

Metformin lactic acidosis and anaesthesia : myth or reality ?

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Abstract : *Aims :* To determine whether a causal or coincidental relationship is indicated in the literature between metformin and lactic acidosis and to recommend clinical guidelines for the withdrawal of metformin prior to surgery.

Method : A broad review of the literature related to metformin associated acidosis was carried out. (There are few publications specifically related to metformin treatment and anaesthesiology).

Results : When metformin-associated lactic acidosis occurs, a concurrent pathology or contraindication to the use of metformin is often found. Anaesthesia and surgery can generate or aggravate concurrent pathologies.

Conclusion : Although no association has been shown between metformin and lactic acidosis under usual conditions of use, vigilance is required when metformin is used prior to surgery. The following clinical guideline is proposed : to withdraw (when possible) metformin 48 hours prior to surgery and to wait until the patient's biological and clinical parameters return to normal before reintroducing it.

Key words : Metformin ; lactic acidosis ; anaesthesia ; surgery.

INTRODUCTION

The biguanidines are currently used in the treatment of non-insulin-dependent diabetes mellitus. They have been in use since the 1920s and three molecules have been marketed from 1950 : metformin, buformin and phenformin. The latter was withdrawn in the 1970s after it proved to be associated with lactic acidosis (40 to 60 cases/100 000 patients/year) (2, 4).

In 1997, a case of metformin associated with lactic acidosis in a healthy patient after a minor surgery was reported (7).

As a result of this publication, a recommendation was made to systematically stop the administration of metformin 72 hours before surgery. The present article considers whether there is a casual or merely coincidental relationship between metformin and lactic acidosis. It investigates need to revise the current guideline of medication for

metformin withdrawal in relation to anaesthesia and surgery.

Indications and pharmacodynamic properties of metformin

Metformin : (Metformax® Glucophage®...), is indicated for the treatment of type II diabetes mellitus, alone or in association with other oral antidiabetic drugs or with insulin. Metformin lowers hyperglycemia.

Three mechanisms of action have been proposed to explain its effect :

1 : Inhibition of gluconeogenesis and glycogenolysis combined with the inhibition of fatty acid oxidation in the liver.

2 : Enhancement of peripheral glucose uptake due to increased sensitivity to insulin.

3 : Delayed intestinal glucose resorption (2, 8).

It should be stated that there is no mention in the literature of hypoglycemia occurring with monotherapy.

Metformin is also used in the treatment of polycystic ovary syndrome. It acts by reducing resistance to insulin, by restoring the ovulatory menses, by facilitating conception and by reducing the rate of first trimester spontaneous abortion (11).

Pharmacokinetic properties of metformin

Oral metformin has a bioavailability of 50 to 60%. Its intestinal resorption takes 6 hours and its distribution volume ranges from 63 to 276 liters.

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Metformin is not metabolized and its binding to plasma proteins is negligible. Elimination of metformin occurs via the kidneys (90%). Its elimination half life is +/- 6h30 (2, 8, 11).

Metformin associated lactic acidosis (M.A.L.A.)

Lactic acidosis associated with metformin is defined as : a metabolic lactic acidosis with a pH lower a 7.35, an increased anion gap and a blood lactate level > 5.0 mmoles/l (2, 6, 9).

Three different types of MALA have been described :

A : Associated with a pathology that generates anaerobic metabolism and lactic acidosis (sepsis, cardiac, hepatic, renal insufficiency) without metformin accumulation.

B : Associated with metformin accumulation but without associated pathology, by overdose or by lack of elimination of metformin (renal insufficiency)

Mixed : A+B. (2)

The exact mechanism underlying metformin-induced lactic acidosis is not totally understood. Investigational studies have shown that metformin at supra therapeutic doses inhibits the mitochondrial respiratory pathway. This leads to an energy shortage with a decrease in adenosine triphosphate and an increase in adenosine monophosphate. A shift takes place from aerobic to anaerobic metabolism. Pyruvate is generated and transformed into lactate. Gluconeogenesis from lactate in the liver is also inhibited (7, 9).

Metformin and lactic acidosis : relation or coincidence ?

When phenformin was withdrawn, the question rose of whether the same lactic acidosis side effect could be expected with metformin. Reports

of lactic acidosis in patients treated with metformin began to appear progressively in the literature.

METHODS

As there is little literature specifically related to MALA in anesthesiology we searched the literature for MALA in general.

A search was made on Medline according to the following sequences "metformin associated lactic acidosis NOT postoperative NOT anaesthesia" with meta-analysis and review as criteria, and "metformin associated lactic acidosis anaesthesia". The search strategy specified "last 5 years, English or French language, word in the text". We found three publications in the broader literature and one concerning anaesthesia.

RESULTS

In 2001 LALAU and RACE (6) reviewed 26 case reports published between 1995 and 2000 (after excluding those due to overdose or to renal failure induced by a contrast medicine). Their aim was to clarify the term "associated" in the definition of MALA.

The authors looked for the presence or absence of plasma metformin overdose. Either they found the blood levels, either they estimated the values indirectly, meaning that they tried to find the follow-up of the biological values of the renal function in order to define the time of onset of the renal insufficiency. It is indeed possible to estimate the duration of metformin exposure concomitant with renal insufficiency and to evaluate the likelihood of overdose. Table I summarizes the probability of overdose for the 26 patients of the case reports.

LALAU and RACE followed up by looking for the presence of lactic acidosis in these patients.

Table I

Likelihood of overdose with metformin

	Number patients with plasma levels of metformin = 4	Number patients with estimated plasma levels of metformin = 22
Number patients were overdose are absent	1	3
Improbable		3
Possible		11
Present	3	
Uncertain		2

Table II

Lactic acidosis and metformin

	Number of cases (%)		Number of deaths (%)
Absence of acidosis	4 (15.4)		1 (25)
Lactic acidosis not exacerbated by Metformin	8 (30.8)		6 (75)
	No overdose	6	
	Precipitating pathology *	2	
Lactic acidosis exacerbated by metformin (classified by co-existing diseases)	12 (46.2)		1 (8,3) treatment refused
	Occlusion	1	
	Heart failure	1	
	Renal failure	10	
Lactic acidosis of uncertain origin	2 (7.7)		2 (100)

* Chronic cardiac and renal failure + shock of unknown origin for one, shock due to pneumonia for the other.

Table III

General characteristics of the studies selected by SALPETER *et al.*

	Metformin group	Non metformin group
Number of patients/year	36 893	30 109
Age in years (standard deviation)	57.1 +/- 8.9	57.2 +/- 9.1
% Gender man/woman	61/39	61/39
Mean study duration in years (range)	2.1 (0.08-10.7)	
Mean study size number of patients (range)	55 (6-683)	76 (8-1362)

Based on co-existing pathologies and metformin levels, they evaluated whether the acidosis observed was due to the metformin or not. Their results are described in table II.

In conclusion, the authors divided MALA in 3 categories :

- A : metformin-unrelated lactic acidosis.
- B : metformin-associated lactic acidosis.
- C : metformin-induced lactic acidosis.

Patient outcome varies considerably between categories. Mortality is much higher in the categories A and B than in category C (respectively 6/8 (75%), 2/2 (100), 1/12 (8,3%)).

In 2003 SALPETER *et al.* (14) reviewed 194 studies comparing metformin with other anti-hyperglycemia treatments (126 prospective comparative trials, 56 prospective cohort studies and 12 retrospective cohort studies).

Their objective was :

A : To compare the risk of fatal and nonfatal lactic acidosis associated with metformin with that associated with placebo and with other treatments in patients with type 2 diabetics.

B : To compare levels of lactic acid (without acidosis) before and during metformin treatment with those for placebo and with those for other glucose lowering drugs.

The authors described two groups, the “metformin group” and the “non metformin group” Both groups were comparable as far as population is concerned (table III).

No cases of lactic acidosis were reported in either the metformin group or the non metformin group. The statistical incidences of lactic acidosis for the metformin and non metformin groups were 8.1 and 9.9/100,000 patient-years respectively.

There were no differences in lactate levels before and during treatment with metformin compared with non metformin. The lactate levels before metformin treatment were 1.1+/-0.2 mmole/l and 1.2+/-0.3 mmole/l after and were not different from those found with non metformin treatments.

The authors noted that sample size may be statically too small (calculated according to Poisson formula (3)).

Table IV

Contraindications to metformin

Absolute contra-indications	Relative contra-indications
Renal insufficiency (creatinine > 133 μ mole/l in man or > 124 μ mole/l in woman) Treated cardiac insufficiency Metabolic acidosis Contrast product with iodium (13)	80 years of age except if normal renal function Clinical or biological liver insufficiency Hypoxemia Alcoholism Pre and post surgery period (13)

Table V

Exclusion criteria

	Number of case
Low quality of the publication	13
Lack of data on acidosis	12
Lactate < 5mmom/l	5
PH > 7.35	1
Same case	2

Table VI

Risk factors for lactic acidosis

Acute risk factors (% cases)	Chronic risk factors (% cases)
Acute renal failure (92)	Cardiovascular disease (51)
Contrast product related renal insufficiency (26)	Chronic renal insufficiency (26)
Shocks (26)	Alcohol (11)
Sepsis (19)	Chronic liver failure (8.5)
Acute heart failure (6.4)	Respiratory insufficiency (4.3)

Taking this limitation into account they concluded that :

1 : there is no evidence that the risk of lactic acidosis is higher with metformin than with other anti hyperglycemic treatments.

2 : they observed (as did other authors (6, 15)) that metformin was contraindicated in 54 to 73% of the patients who received the drug (see Table IV) (5). For example, in the metformin group 16 233 patients/year suffered from renal insufficiency.

In 2004, STADES *et al.* (15) made a review of the 80 case reports published in the period 1957-1999. Thirty three were excluded from the analysis for the reasons explained in Table V, leaving 47 for assessment.

A number of potential risk factors for lactic acidosis were identified and classified as acute or chronic (see Table VI).

The 47 cases were stratified as follows : 1 case had 0 risk factor, 13 cases had 1 risk factor, 20 cases had 2 risks factors, 12 cases had 3 risk factors, and 1 case had 4 risks factors

The authors concluded :

1 : That there was no quantitative relationship between metformin plasma concentration and lactic acid level.

2 : Neither lactic acid concentration nor plasmatic metformin concentration was associated with mortality (37.4 mg/l of metformin in surviving patients and 4.9 mg/l in dead patients).

3 : The main risk factors associated with mortality were sepsis, acute cardiac events and terminal liver insufficiency.

4 : The majority of patients developed lactic acidosis in association with acute renal insufficiency or with increased severity of a chronic renal insufficiency.

5 : The severity of this insufficiency expressed by serum creatinine was not a risk factor for mortality and was not correlated with the concentration of lactic acid or metformin.

Although numerous publications fail to demonstrate any relationship between metformin and lactic acidosis, cases still appear in the literature (4, 8, 9, 10).

For the first million metformin users in the USA, 47 case reports have been published. Of these, 43 concern renal insufficiency or a risk factor for lactic acidosis concomitant with metformin use. Only three patients had no other risk factor than metformin (13).

Generally, an associated risk factor was found that explained the lactic acidosis. In some patients an overdose was reported which could also have generated lactic acidosis. However in some cases there is no explanation for the acidosis.

The three publications mentioned above consider MALA in a general way.

MALA, anesthesia and surgery

Only a small number of articles have been published specifically on the relationship between MALA, anesthesia and surgery. Surgery and anesthesia have not been identified as specific causes of MALA, but patients are at risk of developing it due to perioperative complications (hypotension,

hemorrhage, infarct, sepsis...) (1). A single case report has been published (7).

Case review : A 66-year old healthy male with a history of hypertension, diabetes mellitus type II, peripheral vascular disease, obesity, and pulmonary embolism, whose biological parameters were within normal limits, was treated with nefidipine, isosorbidedimonitrate, metformin and phenprocoumone.

Preoperatively, phenprocoumone was replaced by heparin i.v.. The remaining drugs, including 500 mg metformin were administered until the day before intervention (not on the intervention day).

The intervention, an abdominal wall hernia, was completed without problems.

Drug treatments restarted on the day 1 after surgery. The patient presented mild hypertension and tachycardia and received a low calorie meal (400-800 Kcal/d). Biological parameters indicated hyperglycemia and normal renal function.

Dyspnea appeared on the day 2 and the patient was moved into intensive care on day 4. Hypotension and hyperthermia were also present. Biological parameters showed a fall in white bloodcell and blood platelet counts, metabolic acidosis (pH 7.15, base excess -12.5, lactate 95 mg/dl) and rapidly progressing to renal insufficiency.

Additional investigations indicated only a localized pneumonia. The authors considered that the association of metformin with low calorie diet and respiratory infection were responsible for the lactic acidosis.

The patient died after 7 weeks in intensive care.

The authors concluded that metformin should be withdrawn several days before a surgical intervention and restarted once the patient's state returns to normal.

This is an agreement with the findings set out in the other literature mentioned above. The patient was considered to be in good health. But was he really ? Is it right to say that a patient with a history of diabetes mellitus type II, peripheral vascular disease and hypertension, obesity and pulmonary embolism is not at risk of respiratory failure when he gets pneumonia, becomes hypoxic and develops lactic acidosis ?

Conclusion

The frequency of lactic acidosis is the same in diabetes mellitus type II patients treated or not treated with metformin.

When lactic acidosis occurs with metformin treatment, there is often an associated pathology which could favor the build up of lactate.

Only one case report can be found in the literature that associates anesthesia, surgery, lactic acidosis and metformin. Anesthesia and surgery do not represent exceptional conditions but they might lead to enhance hypoxemia and renal insufficiency. A review of the well-documented case reports and studies observing of metformin under usual conditions of use does not show any association between lactic acidosis to metformin treatment.

However, case reports concerning lactic acidosis and metformin are still published indicating that vigilance is required.

CONCLUSION

The following guidelines are proposed for the withdrawal of metformin prior surgery :

- 1 : to stop the intake of metformin at least 48 hours prior to surgical intervention, where possible.
- 2 : to reinforce postoperative surveillance in cases where intervention has to be done without metformin discontinuation. It is advised not to restart metformin treatment if the patient has acidosis or is at risk of developing acidosis (of whatever origin), as long as his hemodynamic state is unstable or his renal function has not returned to preoperative values. It is also appropriate to delay the re-introduction of metformin until the patient eats and drinks normally.

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