

METFORMIN AND LACTIC ACIDOSIS

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The pathophysiology of type 2 diabetes mellitus (T2DM) is well known and comprises defects in both insulin secretion and insulin sensitivity (1). Therefore, the pharmacological treatment of T2DM may comprise drugs that promote insulin secretion and/or enhance insulin action (2). The biguanide compound metformin is considered as the first drug of choice in all current guidelines for the management of T2DM because it is cheap, with a well characterized efficacy and safety profile, and it has proven its potential in reducing diabetes-related complications, including cardiovascular disease (3). All new glucose-lowering agents should be compared to the reference drug metformin first and then prove their added value compared to placebo when combined with metformin as basal treatment. A recent systematic review of 140 trials and 26 observational studies of head-to-head comparisons of monotherapy or combination therapy that reported intermediate or long-term clinical outcomes or harms supports metformin as a first-line agent to treat T2DM (4). However, almost 35 years ago, two other glucose-lowering agents of the biguanide family, phenformin and buformin, were withdrawn from the market because of an increased risk of lactic acidosis, and a possible withdrawal of metformin was also discussed at that time. Because it could be demonstrated that the incidence of lactic acidosis associated with metformin was much less than that attributed to phenformin and buformin, metformin remained on the European market, and the drug was finally accepted by the US Food and Drug Administration in 1993. In a recent review unravelling the problem, Lalau confirmed that metformin-associated lactic acidosis (MALA) is a rare but still important adverse event (5).

A detailed analysis of the recent literature on metformin revealed two apparently contradictory pieces of information. On the one hand, there are still numerous case reports describing the occurrence of lactic acidosis related to metformin use (6), like that published in the present issue of the journal by Hofkens et al (7). On the other hand, more and more papers suggest that the benefit/risk ratio of the administration of metformin is favourable even in patients classically considered as contra-indications to the use of the drug because they

theoretically present a higher risk of lactic acidosis (8, 9). Such clinical conditions include elderly individuals (8, 9), patients with moderate chronic renal insufficiency (10), subjects with abnormal liver tests (11) or patients with chronic heart failure (12). For instance, in the Reduction of Atherothrombosis for Continued Health (REACH) Registry (comprising 19,691 patients having diabetes with established atherothrombosis), the mortality rates were 6.3% (95% confidence interval [CI], 5.2%-7.4%) with metformin and 9.8%, 95% CI, 8.4%-11.2%) without metformin; the adjusted hazard ratio (HR) was 0.76 (95% CI, 0.65-0.89). Association with lower mortality on metformin was consistent among subgroups, noticeably in patients with an estimated creatinine clearance of 30 to 60 mL/min/1.73 m² (HR, 0.64; 95% CI, 0.48-0.86), in people older than 65 years (HR, 0.77; 95% CI, 0.62-0.95), and in patients with a history of congestive heart failure (HR, 0.69; 95% CI, 0.54-0.90) (9). The conclusion was that metformin use may decrease mortality among patients with diabetes when used as a means of secondary prevention, including subsets of patients in whom metformin use is not now recommended. Even if this benefit remains to be proven in prospective randomized trials, the current guidelines might be revisited in a near future to extend the use of metformin in at risk subgroups of T2DM patients, provided that careful medical supervision is guaranteed.

The incidence of lactic acidosis associated with metformin use is rather low, but this complication is still associated with a high rate of mortality (5). However, the causal relationship between the two events is not always proven. Indeed, the relationship between metformin and lactic acidosis is complex, since use of the drug may be causal, co-responsible or coincidental (5). Some recent data even suggested that metformin is not associated with an increased risk of lactic acidosis (13, 14). Interestingly, pooled data from 347 comparative trials and cohort studies revealed no cases of fatal or nonfatal lactic acidosis in 70 490 patient-years of metformin use or in 55 451 patient-years in the non-metformin group. The upper limit for the true incidence of lactic acidosis per 100 000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the non-metformin group. Thus, there is no evidence from prospective comparative trials or from observational cohort

¹ accompanying the article "Metformin associated lactic acidosis (MALA): case report" printed further on in this issue).

studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other anti-hyperglycaemic treatments (13). Furthermore, the direct metformin-related mortality is close to zero and, somewhat paradoxically, it has been suggested that metformin may even be protective in cases of very severe lactic acidosis unrelated to the drug (5).

Nevertheless, in some exceptional circumstances, metformin therapy may cause a huge rise in plasma lactate concentrations, leading to MALA, which may be fatal. What are the mechanisms leading to such a dramatic scenario? All circumstances leading to severe dehydration may result in acute renal failure and liver hypoperfusion and dysfunction (Figure 1). Therefore, metformin may accumulate as well as lactate due to decreased clearance by both the liver (decreased gluconeogenesis) and the kidney (decreased urinary elimination). Lactate accumulation may conduct to severe lactic acidosis, which may result in consciousness disturbances (even coma), hyperventilation (Kussmaul respiration) and painful abdomen crisis, sometimes mimicking peritonitis (like in the present clinical observation) (7). Gastrointestinal symptoms predominate in MALA and should be taken into account for an early diagnosis (15). Acidosis may aggravate vomiting which, in turn, can exacerbate dehydration. In addition, both dehydration and acidosis may

lead to circulatory shock, which will stimulate anaerobic glycolysis and production of lactate (Figure 1). Thus, several vicious circles are initiated and perpetuated that quite rapidly could render the clinical situation out of control and provoke death. Prompt diagnosis and early supportive intensive care are mandatory. Extrarenal dialysis may be helpful to accelerate the elimination of both excessive metformin and lactate (5).

The role of dehydration appears crucial in most case reports describing severe lactic acidosis treated with metformin (5, 15). Dehydration also seems to play a key role in the clinical observation described by Hofkens et al (7). Therefore, physicians should inform all diabetic patients treated with metformin that they have to stop the drug in all circumstances promoting dehydration such as vomiting and diarrhoea. Another important issue that deserves some interest is the possible role of drug interactions (6). The use of diuretics and/or laxatives may promote dehydration, especially in elderly people. Several medications may interfere with renal function (16). In particular, it has been demonstrated that nonsteroidal anti-inflammatory drugs and compounds inhibiting the renin-angiotensin system may promote acute renal insufficiency, especially among dehydrated individuals (figure 1); both pharmacological classes were incriminated in some cases of MALA (17). In the case report of Hofkens et al (7), a negative role of angiotensin receptor blocker has also been suspected. However, regarding all beneficial effects of both metformin and inhibitors of the renin-angiotensin system, this concern should not hinder a wide use of these two classes of drugs in the management of patients with T2DM, a population at high risk of cardiovascular disease.

For the clinician, another interesting point of discussion is the classical contraindication of maintaining metformin therapy when iodinated contrast medium is used in T2DM patients, because of the potential risk of acute renal insufficiency and consequently MALA. In a recent systematic review assessing the quality of five current guidelines for the use of contrast medium in patients who are taking metformin, substantial inconsistencies have been emphasized. According to the authors, these are, in part, caused by the low level of evidence underpinning guideline recommendations (18). Systematically stopping metformin preventively is presumably not mandatory and again probably a too strict recommendation. However, interrupting metformin therapy 48 hours before the radiologic exam should be advised in patients at higher risk of renal failure. Furthermore, if renal dysfunction occurs after injection of iodinated contrast medium, metformin therapy should be interrupted immediately until full recovery of renal function.

In view of the impressive overall effectiveness profile of metformin, it would be paradoxical to deny the majority of patients with long-established T2DM access to metformin because of the high prevalence of contraindications and the fear of lactic acidosis (5). Some authors do not hesitate to consider that "metformin's contraindications should be contraindicated" (8). Nevertheless, caution is required in presence of conditions capable to induce dehydration and metformin should be temporarily stopped in all these circumstances, especially when nausea, vomiting and/or diarrhoea are present. Conversely, all patients treated with metformin presenting with vomiting and abdominal pain should be checked for lactic acidosis (15), especially if renal and/or hepatic insufficiency are documented, in order to avoid delayed diagnosis and useless

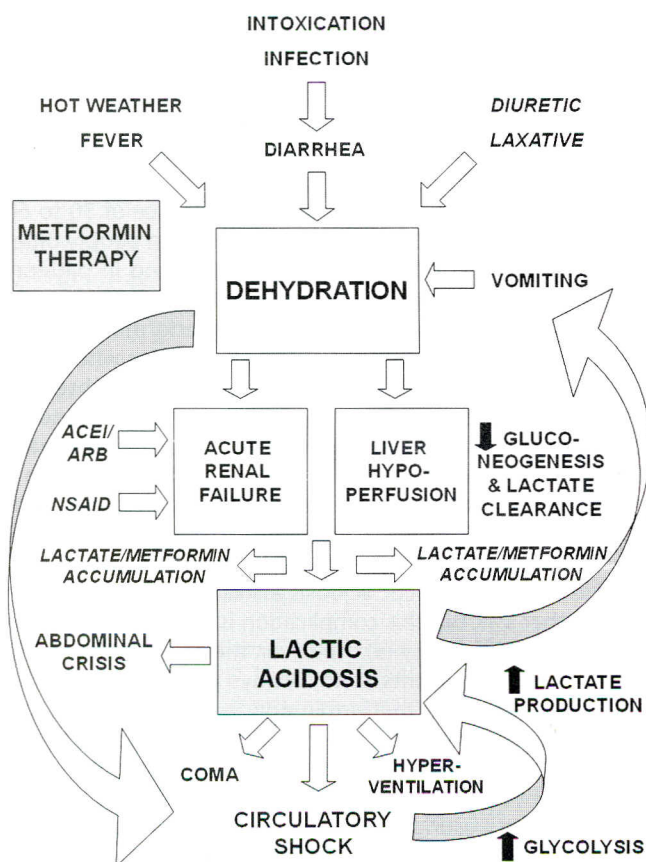


Figure 1: Various circumstances capable of initiating vicious circles that may conduct to metformin-associated lactic acidosis (MALA). In all circumstances that can provoke severe dehydration, metformin therapy must be interrupted. ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. NSAID: nonsteroidal anti-inflammatory drug.

exploratory surgical procedures as in the interesting clinical observation reported by Hofkens et al (7).

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