Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4

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OBJECTIVE

This study was conducted to define a safe, effective dose regimen for metformin in moderate and severe chronic kidney disease (CKD; stages 3A/3B and 4, respectively), after the lifting of restrictions on metformin use in patients with diabetes with moderate-to-severe CKD in the absence of prospective safety and efficacy studies.

RESEARCH DESIGN AND METHODS

Three complementary studies were performed: *1*) a dose-finding study in CKD stages 1–5, in which blood metformin concentrations were evaluated during a 1-week period after each dose increase; *2*) a 4-month metformin treatment study for validating the optimal metformin dose as a function of the CKD stage (3A, 3B, and 4), with blood metformin, lactate, and HbA_{1c} concentrations monitored monthly; and *3*) an assessment of pharmacokinetic parameters after the administration of a single dose of metformin in steady-state CKD stages 3A, 3B, and 4.

RESULTS

First, in the dose-finding study, the appropriate daily dosing schedules were 1,500 mg (0.5 g in the morning [qam] +1 g in the evening [qpm]) in CKD stage 3A, 1,000 mg (0.5 g qam + 0.5 g qpm) in CKD stage 3B, and 500 mg (qam) in CKD stage 4. Second, after 4 months on these regimens, patients displayed stable metformin concentrations that never exceeded the generally accepted safe upper limit of 5.0 mg/L. Hyperlactatemia (>5 mmol/L) was absent (except in a patient with myocardial infarction), and HbA_{1c} levels did not change. Third, there were no significant differences in pharmacokinetic parameters among the CKD stage groups.

CONCLUSIONS

Provided that the dose is adjusted for renal function, metformin treatment appears to be safe and still pharmacologically efficacious in moderate-to-severe CKD.

The biguanide drug metformin is not metabolized, does not bind to proteins, and is rapidly eliminated by the kidneys (1). Consequently, most guidelines and reviews discourage the use of metformin in patients with moderate-to-severe chronic kidney disease (CKD) because of the fear of lactic acidosis attributed to metformin accumulation (2). Although metformin is linked to lactate metabolism in several ways, including the inhibition of lactate conversion via gluconeogenesis, the strength of the link between metformin and lactic acidosis has been greatly overstated (3,4).

In 2016, the European Medicines Agency (5) and the U.S. Food and Drug Administration (FDA) (6) removed the contraindication on the use of metformin in CKD stages 3A and 3B (glomerular filtration rate [GFR] for CKD stages 1, 2, 3A, 3B, 4, and 5: 120–90,

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89–60, 59–45, 44–30, 29–15, and <15 mL/min/1.73 m^2, respectively). However, these decisions were made in the absence of prospective studies.

Here, we report results of a comprehensive investigation in CKD, with three complementary studies: a dose-finding study, a chronic metformin treatment study, and a pharmacokinetic (PK) study.

RESEARCH DESIGN AND METHODS

Overall Study Design

The three studies had an open-label, single-center design. Given the clinical importance of distinguishing between CKD stages 3A and 3B, we studied these separately.

The study medication was an immediate-release tablet formulation of metformin. Patients having participated in the first (dose-finding) study were invited to participate in the two other studies (Supplementary Fig. 1). The local Institutional Review Board (Le Comité de Protection des Personnes [CCP] Nord-Ouest II, Amiens, France) approved the studies (reference: 2012-15).

Study 1: Dose Finding

Design

The inclusion criteria were as follows: type 2 diabetes; any CKD stage (stages 1–5); stable renal function, defined as a difference of <30% between two consecutive estimated (e)GFR values in the 3 months immediately before the study; treatment with metformin or treatment with other antidiabetic drugs in patients with HbA_{1c} >6.5% (>48 mmol/mol); and a lactate concentration of <2.5 mmol/L. The main exclusion criteria were severe liver failure, pregnancy, and breast-feeding.

In view of possible changes in the eGFR during the study, patients were withdrawn from the analysis if they changed CKD stage twice or more during the course of the study.

Metformin Dosing and Visit Schedule

All patients underwent three 1-week blocks of metformin treatment at an increasing dosage, each of which was followed by a 1-week washout period: 500 mg/day in the evening in step 1, 1,000 mg/day (500 mg in the morning and in the evening) in step 2, and 2,000 mg/day (1,000 mg in the morning and in the evening) in step 3. Plasma and erythrocyte metformin concentrations were assayed 12 h after the last metformin intake. Lactate concentrations were also assayed in CKD stage 3–5 patients.

Medications likely to influence renal function were prohibited. Patients were asked to record their treatment compliance in a study diary.

Categorization of Blood Metformin Concentrations

Plasma and erythrocyte concentrations of metformin were both measured because the latter may better reflect the deep compartment and thus the risk of metformin accumulation (7). With regard to plasma concentrations, *1*) Graham et al. (1) suggested "that the mean plasma concentrations of metformin over a dosage interval [should] be maintained below 2.5 mg/L"; *2*) the FDA has stated that "during controlled clinical trials, which served as the basis of approval for metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses" (8); and *3*) the International Association of Forensic Toxicologists reference list of "therapeutic substances" states that serum metformin concentrations between 1 and 4 mg/L are "therapeutic" (9).

On the basis of these statements and a large database of plasma metformin concentrations (n = 798) (10), we propose making a pragmatic distinction between moderately elevated values (between 2.5 mg/L and 5 mg/L) and clearly elevated values (i.e., >5 mg/L).

Safety

Metformin was to be withdrawn after *1*) a plasma lactate value >5 mmol/L (the criterion for hyperlactatemia in lactic acidosis) (11) or *2*) two consecutive blood lactate values ≥2.5 mmol/L (i.e., abnormal values) (12,13).

Study 2: Chronic Metformin Treatment With Dose Adjustment

Design

This study was performed in patients with type 2 diabetes and stage 3A, 3B, or 4 CKD. The participants underwent 4 months of metformin treatment at a fixed dosage: 1,500 mg/day (500 mg in the morning [qam] and 1,000 mg in the evening [qpm]) for CKD stage 3A, 1,000 mg/day (500 mg qam and 500 mg qpm) for CKD stage 3B, and 500 mg/day (in the morning) for CKD stage 4. Plasma and erythrocyte metformin levels were assayed at the end of each month (12 h after the last dose of metformin in CKD stages 3A and 3B patients, and 24 h after in CKD stage 4 patients).

Because the goal was not to change the metformin dose during the study for a given CKD stage, the decision was made to withdraw patients from the analysis if they changed CKD stage twice or more over the course of the study. As in study 1, medications likely to influence renal function were prohibited.

Patient Selection

The inclusion and exclusion criteria were the same as in study 1.

Safety

The safety conditions were the same as in study 1.

Study 3: The PK Study

Design

This study was performed in patients with CKD stage 3A, 3B, or 4 (n = 5 per group) after at least 1 month of treatment (Supplementary Table 4), during which the daily amount was divided into two doses: a morning dose of 500 mg and an evening dose that depended on the CKD stage. Hence, all of the patients in the PK study had continued to take an oral morning dose of 500 mg at 8:30 A.M. Blood samples were collected 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 h thereafter and were assayed for plasma and erythrocyte metformin levels.

Patient Selection

The inclusion criteria were type 2 diabetes, CKD stage 3 or 4, and treatment with metformin for at least the previous month.

Noncompartmental PK Analysis

Standard, noncompartmental analyses were based on the changes over time in plasma and erythrocyte metformin concentrations. The peak metformin concentration (C_{max}), the time to C_{max}, and the trough concentration at 24 h were recorded for each individual. We calculated the linear-up log-down trapezoidal area under the concentration-time curve (AUC) from 0 to 24 h, the elimination rate constant, the terminal half-life, and the average steady-state concentration (C_{avss}) over the 12-h (CKD stage 3) or 24-h (CKD stage 4) dosing interval. Noncompartmental analyses were performed using Kinetica 5 software (InnaPhase Corporation, Philadelphia, PA).

Estimation of the GFR

The GFR was estimated according to the four-variable Modification of Diet in Renal Disease (MDRD) equation: eGFR (mL/min per 1.73 m^2) = 175 × (serum creatinine, mg/dL)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American) (conventional units).

Analytical Methods

Creatinine

Creatinine was assayed using the creatininase method (Siemens Healthcare Diagnostics, Tarrytown, NY). A standard from the serum creatinine reference system was used. The coefficients of variation (CVs) obtained with in-house quality controls were 1.73% for a mean creatinine value of 68 μmol/L and 0.81% for a mean value of 577 μmol/L.

HbA_{1c}

HbA_{1c} was assayed in whole blood using the Variant II Turbo HbA_{1c} Kit-2.0 (Bio-Rad Laboratories, Hercules, CA) and ion-exchange high-performance liquid chromatography. The inter- and intraassay CVs were, respectively, 0.043% and 0.072% at an HbA_{1c} concentration of 5.1% (>32 mmol/mol), and 0.045% and 0.049% at a concentration of 13.6%.

Metformin

Metformin was isolated from plasma and erythrocytes, as previously described (14). Solutes were separated on a 10-μm, 4.6- × 250-mm Spherisorb SCX column (Waters, Saint-Quentin-en-Yvelines, France) using a mobile phase of 50% acetonitrile and 50% 2 mmol/L NaH_2PO_4 pH 3.8 buffer and a flow rate of 1 mL/min. The eluate was monitored at 230 nm using a diode array detector (Waters). The retention time for metformin was 8 min. The method showed good linearity ($r > 0.997$) over the concentration range 0.10–15.0 mg/L. The lower limits of detection and quantification were 0.05 mg/L and 0.1 mg/L, respectively. The upper limit of quantification was confirmed as 100 mg/L. Precision and accuracy were measured for quality control samples at three different concentrations (0.5, 2, and 8 mg/L). The intra- and interassay precision values (measured as the percentage CV over the quality controls' concentration range) were all <15%. The intra- and interassay accuracy (defined as the absolute value of the ratio between the calculated mean values for quality controls and their respective nominal values, expressed as a percentage) ranged from 91% to 109.8%.

Lactate

Lactate was assayed in venous blood using the LA Flex reagent cartridge (Siemens, Newark, NJ). This modification of the Marbach and Weil technique is based on the oxidation of lactate to pyruvate. The expected maximum SD for repeatability (within-run precision) using $n = 5$ replicates was 0.1 mmol/L for a mean lactate value of 2.7 mmol/L (i.e., corresponding roughly to our upper normal limit).

Statistical Analysis

Quantitative variables were expressed as the mean ± SD. Comparisons were performed using a Kruskal-Wallis test; if a significant difference was found, an additional Mann-Whitney *U* test was performed. The results of the Mann-Whitney test were checked with the Bonferroni post hoc test, depending on the number of study groups.

Correlations were assessed by calculating the correlation coefficient (*r*). We used SPSS 20.0 software to calculate the SE of residuals and estimate the statistical significance of differences between slopes of regression curves. To determine the significance of the difference between two slopes, two extra dummy variables were included for the different doses, and their interaction term with the eGFR was added to the linear model. The null hypothesis was then tested.

RESULTS

Study 1: The Dose-Finding Study

The study enrolled 83 patients, 78 were included, and 69 completed the study (the reasons for noncompletion are specified in Supplementary Table 1).

Baseline Characteristics and Changes Over Time in Clinical Biochemistry Parameters

The patients' baseline characteristics and changes over time in study parameters are summarized in Supplementary Fig. 2 and Supplementary Table 2.

Blood Metformin Concentrations

Individual plasma and erythrocyte metformin concentrations over the whole range of eGFRs are presented in Fig. 1 as a function of the eGFR and the metformin dose.

At the lowest dose (500 mg qpm daily), only 1 of the 75 plasma metformin values was above 2.5 mg/L and none was above 5 mg/L. At 500 mg b.i.d. daily, 5 of the 74 values were above 2.5 mg/L and 1 was above 5 mg/L (all in CKD stages 4–5). At 1,000 mg b.i.d. daily, 17 of the 68 values were above 2.5 mg/L and 2 were above 5 mg/L (in patients with CKD stages 3A, 3B, 4, and 5). The erythrocyte metformin concentrations followed much the same pattern as the plasma concentrations.

For each dose level, there was a significant ($P < 0.001$) inverse relationship between eGFR and the metformin concentration 12 h after the last dose after 1 week of treatment (Fig. 1). This increase was similar for plasma and erythrocyte metformin concentrations at all three dose levels. For the plasma metformin concentration, the slopes (95% CI) of the different curves (eGFR vs. metformin level) were −0.010 (−0.014 to −0.007) for 500 mg qpm, −0.013 (−0.018 to −0.009) for 500 mg b.i.d., and −0.026 (−0.033 to −0.018) for 2,000 mg b.i.d. The slopes for 500 mg qpm and 500 mg b.i.d. dose levels did not differ significantly. There was a significant difference between the slopes for the two lowest dose levels and the highest dose level (1,000 mg b.i.d.) ($P < 0.0034$ and $P = 0.00013$); the latter slope was clearly steeper.

When the erythrocyte metformin concentration was considered, the slopes (95% CI) were 0.008 (−0.005 to 0.012) for 500 mg metformin, 0.009 (−0.006 to 0.014) for 1,000 mg, and 0.022 (−0.032 to 0.016) for 2,000 mg. The slopes for the 500 mg and 1,000 mg dose levels did not differ significantly. There was a significant difference between the slopes for the two lowest dose levels and the highest dose of 1,000 mg b.i.d. ($P < 0.00013$ and $P < 0.000013$, respectively); the latter slope was clearly steeper.

On the basis of these results, we selected a daily dosing schedule of 1,500 mg (500 mg qam and 1,000 mg qpm) in patients with CKD stage 3A, 1,000 mg (500 mg qam and 500 mg qpm) in patients with CKD stage 3B, and 500 mg (qpm) in patients with CKD stage 4.

Blood Lactate Concentrations

True hyperlactatemia (>5 mmol/L) was never observed. Only one CKD stage 3A patient displayed two consecutive lactate values >2.5 mmol/L (2.7 and 3.0 mmol/L, during treatment blocks 1 and 2, respectively). We decided not to apply our "metformin withdrawal rule" in this case, for the following reasons: *1*) the patient did not tolerate other antidiabetic agents well, *2*) the lactate values did not increase dramatically, and *3*) metformin accumulation was not observed (plasma metformin: <2 mg/L). The lactate value obtained during treatment block 3 was 2.37 mmol/L (plasma metformin: 1.95 mg/L). The patients with the highest metformin levels (>5 mg/L) did not display elevated lactate values.

Study 2: Chronic, Dose-Adjusted Metformin Treatment

Forty-six patients were included. Changes in the CKD stage during the study, abnormal

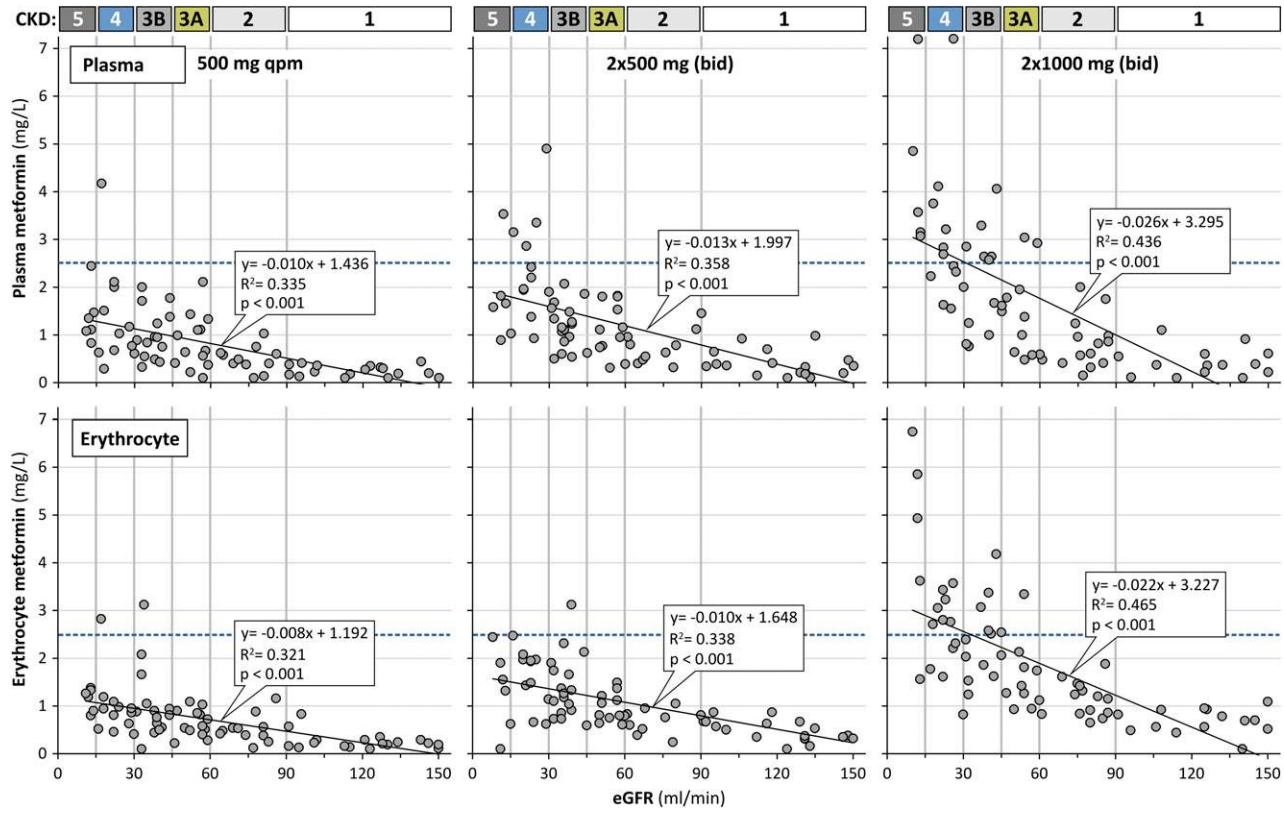

Figure 1—Plasma and erythrocyte metformin concentrations 12 h after the last dose of metformin, after 1 week of treatment (GFR for CKD stages 1, 2, 3A, 3B, 4, and 5: 120–90, 89–60, 59–45, 44–30, 29–15, and <15 mL/min/1.73 m^2, respectively).

lactate values during the study, and reasons for study noncompletion are specified in Supplementary Fig. 3. Laboratory data measured at the end of each month of the study are summarized in Supplementary Table 3.

HbA_{1c} Levels

In patients who completed the study, the HbA_{1c} values did not change significantly at any of the measurement time points (data not shown).

Metformin Concentrations

Overall, the plasma and erythrocyte metformin concentrations both remained remarkably stable throughout the study (Fig. 2). The peak metformin levels observed were 3.54 mg/L in plasma and 3.26 mg/L in erythrocytes, which were clearly below the FDA's maximum safe value in plasma of 5 mg/L (8).

Blood Lactate Concentrations

The few elevated lactate values (>2.5 mmol/L) were not chronologically related to metformin concentrations (Fig. 2). Figure 3 shows the changes in the lactate concentration over time. Considering the study population as a whole (i.e., regardless of whether or not the CKD stage had changed), six patients experienced a lactate value >2.5 mmol/L at least once, and five of these met the criteria for metformin withdrawal: four patients with a lactate level >2.5 mmol/L on two consecutive occasions and one patient with lactate level >5 mmol/L in a context of myocardial infarction. However, Fig. 3 shows that metformin was withdrawn in only two of these patients because the other three had changed their CKD stage or had displayed elevated lactate levels during the last month of treatment (Supplementary Fig. 3).

The correlation between metformin concentrations and lactate concentration was studied after excluding data from patients whose CKD stage had changed (n = 7); no statistically significant relationships were observed for plasma or erythrocyte levels.

Study 3: The PK Study

The characteristics of the study population are summarized in Supplementary Table 4. The time courses of the individual plasma and erythrocyte metformin concentrations after a single, oral dose of 500 mg are shown in Supplementary Fig. 4. The concentration at time 0 corresponds to the trough level (which did not significantly differ when the three CKD groups were compared) after the last dose during chronic treatment. Supplementary Fig. 4 shows the clear overlap between the curves (for both plasma and erythrocyte metformin concentrations) in the three CKD stages. The erythrocyte concentration (but not the plasma concentration) was stable during the dosing interval. Therefore, only AUC and C_{avss} were calculated for the erythrocyte concentration.

Table 1 reports the PK parameters for metformin in plasma and erythrocytes. We did not observe significant differences in any of these parameters when comparing the three CKD stages.

CONCLUSIONS

The current study is the first to provide a solid basis for continuing metformin treatment (with eGFR-adjusted doses) in patients with moderate or severe CKD. Importantly, the European Medicines Agency and the FDA extended the use of metformin in CKD stage 3 patients in the absence of prospective pharmacodynamic and PK data in this population.

Our results indicate that a metformin dose of 500 mg/day does not result in a

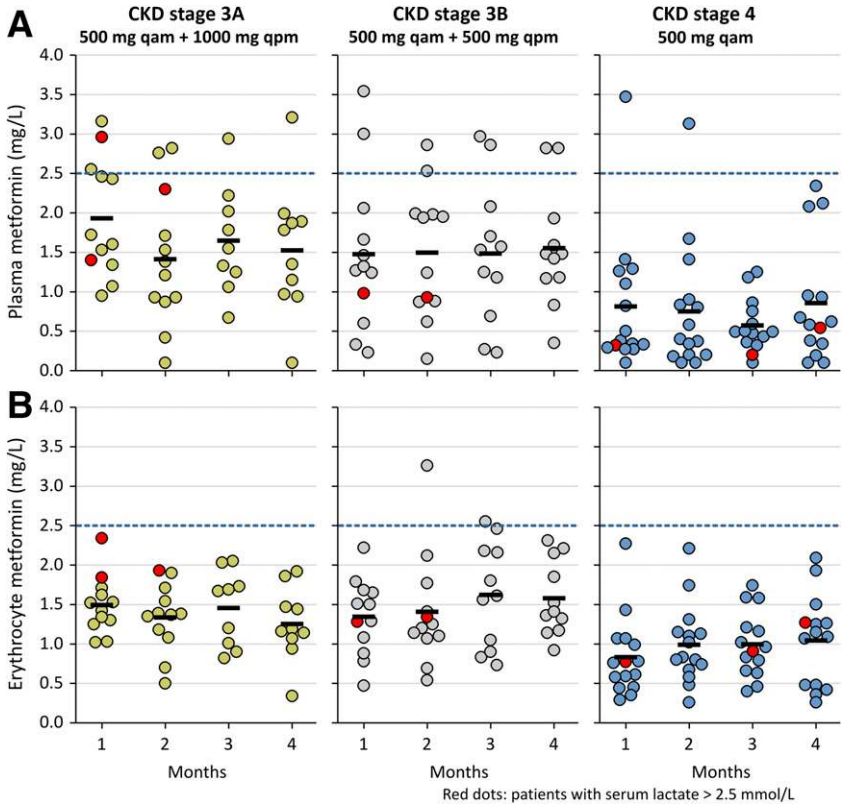

Figure 2—Individual metformin concentrations in plasma (*A*) and in erythrocytes (*B*) as a function of the CKD stage during 4 months of treatment with dose-adjusted metformin. The data were obtained 12 h (for CKD stages 3A and 3B) or 24 h (for CKD stage 4) after the last administration of metformin in patients who completed the study without changing their CKD stage. The symbol "–" indicates the mean value for the group at each measurement.

drug concentration >5 mg/L, which the FDA considers as the level not to be exceeded (8). In contrast, a twice-daily dose of 1,000 mg was clearly too high in patients with CKD stages 3–5. The intermediate dose of 1,000 mg/day was associated with a certain number of metformin concentrations >2.5 mg/L in CKD stage 4/5 patients. For all three dose levels, there was a significant, inverse relationship between eGFR and metformin concentrations 12 h after the last dose after 1 week of treatment.

In subjects with normal kidney function, the renal clearance rate for metformin is 510 ± 130 mL/min (1); this indicates that glomerular filtration of unbound metformin is combined with saturable, active, tubular secretion (15). Hence, the elimination of metformin by tubular secretion tends toward a constant. At increasing doses and plasma concentrations, tubular secretion becomes saturated and thus has a progressively less important role in the renal elimination of metformin (16). This may explain why there was a significant difference between the slopes of the eGFR/metformin concentration curve for the two lowest dose levels versus the highest dose level (1,000 mg b.i.d.); the latter slope was clearly steeper.

On the basis of the dose-finding study's results, we selected a chronic dosage regimen of 1,500 mg/day for patients with CKD stage 3A, 1,000 mg/day for patients with CKD stage 3B, and 500 mg/day for patients with CKD stage 4. We expected that this dose regimen would be safe but still pharmacologically efficacious in a context of moderate-to-severe kidney failure. The blood metformin concentrations were remarkably stable. The absence of any upward trend over the study period thus validated our chosen metformin regimens. However, the question of what constitutes a stable but overly low blood metformin concentration (i.e., lacking therapeutic efficacy) or an excessively high blood metformin concentration (possibly associated with hyperlactatemia) remains. Surprisingly for such an old drug, the "therapeutic concentration" of metformin has never been clearly determined. In fact, major methodological and conceptual errors have confounded the literature studies of so-called therapeutic concentrations (for a review, see Kajbaf et al. [17]). A dose-efficacy study that relates blood glucose control to the plasma metformin concentration during chronic treatment is therefore still lacking. Had the metformin doses selected here been too low, the HbA_{1c} level would have increased toward the end of the treatment period, particularly in CKD stage 4 patients treated with one-fourth/one-sixth of the standard dose. In fact, the HbA_{1c} level did not increase in the absence of a change in the patients' antidiabetic medication (except for insulin dose increases in two cases).

With regard to high metformin levels, it should be borne in mind that massive metformin intake may induce hyperlactatemia (18–22). In contrast, plasma metformin concentrations well above 10 mg/L are not necessarily accompanied by hyperlactatemia (23). Caution is therefore recommended when trying to link metformin to lactic acidosis (10,24).

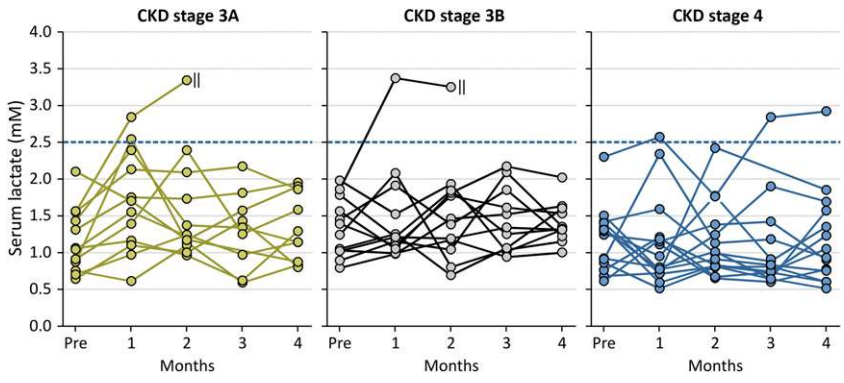

Figure 3—Individual blood concentrations of lactate during 4 months of treatment with dose-adjusted metformin. The data come from patients who completed the study without changing their CKD stage. The symbol "‖" indicates the withdrawal of metformin before the end of the study.

Table 1—Data from the PK study

Parameters	Compartment	CKD stage 3A	CKD stage 3B	CKD stage 4	*P* value (comparison of the CKD stages)
AUC, h · mg/L	Plasma	26.01 ± 8.89 (14.64–35.94)	38.54 ± 11.00 (27.78–53.19)	31.35 ± 11.06 (16.03–44.39)	0.31
	Erythrocyte	25.85 ± 6.19 (32.99–61.55)	46.40 ± 12.50 (14.64–35.94)	23.07 ± 15.00 (5.27–41.93)	0.11
T_{max}, h	Plasma	3.40 ± 1.95 (1.0–6.0)	4.20 ± 2.49 (1.0–8.0)	4.00 ± 00.00 (4.0–4.0)	0.88
$t_{1/2}$, h	Plasma	6.88 ± 2.8 (3.23–10.05)	7.69 ± 1.15 (6.22–8.7)	11.10 ± 5.87 (5.85–19.85)	0.28
C_{max}, mg/L	Plasma	2.13 ± 0.57 (1.33–2.74)	3.38 ± 1.60 (2.13–5.94)	2.30 ± 0.83 (1.32–3.28)	0.43
C_{avss}, mg/L	Plasma	1.57 ± 0.54* (1.00–2.17)	2.31 ± 0.78* (1.77–3.51)	1.31 ± 0.46† (0.67–1.85)	0.22
	Erythrocyte	1.17 ± 0.20* (1.07–1.54)	1.96 ± 0.55* (1.27–2.66)	0.96 ± 0.62† (0.22–1.75)	0.11

Data are shown as the mean ± SD (range). $t_{1/2}$, terminal half-life; T_{max}, time to C_{max}. *C_{avss} at 12 h. †C_{avss} at 24 h.

Another important issue concerns the need (or not) to monitor metformin concentrations, given that metformin assays are costly and not always readily available. Based on the present results, we do not recommend the monitoring of metformin levels in plasma or erythrocytes. Indeed, these levels can be predicted in patients with a stable eGFR once the metformin dose has been adjusted to the renal function. In fact, the main question is whether or not metformin treatment is metabolically tolerated (i.e., not associated with hyperlactatemia) rather than whether or not metformin concentrations are elevated. In this respect, 6 of the 46 patients displayed a lactate value above the upper normal limit (i.e., >2.5 mmol/L) at least once. However, these values remained well below the criterion for true hyperlactatemia (>5 mmol/L [11]), with the exception of a patient with myocardial infarction. In each CKD stage, the mean lactate values did not rise from 1 monthly measurement to another. There was no correlation between the lactate concentration and the plasma or erythrocyte metformin concentration. The highest metformin concentrations were not accompanied by high lactate values, and vice versa, the highest lactate values were not observed in patients displaying high metformin concentrations.

There are a few PK studies of metformin in patients with CKD (25,26). Based on a population with various dosing regimens, dose formulations, and degrees of renal function, Duong et al. (26) developed a PK model that simulated the metformin dose for each CKD stage and also proposed a dosing algorithm for various degrees of kidney function and the maintenance of consistent metformin exposure (C_{max} <5 mg/L) (27). However, PK parameters have never been assessed in CKD in a steady state. Our results highlighted marked interindividual variations in metformin concentrations in the various CKD groups. These variations are mainly due to large differences in metformin bioavailability, genetic variability in metformin transporters, and renal clearance (28). The three CKD groups did not differ significantly with regard to any of the PK parameters or the metformin concentrations. The C_{avss} measurements in plasma and erythrocytes (providing a better idea of total drug exposure than the trough level alone) were below the value of 2.5 mg/L recommended by Graham et al. (1), and the C_{max} values did not exceed the safe upper limit of 5.2 mg/L suggested by Duong et al. (27). These results demonstrate that the metformin dose had been correctly adjusted for each of the three CKD stages studied here.

Overall, the number of participants was relatively small, and our lack of data on plasma bicarbonate levels prevented us from assessing the participants' acid-base status more precisely. Concerning safety, the variation in lactate levels in CKD stage 3–4 patients receiving chronic metformin treatment could have been compared with that of patients with normal renal function or CKD stage 2. The classic parameter of HbA_{1c} was used as an index of the efficacy of metformin treatment; however, a further analysis after 3–4 months would have strengthened our observations.

The current study's main limitation was the risk of overinterpreting its satisfactory safety and efficacy results in CKD stage 4 patients (i.e., during off-label use). Indeed, our satisfactory results do not constitute a direct call for the use of metformin in those patients but rather provide a solid basis for a larger, longer-term prospective study.

Guidance for Clinical Practice

Concerning the metformin dose:

- The suggested daily adjusted doses of metformin in CKD stages 3A and 3B are 1.5 g (0.5 g qam + 1 g qpm) and 1 g (0.5 g qam + 0.5 g qpm), respectively.
- eGFR should be assessed every 6 months in CKD stage 3.
- Metformin should be withdrawn in patients likely to experience acute kidney injury in the context of severe pathologies.

Concerning safety:

- Lactate should be measured in fragile patients, particularly in the context of intercurrent disease. A value >5 mmol/L means that metformin must be withdrawn. If a value >2.5 mmol/L is observed during metformin treatment, the measurement should be repeated soon afterward. Metformin should be withdrawn if two consecutive values are >2.5 mmol/L.

Conclusion

The present studies are the first to have validated a metformin dose adjustment as a function of the eGFR in CKD patients. Our results support recent guidelines on metformin treatment in moderate-to-

severe CKD and open the way for the initiation of metformin treatment in severe CKD, providing that the metformin dose is adjusted to the eGFR.

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