Short report

Metformin accumulation without hyperlactataemia and metformin-induced hyperlactataemia without metformin accumulation

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Abstract

Aim. – These case reports demonstrate that, at the individual level, blood metformin concentrations and metformin effects on lactate do not always correlate.

Methods. – We report here on two unusual cases: metformin accumulation in the absence of hyperlactataemia; and metformin-induced hyperlactataemia with no metformin accumulation.

Results. – Patient #1 presented with severe kidney failure, severe acidosis (pH: 7.04), normal lactataemia (0.90 mmol/L) and marked metformin accumulation. Patient #2 presented with hyperlactataemia, even after dose reduction, during otherwise well-tolerated metformin treatment. Arterial lactate levels were 8.8, 8.2 and 4.7 mmol/L during metformin therapy with daily doses of 2550, 1700 and 850 mg, respectively. After withdrawal, metformin was reintroduced for 5-day periods at 500 mg/day up to 2000 mg/day with washout intervals. Lactate concentration, normal at baseline, rapidly exceeded 2 mmol/L after metformin administration.

Conclusion. – These clinical data suggest a new concept for metformin therapy: there may be either resistance or, conversely, hypersensitivity to metformin effects on lactate generation according to the individual patient.

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1. Introduction

It is commonly believed that the higher the blood metformin concentration, the more severe the metabolic impairment [1]. However, some individuals with massive metformin accumulation do not display hyperlactataemia [2], although such cases have not been reported in detail. There have also been cases of hyperlactataemia in patients being treated with the usual therapeutic doses of metformin therapy. For this reason, it was decided to describe these intriguing cases as precisely as possible.

2. Methods

The present report concerns two well-documented cases: one patient displayed severe blood metformin accumulation in the absence of hyperlactataemia; the other patient developed hyperlactataemia during conventional metformin therapy.

The criteria for hyperlactataemia, lactic acidosis and metformin accumulation were blood lactate concentration >2 mmol/L [3], arterial pH <7.35 and blood lactate concentration >5 mmol/L [4], and plasma metformin concentration >1.35 mg/L, respectively [5].

3. Results

3.1. Case 1: metformin accumulation without hyperlactataemia

A 54-year-old Caucasian woman, who had type 2 diabetes and was overweight, presented at the emergency room with
bradyphemia, gait problems and acute dyspnoea. Her recent medical history included clonus of the legs and eyes over the preceding days. Her medical history also featured depression and corticosteroid therapy for pulmonary sarcoidosis. Kidney function had been recorded as “normal” 14 months previously. Crackling sounds were noted in the lower quadrant of the right lung, and the last available HbA1c value was 6.6%. The patient’s medication included metformin hydrochloride (1000 mg three times a day), alendronic acid, clorazepate dipotassium, flunarizine, hydrocortisone, fenofibrate, metotrexate, pantoprazole and paroxetine.

On admission, the patient was in a state of severe confusion. Vital signs included a raised temperature at 38.2 °C, blood pressure at 90/50 mmHg, heart rate at 130 beats/min and oxygen saturation at 87%. Our initial investigation revealed kidney failure (serum creatinine: 720 µmol/L; serum urea nitrogen: 32 mmol/L), metabolic acidosis (pH: 7.04; total CO2: 11.2 mmol/L), but neither ketosis nor hyperlactataemia (lactate: 0.9 mmol/L). Blood glucose concentration was 114 mg/dL (6.33 mmol/L). Plasma benzodiazepine concentration was moderately elevated. Initial treatment comprised intravenous administration of sodium bicarbonate, insulin, furosemide and amoxicillin.

On day 2, the patient was referred to our intensive care unit. Her Glasgow Coma Scale (GCS) score was 12, but improved rapidly upon administration of flumazenil. Biochemical parameters were similar to those recorded the day before (serum creatinine: 776 µmol/L; serum urea nitrogen: 32 mmol/L; serum pH: 7.07; total CO2: 10.9 mmol/L; pO2: 119 mmHg; pCO2: 35 mmHg; lactate: 1.1 mmol/L; anion gap: 20.8 mmol/L). C-reactive protein (CRP) level was 213 mg/L, and plasma and erythrocyte metformin concentrations were 38 mg/L and 29 mg/L, respectively (normal values: <1.34 mg/L and <1.65 mg/L, respectively). The patient’s outcome was positive after daily haemodialysis from days 2 to 9. No explanation was found for the renal failure, although kidney biopsy revealed non-specific lesions often associated with tubular nephritis.

3.2. Case 2: metformin-induced hyperlactataemia without metformin accumulation

A 69-year-old Caucasian man with type 2 diabetes, stage 2 chronic obstructive pulmonary disease and peripheral arterial occlusive disease was diagnosed with metabolic acidosis during routine consultation (pH: 7.33; total CO2: 12.9 mmol/L; pCO2: 24.9 mmHg; pO2: 84.7 mmHg; lactate: 8.8 mmol/L). At the time of diagnosis, he was taking metformin at a daily dose of 2550 mg. Creatinine clearance had fallen sharply and inexplicably (from 105 mL/min during the previous month to 32 mL/min at the time of consultation). CRP level was normal.

Initial treatment comprised rehydration and metformin withdrawal. On day 2, creatinine clearance was 59 mL/min and lactate concentration was 2.7 mmol/L (pH: 7.41). On day 3, the creatinine clearance rate was 57 mL/min and lactate concentration was 1.4 mmol/L (pH: 7.38) and, on day 4, plasma and erythrocyte metformin levels were 0.84 mg/L and 0.50 mg/L, respectively. The patient was discharged and his daily dose of metformin reduced to 1700 mg.

One year later, asymptomatic metabolic acidosis was again noted during a routine visit (pH: 7.33; pCO2: 28.8 mmHg; pO2: 95.5 mmHg; lactate: 8.2 mmol/L). The patient was still taking metformin at 1700 mg/day. Creatinine clearance was 71 mL/min, and plasma and erythrocyte metformin levels were normal (1.34 mg/L and 1.01 mg/L, respectively). Metformin was discontinued and reintroduced 3 weeks later (at a daily dose of 850 mg). Six weeks after admission, the patient’s lactate concentration was 4.4 mmol/L (pH: 7.36), while plasma and erythrocyte metformin levels were 0.65 mg/L and 0.34 mg/L, respectively. Given the absence of lactate acidosis at this time, metformin therapy was continued. However, 5 weeks later, persistent hyperlactataemia (lactate: 4.7 mmol/L; pH: 7.38; plasma and erythrocyte metformin levels: 0.52 mg/L and 0.4 mg/L, respectively) prompted withdrawal of the drug.

Three years after the first episode of acidosis, metformin was reintroduced because of overt decompensated diabetes. Metformin was then given for 5-day periods at increasing dosages (500 mg, 1000 mg and 2000 mg/day), with a 9-day washout interval. Blood lactate levels were monitored daily and exceeded the threshold for hyperlactataemia within the first few days of treatment. Blood metformin concentrations, however, remained within the therapeutic range (Fig. 1).

4. Discussion

Presented here are the first well-documented cases of a patient with marked metformin accumulation and severe metabolic acidosis, yet no concomitant hyperlactataemia and, in contrast, another patient with metformin-induced hyperlactataemia during otherwise well-tolerated metformin therapy (no drug accumulation).

When seeking to explain massive metformin accumulation in the absence of concomitant hyperlactataemia (patient #1), it is essential to be sure that lactate was measured early enough (prior to any potential treatment interventions) to rule out the possibility of true, but subsequently corrected, hyperlactataemia. In our patient, blood gases were measured immediately on admission and prior to initiation of any treatment. Furthermore, the patient’s metformin accumulation had probably been present for some time, given that both her plasma and erythrocyte metformin concentrations were similarly high (reflecting accumulation in a deep compartment) [5]. For this reason, the possibility of undetected but resolved hyperlactataemia can be reasonably ruled out. It may be speculated that the metabolic acidosis in our patient was the consequence of the anion retention that accompanied her severe kidney failure [6].

Patient #2 presented with three episodes of marked hyperlactataemia, of which two were accompanied by metabolic acidosis. These episodes occurred during longstanding metformin therapy at the usual dosages and even at reduced ones. For this reason, the effect of metformin on lactate levels during three 5-day blocks of metformin updosing was examined, and found to provoke hyperlactataemia every time. Although
the peak lactate concentration during these episodes was not especially high (it was lower than that observed previously during longstanding metformin treatment), the highly curtailed lag time for developing hyperlactataemia (within a day) was particularly noteworthy. Even though lactate levels varied from one metformin block to another, it should be borne in mind that this parameter is known to vary markedly — and even hourly — under emergency conditions.

Our two cases should be considered in the light of recent research into variations in the genes coding for metformin and lactate transporters that may be able to modulate metformin pharmacodynamics, pharmacokinetics and metabolic effects [7–9]. The clinical impact of these kinds of polymorphisms has been confirmed in patients taking 1 g of metformin twice a day [10]. Strikingly, in this case, an 80-fold interindividual variation in trough steady-state plasma concentrations of metformin was documented.

In view of our present observations, a new concept of metformin therapy is proposed here that challenges the conventional view in which the higher the blood metformin concentration, the higher the blood lactate concentration (at least at the individual level). In fact, some patients display marked metformin
accumulation without hyperlactataemia, a situation that could be described as ‘hyposensitivity’ to metformin metabolic effects. In contrast, other patients receiving guideline-compliant metformin therapy can develop hyperlactataemia in the absence of metformin accumulation, a situation that could be described as ‘hypersensitivity’ to metformin.

5. Conclusion

Our present case reports offer two new insights: first, severe metformin accumulation does not necessarily lead to hyperlactataemia; and, second, guideline-compliant metformin therapy can still lead to hyperlactataemia. These observations may be considered as throwing new light towards guidelines for individualizing the pharmacological treatment of diabetes.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.12.003.

References