediones or α-glucosidase inhibitors have a lower incidence of this complication, compared to those treated with a different therapy [11].

Acute pancreatitis as side effect of metformin is very rare, either in therapeutic dosage or overdose, and it has been attributed to an intrinsic toxicity mechanism. With regard to that, we performed a review of the literature in order to report all cases in which pancreatitis was referred to metformin use (Table 1).

Case	Sex Age (Y)	Medication History	Supposed Toxicity from	Metformin Accumulation/ Overdose	Metabolic Acidosis (Y/N)	Pancreatitis (Clinical/ Tomographic Signs)	Serum Amylase (UI/L)/ Lipase (UI/L)	Glycemia (mg/dl)	Rechallenge (+/-)	Death (Y/N)	Year of Publication, Authors
1	F 21	• Daily ethanol and tobacco use • 45 g of Metformin once	Metformin	Intentional overdose	Y	(+/+)	121/724	23 → 2 h after: 25	/	N	2002, Ben et al. [13]
2	F 61	• Aspirin, Atenolol, Clopidogrel, Amlodipine, Lisinopril, Nitrate, Metformin, Nateglinide, Ibuprofen (all stopped from 4 days because of vomiting, except the antidiabetic drugs)	Metformin	Accumulation caused by KF	Y (↑lactate)	(+/+)	250/NA	162	/	N	2004, Mallick [14]
3	F 61	• Fluvastatin (80 mg/day), Metformin (3 g/day)	Metformin	Accumulation caused by KF	Y (normal lactate)	(+/+)	270/1.813	NA	/	N	2006, Fimognari et al. [15]
4	F 74	• Metformin (750 mg/8 h), Glibenclamide (5 mg/8 h)	Metformin	Accumulation caused by KF	Y (↑lactate)	(+/+)	2.605/NA	214	/	N	2006, Ortega Carincer et al. [16]
5	F 50	• L-thyroxine, Metformin, Acetaminophen/Codeine, Aspirin, Simvastatin, Omeprazole, Pregabalin, Tizanidine, Candesartan, Hydrochlorothiazide, Aripiprazole • In the last 2 months: Celecoxib	Metformin	Accumulation caused by KF	Y (↑lactate)	(+/-)	403/275	42 → ½ h after: <40	/	N	2008, Audia et al. [17]
6	M 29	• Daily ethanol and tobacco use • Between 64 g and 85 g of Metformin once with ethanol	Metformin Ethanol	Intentional overdose	Y (↑lactate)	(+/NA)	NA/NA	180 → 1 h after: 707	/	Y	2008, Suchard and Grotsky [2]
7	F 22	• Past 3 years: Fluvastatin, L-thyroxine • In the last 48 h: Metformin (850 mg/8 h)	Metformin	No accumulation No overdose	Y (↑lactate)	(+/+)	1.023/2.142	Normal, NA	/	N	2008, Molina Infante et al. [18]
8	M 19	• Metformin (2 g/day)	Metformin	No accumulation No overdose	N	(+/+)	462/1.378	NA (HbA1c 7.7%)	+	N	2013, Alsubaie and Almalki [19]
9	F 54	• Enalapril, Metformin, Glimepiride, Nimesulide, Imipramine, Aspirin, Ibuprofen	Metformin	Accumulation caused by KF	Y (↑lactate)	(+/+)	386/595	168 → 17 h after: 316	/	N	2013, Kalantar-Zadeh et al. [20]
10	M 56	• Metformin(1.5 g/day), Pregabalin, benzodiazepines if needed	Metformin	NA	Y (↑lactate)	(NA/NA)	2.050/114	140 → 1 h after: 177	/	Y	present case

For each patient appropriate exams excluded obesity, hypertriglyceridemia and gallstones; h, hours; KF, Kidney Failure; NA, data not available

Table 1: Review of the international medical literature: cases of metformin intoxication associated to acute pancreatitis.

We found nine cases, the oldest one was published in 2002 and the most recent in 2013. Patients were both male and female. We also found a wide variation between the age of the subjects (the youngest was 21 and the oldest 74 years old).

Among the nine cases we found that metformin intoxication was due to an intentional overdose in two cases and in five cases was due to a progressive accumulation caused by renal failure.

The two cases (no- 7 and 8) in which there was no overdose or kidney failure, had affected young patients without comorbidities: it is probably due to an individual susceptibility, since it happened in good clinical conditions, Type 2 Diabetes Mellitus apart from, and the rechallenge was positive for the case no-8.

Patient no. 8 didn't present lactic acidosis: many authors hypothesized that metformin intoxication isn't sufficient to determine metabolic acidosis without other risk factors[5,19].

In all cases metformin has been responsible for the rare adverse effect of pancreatitis, but most patients had taken many drugs and we could not exclude their contribute. Polypharmacy is very common, especially for old patients, and it can lead to harmful interactions [20]. For example, all statins are known to cause acute pancreatitis, such as most of ACE-inhibitors, some NSAIDs, amlodipine, hydrochlorothiazide and acetaminophen [21]. Albeit polypharmacy may represent a risk factor for the development of pancreatitis, our sample size is too small for such a considerations.

Metformin increasing dose has been associated to a higher risk of acute pancreatitis [22]. In the cases reporting this information, the maximum metformin recommended was 2500 mg/die or even higher.

Only one patient died after a suicide attempt; our patient deceased, too but he presented very severe clinical conditions and negative prognostic factors (the coma state and the cardio-circulatory shock) [14], which rendered all therapies ineffective. Even if the mortality rate for lactic acidosis is about 50% [23] and for acute pancreatitis is 2% to 5% [11], the review shows that a timely and appropriate therapy against metformin intoxication allows a good recovery of patient's condition.

With regard to glucose blood level only in seven cases blood glycaemia was specified: high level in four cases, low in two and normal in one.

Blood glucose level is not commonly impaired by metformin in therapeutic dosages. Hypoglycemia may be attributed to metformin intoxication [24] while hyperglycemia may be linked to the acute pancreatitis, responsible of low insulin production [2,25].

Anyhow our review shows that metformin related pancreatitis is not always associated with hyperglycemia (presented in our case). It is possible to assume that the presence of hyperglycemia depends on the extent of pancreatitis that if much extended could lead to a deficit of insulin release and to an increase of blood glucose levels.

In conclusion our small case history confirms that pancreatitis is a very rare side effect of metformin. Previous literature considered metformin induced acute pancreatitis an unlikely event given therapeutic drug dose and normal renal functioning. Otherwise our review shows that this complication should be taken in consideration.

That being said no risk factor has been established with certainty. In metformin intoxication, polypharmacy and high doses might be possible risk factors in order to develop pancreatitis. This is compatible with the fact that the exact mechanism is unknown, but toxicity may probably secondary to acinar cell injury leading to intercellular leakage of digestive enzymes from ductules.

Furthermore we found that there is not a specific association of pancreatitis with hyperglycemia, even if pancreatitis is generally linked to glucose homeostasis alterations.

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