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Metformin-associated lactic acidosis requiring hospitalization. A national 10 year survey and a systematic literature review

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Abstract. – BACKGROUND: Metformin is known to be rarely associated with lactic acidosis, a serious condition with a poor prognosis.

AIM: To review the National Pharmacovigilance Network of the Italian Medicines Agency reporting cases of metformin-associated lactic acidosis.

MATERIALS AND METHODS: The National Pharmacovigilance Network of the Italian Medicines Agency, was searched for cases of lactic acidosis that occurred in a 10 years period (from November 2001 to October 2011). Data were analyzed, to identify associated clinical features. A systematic literature research was performed to identify other large case series on metformin associated lactic acidosis.

RESULTS: Metformin was the antidiabetic drug most frequently associated with lactic acidosis in the assessed period. Metformin-associated lactic acidosis was the most frequent serious adverse reaction related to metformin reported to the national authority (18.2% of all 650 adverse drug reactions reported). There were 59 cases of metformin-associated lactic acidosis (mortality rate of 25.4%). In most patients (89.8%) there was at least one risk factor for the occurrence of lactic acidosis. The predictors of death were low arterial blood pH and absence of acute renal failure. The systematic research of the literature identified only six case-series with more than 30 patients.

CONCLUSIONS: This is the second largest case series ever reported on metformin-associated lactic acidosis. We confirmed that this rare complication of metformin is frequently fatal. Death can be predicted when the patient arrive in the hospital with low pH and, not intuitively, if the patient has no acute kidney injury. Risk minimisation measures taken at national level to prevent this serious complication are described.

Key Words:
Metformin, Intossication, Intensive care, MALA, Acute kidney injury.

Introduction

Metformin is a commonly used drug, featuring advantageous pharmacological profile. Both the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD), the American Association of Clinical Endocrinologists (AACE) and the treatment guidelines of the American College of Endocrinology (ACE), recommend starting metformin in most patients with diagnosis of type 2 diabetes mellitus (DM2)[1] as first line treatment after lifestyle measures failure[2]. Unlike the sulfonylureas, metformin is not associated with hypoglycaemia or weight gain[3] and it exerts beneficial effects on circulating lipids linked to reduced fatty liver[4].

Metformin is a biguanide that acts as insulin-sensitizer. The antihyperglycemic properties of metformin are mainly attributed to suppressed hepatic glucose production, and increased peripheral tissue insulin sensitivity[5]. It doesn't bind to plasma proteins and doesn't undergo hepatic metabolism, being excreted unmodified by kidneys[6]. Its elimination half-life in healthy patients ranges from two to eight hours, being considerably longer in the end stage renal disease. Urinary clearance ranges from about 500 ml/min in healthy subjects to over than 1000 ml/min in diabetic patients with good renal function; hemodialysis clearance is 170 ml/min[6,7].

A rare but potentially lethal (10 to 45%)[8,9] adverse reaction is the development of high anion gap metabolic acidosis with high circulating lactates level in the absence of hypoperfusion (Type B2 in the Cohen and Woods' classification)[10], also called Metformin Associated Lactic Acidosis (MALA). It usually develops in the presence of other factors affecting its clearance or energy metabolism such as altered renal function, conges-

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tive heart failure, dehydration, hepatic and respiratory failure, concomitant medications (non steroid anti inflammatory drugs, angiotensin converting enzyme inhibitors, antiretroviral). Overdose, either accidental or suicidal, is another common cause of MALA[8,9,11-16].

The incidence of MALA widely differs in published studies. A recent meta-analysis, found no evidence of increased incidence of lactic acidosis in patients treated with metformin when compared to other anti-hyperglycemic treatments, in the context of prospective comparative trials and observational cohort studies[17]. Nonetheless, incidence of MALA in less controlled situations (as in general practice), previously reported as 9 per 100,000 person-years, has been recently revalued to 47 per 100,000 person-years and is associated with risk factors for lactic acidosis[15]. Nevertheless, it remains a rare condition, and single case reports and small case series have been reported in literature[8,9,11-13].

The serious episodes of MALA of the last 10 years were extracted from the National Pharmacovigilance Network of the Italian Medicines Agency and has been described the action taken to reduce the incidence of this adverse reaction at the national level.

Materials and Methods

The National Pharmacovigilance Network, a system for data collection and management of suspected adverse reactions of the Italian Medicines Agency, was analyzed for metformin-associated lactic acidosis. The research was conducted following a suspect increase of the MALA reports in patients with type 2 DM.

A systematic review of literature has been performed through a PubMed search on November 1st 2011 with the terms "metformin" and "lactic acidosis" with the aim to include every cases series ever reported on MALA in humans subjects with at least 30 patients.Contacts with experts and backward snowballing (scanning of references of retrieved articles and pertinent reviews) were performed as well. No language restriction were enforced.

In the period from November 2001 (launch of the database) to October 2011 "metformin" and "metformin chloridrate" were investigated. The term lactic acidosis, corresponding to the "metabolism and nutrition disorders" as a systemic organic class, was selected according to the medical dictionary for the regulatory agencies MedDRA. MedDRA version 3.0 was developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

In the extracted data were included the underlying clinical condition, the severity of MALA, concomitant medications and laboratory findings. The causality assessment, was performed according to Naranjo algorithm[18]. The data were shared with scientific societies and associations of physicians and pharmacists. Risk minimisation measures were discussed. In July 2011, AIFA released a safety recommendation. Its diffusion was obtained by the publication on the AIFA web-portal (www.agenziafarmaco.it), the communication through the National Pharmacovigilance Network mail to 20 regional authorities, more than 200 Local Health Authorities, about 100 Hospitals, 43 Research Institutes and through the stakeholders websites and their mailing lists.

The communication provided a reminder to metformin contraindications, and recommended assessing renal function when the drug is prescribed by calculating creatinine clearance (once or twice a year, depending on previously assessed renal function). It reminded the existence of conditions that advice the drug interruption, like dehydration, infections, hypotension or medical interventions like surgery or hyperosmolar contrast agent infusion.

Statistical Analysis

Data were analysed, with STATA 11.1 (StataCorp LP, College Station, TX, USA) and Instat (GraphPad Software inc., La Jolla, CA, USA). Seasonal association was tested with Pearson ^{2}. Clinical and demographical variables were tested as predictors of mortality with Fischer exact test for categorical variables and Mann-Whitney U-Test for continuous variables, a two tailed $p < 0.05$ was deemed as significant.

Results

In the study period there were, overall, 650 metformin related adverse effects with 47 (7.2%) deaths. The most frequently reported adverse effects were MALA (18.2%) followed by diarrhoea

(17.5%), hypoglycemia (12.2%), acute renal failure (8.3%), abdominal pain (6.6%), nausea (6.5%) and vomiting (5.8%).

Metformin was the antidiabetic drug most frequently associated with lactic acidosis in the study period (Table I).

A total of 59 new cases of MALA were reported in the 10 year period November 2001 to October 2011. Eleven further reports from published literature were included in the national database but not considered in the present analysis.

MALA was the most frequent metformin related adverse reaction. All MALA patients required hospitalization and 95% of MALA reports came from hospital physicians as reporters. In this cohort there were statistically significant seasonal variations ($p = 0.030$) with the highest percentage of events occurring in spring (32.2%) and winter (28.7%) and the lowest occurring in autumn (20.3%) and summer (18.6%).

Patients were 68 (SD 10.5) years old (range 35-87) and 61% were females. Mortality rate was 25%, while 42% had a life-threatening scenario and in the remaining 32% of cases there was need of hospitalization or a prolongation of hospitalization. Recovery with sequelae occurred in 28% patients.

Daily dose of metformin ranged from a minimum of 400 mg to a maximum of 3000 mg (median 2000, interquartile range from 1000 to 2250 mg).

Table I. Antidiabetic drugs associated with lactic acidosis in the study period.

Suspected active substances	Percentage
Metformin	71.1%
Glibenclamide/phenformin	15.6%
Glibenclamide/metformin	7.2%
Glimepiride	2.4%
Exenatide	2.4%
Clorpropamide/phenformin	1.2%

Six patients (12%) started metformin less than a month before the reported reaction, while for 12 (23%) of them, MALA occurred after more than ten years from the first metformin prescription (median 3 years, interquartile range 1-7 years). Six out of 12 (50% mortality) patients died among those who developed MALA after more than ten years, vs none of the six patients who had just started metformin ($p = 0.054$). Five out these six patients who recently started metformin had acute renal failure.

In most patients (90%) there was at least one risk factor for the occurrence of lactic acidosis such as comorbidities (e.g. renal failure was present in half of the patients) and concomitant medications (Table II).

The only predictors of death were low arterial blood pH and normal renal function (Table II).

Table II. Sample description including concomitant comorbidities or medications known as risk factors (total exceeds 100% for more than one condition is contemporary present in one patient) and outcome predictors. Fischer Exact test for categorical variables. Mann-Whaitney U test for continuous variables.

Characteristic		Overall population (n = 59)	Died (n = 15)	Survived (n = 44)	*p*-value
Age, mean (SD)	Years	67.9 (10.6)	67.9 (7.5)	67.8 (11.5)	0.7
Daily metformin, mean (SD)	mg	1910 (853)	1913 (751)	1909 (896)	0.9
Arterial pH, mean (SD)		6.97 (0.23)	6.79 (0.14)	7.03 (0.22)	0.032
Lactate, mean (SD)	mmol/l	15.2 (6.6)	19.1 (1.3)	14.6 (7.1)	0.4
Creatinine, mean (SD) (in pt with renal failure, n 30)	mg/dl	7.0 (3.1)	7.7 (3.1)	6.8 (3.2)	0.7
Female sex	n (%)	36 (61%)	10 (67%)	26 (59%)	0.8
Renal Failure	n (%)	30 (51%)	4 (27%)	26 (59%)	0.039
Diuretics	n (%)	20 (34%)	7 (47%)	13 (29%)	0.3
Angiotensin converting enzyme inhibitors	n (%)	15 (25%)	4 (27%)	11 (25%)	0.9
Angiotensin II receptors blockers	n (%)	15 (25%)	2 (13%)	13 (29%)	0.3
Shock	n (%)	9 (15%)	2 (13%)	7 (16%)	0.9
Ventilatory distress	n (%)	7 (12%)	1 (6.7%)	6 (14%)	0.7
Non steroidal anti inflammatory drugs	n (%)	7 (10%)	4 (27%)	3 (6.8%)	0.06
Cardiac disease	n (%)	6 (10%)	3 (20%)	3 (6.8%)	0.16
Diarrhea/vomit	n (%)	5 (8.5%)	1 (6.7%)	4 (9.1%)	0.9
Haepatic failure	n (%)	1 (7%)	0 (0%)	1 (2.3%)	0.9

AIFA published its MALA safety warning on August 4th 2011 on its website and 632 visits in August, 88 in September and 48 in October were recorded.

Our systematic review of the literature,identified 514 papers out of which, 488 from PubMed. Six papers reported more than 30 patients and are summarized in Table III[8,9,11-14].

Discussion

We reported the second largest case series ever reported on MALA using the 10 year experience of the Italian medicines agency database. All adverse reactions caused hospitalization or prolongation of hospitalization and most of them were associated to death (25%) or to important sequelae (28%).

The worldwide prevalence of type 2 DM has risen dramatically over the past two decades. A study published in 2004 estimates that the 2.8% global prevalence of DM in 2000, is expected to raise to 4.4% in 2030[19]. Metformin is a mainstay of type 2 DM therapy, providing numerous beneficial effects, with a good therapeutic index and safety profile[3]. A rare but worrisome adverse reaction, is the development of MALA, associated to a mortality rate ranging from 10 to 45%[8,9]. Intensive management includes alkalinization, bicarbonate buffered hemodialysis (or continuous renal replacement therapy if the patient has hemodynamic instability) to remove the drug and correct the acidosis, vital function support, treatment of underlying conditions[20].

Our systematic review of the literature identified only one case series larger than the present one[14], based on the Toxic Exposure Surveillance System of the American Association Poison Control Centers, and reporting 68 cases of acidosis. In this report there was no description of underlying clinical conditions, the Authors did not report elevation in serum lactate levels and stated that only 20 patients had an elevated anion gap. On top of that, the mortality rate in this case series was very low (13.2%) suggesting that probably only a part of these 68 patients were affected by MALA.

The third largest case series published so far is a report from France, including 49 MALA patients. All patients had at least one risk factor for MALA (acute or chronic renal failure was present in 73% of patients); in 55% of cases more than one risk factor was present. Authors found no association between metformin and lactate concentration in plasma and no association in plasma lactate concentration between survivors and non-survivors. Metformin plasma concentration was higher in survivors[9].

A recent case series by Li Cavoli et al[8], focused on the incidence of metformin associated acute kidney injury in a Nephrology and Dialysis Department, from January 2008 to December 2009, finding MALA as associated condition in all 47 cases reported. Concurrent conditions included gastrointestinal disorders (63%), concomitant therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (63%), or furosemide (31%).

Another case series of 47 patients was published in 1998 by Misbin at al[11]. One or more risk factors for lactic acidosis were present in 91.5% of cases, including congestive heart failure (38%), renal insufficiency (28%), and two patients were already receiving dialysis.

A ten year retrospective analysis of patients admitted in intensive care unit for MALA, was published by Seidowsky et al[12] in 2009. It included 42 cases (13 voluntary intoxications and 29

Table III. Largest case series on metformin-associated lactic acidosis requiring hospitalization.

Author	Country	Journal	Year	Period	Mortality	Risk factors	Nr of patients
Spiller and Quadrani	USA	The Annals of Pharmacotherapy	2004	1996-2000	13%	Not Reported	68
Renda et al.	Italy	Eur Rev Med Pharmacol Sci	2012	2001-2011	25%	89%	59
Lalau and Race	France	Drug Safety	1999	Not Reported	45%	100%	49
Li Cavoli et al.	Italy	American Journal of Emergency Medicine	2011	2008-2009	10%	100%	47
Misbin et al.	USA	New England Journal of Medicine	1998	1995-1996	42%	91%	47
Seidowsky et al.	France	Critical Care Medicine	2009	1998-2007	33%	69%	42
Peters et al.	France	Critical Care	2008	2002-2007	30%	100%	30
Total							**283**

accidental). All patients in the suicidal group survived to the acidosis, while mortality in accidental intoxication group was 48.8%.

A common feature of the above described case series is that the associated condition precipitating MALA seems to carry a stronger prognostic effect on survival than metformin dosage or accumulation due to impaired elimination.

Mortality in MALA patients ranged between 10.8% and 45% in the largest case series reported and being 25.4% in our report. Therefore, it can be confirmed that MALA is frequently fatal. Counter intuitively, mortality was significantly lower in patients presenting with renal failure.

This data confirm that accumulation of the drug is less dangerous than other coexisting risk factors for lactic acidosis. Another important point of our manuscript is to confirm that most MALA are associated to an inappropriate use of metformin in patients with risk factors for lactic acidosis. Metformin prescription or assumption despite the presence of contraindications or precipitating factors for MALA is a common problem in all papers reviewed. It should be highlighted that the present manuscript describes for the first time the adoption of risk minimization measures performed by a national medicine agency.

Conclusions

MALA is a rare but fatal complication of metformin treatment and most of the times is associated to comorbidities and risk factors. Mortality was associated to the extent of acidosis while acute renal failure was associated to a low mortality in our case series of 59 MALA patients, suggesting that accumulation of metformin is less important than other coexisting risk factors. We reported for the first time an increased number of MALA during the spring season and we also report the adoption of risk minimization strategies by a national medicines agency.

References

1) Kruger DF, Boucher JL, Banerji MA. Utilizing current diagnostic criteria and treatment algorithms for managing type 2 diabetes mellitus. Postgrad Med 2011; 123: 54-62.
2) Schroner Z, Javorsky M, Kozarova M, Tkac I. Pharmacogenetics of oral antidiabetictreatment. Bratisl Lek Listy 2011; 112: 441-446.
3) United Kingdom prospective diabetes study group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352: 854-865.
4) Marchesini G, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. Lancet 2001; 358: 893-894.
5) Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med 2002; 137: 25-33.
6) Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 1996; 30: 359-371.
7) Parke C, Lien YH. Profound metabolic acidosis and abdominal pain in a diabetic patient on long-term hemodialysis. Am J Kidney Dis 2011; 57: A25-27.
8) Li Cavoli G, Tortorici C, Bono L, Giammarresi C, Ferrantelli A, Zagarrigo C, Schillaci O, Tralongo A, Rotolo U. Acute kidneyinjuryassociated with metformin. Am J Emerg Med 2011; 29: 568-569.
9) Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Drug Safety 1999; 20: 377-384.
10) Woods HF, Cohen R. Clinical and biochemical aspects of lactic acidosis. 1st Ed. Oxford Blackwell Scientific; 1976.
11) Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA. Lactic acidosis in patients with diabetes treated with metformin. N Engl J Med 1998; 338: 265-266.
12) Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: a prognostic and therapeutic study. Crit Care Med 2009; 37: 2191-2196.
13) Peters N, Jay N, Barraud D, Cravoisy A, Nace L, Bollaert E, Gibot S. Metformin-associated lactic acidosis in an intensive care unit. Crit Care 2008; 12: R49.
14) Spiller A, Quadrani DA. Toxic effects from metformin exposures. Annals Pharmacother 2004; 38: 776-780.
15) Van Berlo-Van de Laar IR, Vermeij CG, Doorenbos CJ. Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. J Clin Pharm Ther 2011; 36: 376-382.
16) Aperis G, Paliouras C, Zervos A, Arvanitis A, Alivanis P. Lactic acidosis after concomitant treatment with metformin and tenofovir in a patient with HIV infection. J Ren Care 2011; 37: 25-29.
17) Salpeter SR, Greyber E, Pasternak GA, Salpeter Posthumous EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010; 20: CD002967.
18) Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domeco C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.
19) Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-1053.
20) Pan LT, MacLaren G. Continuous veno-venous haemodiafiltration for metformin-induced lactic acidosis. Anaesth Intens Care 2009; 37: 830-832.