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PHARMACOKINETICS AND DISPOSITION

A dosing algorithm for metformin based on the relationships between exposure and renal clearance of metformin in patients with varying degrees of kidney function

Janna K. Duong[1,2,3] · M. Y. A. M. Kroonen[4] · S. S. Kumar[1,2] · H. L. Heerspink[4] · C. M. Kirkpatrick[5] · G. G. Graham[1,2] · K. M. Williams[1,2] · R. O. Day[1,2,6]

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Abstract
Purpose The aims of this study were to investigate the relationship between metformin exposure, renal clearance (CL_R), and apparent non-renal clearance of metformin (CL_{NR}/F) in patients with varying degrees of kidney function and to develop dosing recommendations.
Methods Plasma and urine samples were collected from three studies consisting of patients with varying degrees of kidney function (creatinine clearance, CL_{CR}; range, 14–112 mL/min). A population pharmacokinetic model was built (NONMEM) in which the oral availability (F) was fixed to 0.55 with an estimated inter-individual variability (IIV). Simulations were performed to estimate $AUC_{0\text{-}\tau}$, CL_R, and CL_{NR}/F.
Results The data (66 patients, 327 observations) were best described by a two-compartment model, and CL_{CR} was a covariate for CL_R. Mean CL_R was 17 L/h (CV 22%) and mean CL_{NR}/F was 1.6 L/h (69%).The median recovery of metformin in urine was 49% (range 19–75%) over a dosage interval. When CL_R increased due to improved renal function, $AUC_{0\text{-}\tau}$ decreased proportionally, while CL_{NR}/F did not change with kidney function. Target doses (mg/day) of metformin can be reached using $CL_{CR}/3 \times 100$ to obtain median $AUC_{0–12}$ of 18–26 mg/L/h for metformin IR and $AUC_{0–24}$ of 38–51 mg/L/h for metformin XR, with $C_{max} < 5$ mg/L.
Conclusions The proposed dosing algorithm can be used to dose metformin in patients with various degrees of kidney function to maintain consistent drug exposure. However, there is still marked IIV and therapeutic drug monitoring of metformin plasma concentrations is recommended.

Keywords Metformin · Pharmacokinetics · Population modelling · Renal clearance · Kidney disease · Type 2 diabetes mellitus

✉ Janna K. Duong
jkduong@gmail.com

1 School of Medical Sciences, Medicine, University of New South Wales, Sydney, Australia

2 Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, Australia

3 Faculty of Pharmacy, The University of Sydney, Sydney, NSW 2006, Australia

4 Department of Pharmacy and Pharmacology, University of Groningen, Groningen, The Netherlands

5 Centre for Medicine Use and Safety, Monash University, Parkville, Australia

6 St Vincent's Clinical School, Medicine, University of New South Wales, Sydney, Australia

Introduction

Metformin is the first-line pharmacotherapy in the treatment of type 2 diabetes mellitus (T2DM). Metformin has an excellent safety profile, with favourable properties including weight neutrality and no increased risk of hypoglycaemia. The long-term use of metformin is also associated with a reduction in the risk of diabetes-related deaths [1] and the risk of some cancers [2].

Metformin is cleared by the kidneys, and a dose-proportional reduction with renal function is recommended to reduce the risk of adverse effects such as lactic acidosis [3]. The accumulation of metformin has been previously assessed using peak concentrations of metformin ($C_{max} < 5$ mg/L) [4, 5], and we have proposed dosage regimens of metformin at various stages of renal function to maintain $C_{max} < 5$ mg/L [6].

The pharmacokinetic parameters of immediate release (IR) metformin include a moderate and variable oral availability (55 ± 16% mean ± SD) in healthy subjects [7]. The fractional availability of the extended release (XR) metformin is very similar [8]. There is, however, large inter-individual variability (IIV) in the estimate of the total clearance of metformin (CL_{TOTAL}/F) which is influenced by its oral availability (F). The renal clearance of metformin (CL_R), on the other hand, is not affected by F and, therefore, is expected to have a lower IIV than CL/F.

In the present study, we have utilized population pharmacokinetic approaches to investigate the proportion of metformin cleared by the kidneys (CL_R), the proportion of the drug not cleared by the kidneys (non-renal clearance of metformin, CL_{NR}/F) and the drug exposure ($AUC_{0–12}$, $AUC_{0–24}$) of metformin in a large sample of patients with varying degrees of renal function.

Methods

Patients

Patients receiving metformin (immediate release, IR; extended release, XR) for T2DM were recruited from the outpatient Diabetes Clinic at St Vincent's Hospital (Australia) and Ziekenhuisgroep Twente Hospital (Almelo, The Netherlands). Demographic characteristics and data on medical comorbidities and concurrent medications were collected. Informed consent was obtained from all individual participants included in the study. Studies 1 and 2 were approved by the Human Research Ethics Committee at St Vincent's Hospital and University of New South Wales, Sydney (08209/SVH08/035; 09280/SVH09/080), and were registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000908932). Study 3 was approved by the Ethics Committee of the University Medical Center Groningen (Almelo, The Netherlands; METc 2013.178).

Study design

This was an observational, open-label, cross-sectional study consisting of intensive and sparse blood and urine sampling designs from three studies (studies 1–3, Fig. 1). Blood samples were collected to determine metformin and lactate concentrations in plasma, as well as serum creatinine and HbA1c concentrations. Urine samples were collected to determine metformin and creatinine concentrations. All patients were taking metformin in the long term for the treatment of T2DM.

Study 1

Study 1 was an intensive blood sampling study of patients with a range of kidney function attending the Diabetes Clinic, St Vincent's Hospital (Sydney, Australia). Information on dosing regimen, dosage and times of last dose prior to blood sampling was collected. All patients were admitted to an observation ward for the study. Patients treated with metformin IR (n = 7) provided blood samples at 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h after metformin administration. Urine samples were collected from 0 to 12 h after a regular dose. The blood sampling times for patients treated with metformin XR (n = 9) were 0, 2, 4, 6, 12, 16, 20 and 24 h after their metformin dose. Urine samples for patients treated with metformin XR were collected from 0 to 24 h post dose.

Study 2

Study 2 was a sparse blood sampling study design of patients with chronic kidney disease (CKD; creatinine clearance, CL_{CR} < 40 mL/min) attending the Diabetes Clinic at St Vincent's Hospital (Sydney, Australia). These patients (n = 5) participated in an interventional study of metformin conducted over 6 weeks [4] and were prescribed daily doses of 500 mg metformin IR. Information on dosing regimen, dosage and times of last dose was collected. A total of eight blood samples and timed urine samples (2–4 h) were collected from each patient. The patients noted the time of their last void, and the 2-h urine sample was collected at the clinic.

Study 3

Study 3 was conducted in patients with mild to moderate kidney disease (n = 45, CL_{CR} < 60 mL/min) attending an outpatient Diabetes Clinic at Ziekenhuisgroep Twente Hospital (Almelo, The Netherlands). Prior to entering the study, patients withheld their usual dose of metformin. The baseline sample was then collected for metformin determination (pre-dose), and patients voided their bladder. After taking their usual dose of metformin, a 2-h blood sample was collected to determine the concentration of metformin in plasma. Urine was collected over 24 h and metformin and creatinine concentrations measured. Patients did not take another dose of metformin during this time interval. The patients collected urine samples at home.

Information on the patients' dosing regimen was collected; however, the times of last dose were not recorded. Therefore, some assumptions were made when dealing with these data (see "Missing dosage times" section).

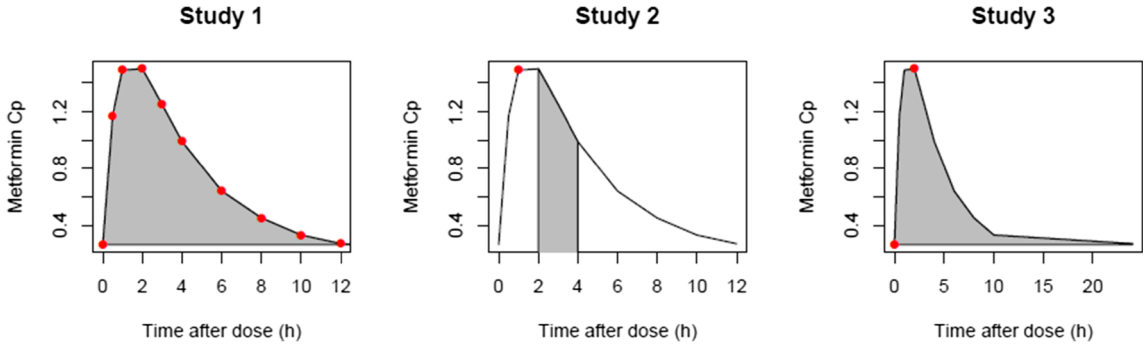

Fig. 1 Study design of study 1, study 2 and study 3. The *red dots* are the blood sampling time-points, and the *grey-shaded area* is the urine collection interval (colour figure online)

Metformin assay

Metformin concentrations in plasma and urine samples were analysed at the Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Australia. For samples collected at Almelo Hospital, plasma and urine samples were stored at −4 °C before transport to St Vincent's Hospital. The plasma concentrations of metformin were assayed by HPLC using a validated method [6]. Urinary concentrations were assayed similarly.

Population modelling

The plasma concentration data and the accumulated amount of metformin in the urine (mg) were used for population pharmacokinetic analyses. The data were analysed by non-linear mixed effect modelling using NONMEM® version 7.2 (ICON Development Solutions, Ellicott City, MA, USA) with the first-order conditional estimation method with interaction (FOCE-I). For nested models, model selection was informed by using the objective function value (OFV, −2log likelihood), whereby a decrease of >3.84 was considered statistically significant ($P < 0.05$, χ^2 distribution). The Akaike information criterion (AIC) was used to select the best model between non-nested models. Model runs were executed using Perl-speaks-NONMEM 3.5.3 [9], model development was managed using Pirana 2.8.1 [10] and all plots were generated with R (Version 3.2.0) [11].

Missing dosage times

Because the time of the last dose of metformin was not recorded in study 3, some assumptions regarding the dosing history were necessary for the population pharmacokinetic analyses. Firstly, all subjects using metformin were assumed to be at steady state, receiving metformin IR and compliant with their metformin dosing. Secondly, dosage intervals were assumed to be equal i.e. doses taken every 24 h for once daily dosing, every 12 h for twice daily dosing and every 8 h for thrice daily dosing. Lastly, the patients were asked to withhold their scheduled dose of metformin prior to the start of the study. This was assumed to be the dose of metformin immediately prior to the start of the study. These assumptions were evaluated by investigating the agreement between the observations and the predictions, with and without using the pre-dose time-point for study 3.

Structural and statistical model

A previously developed population PK model was used [6]. This was a two-compartment model with first-order absorption (k_a) for metformin IR, and zero-order absorption for metformin XR (D) (Fig. 2). The renal clearance of metformin (CL_R) was estimated using the accumulated amount of metformin excreted in the urine. Unabsorbed drug together with clearance by all other means is termed the non-renal clearance (CL_{NR}/F).

The following parameters were estimated by the model: CL_{NR}/F, CL_R, central volume of distribution (V_C/F), intercompartmental clearance (Q/F) and peripheral volume of distribution (V_P/F). The total clearance of metformin (CL_{TOTAL}/F) was calculated using CL_R and CL_{NR}/F. From previous studies, the median value of F was 55% [7, 12]. Therefore, F was fixed to a value of 0.55 with an estimated IIV. The IIV for the pharmacokinetic parameters was described using a log-normal distribution:

$$P_i = P_{TV} \times \exp^{(n_i)} \quad (1)$$

where P_i is the pharmacokinetic parameter of the i^{th} individual, P_{TV} is the typical population parameter value and n_i describes the variability between the i^{th} individual and the population parameter which follows a normal distribution with a mean of 0 and a variance of ω^2 i.e. $N(0, \omega^2)$.

Several residual error models were tested for metformin concentrations in the plasma and urine. Different error models were tested for each study to account for inaccuracies in

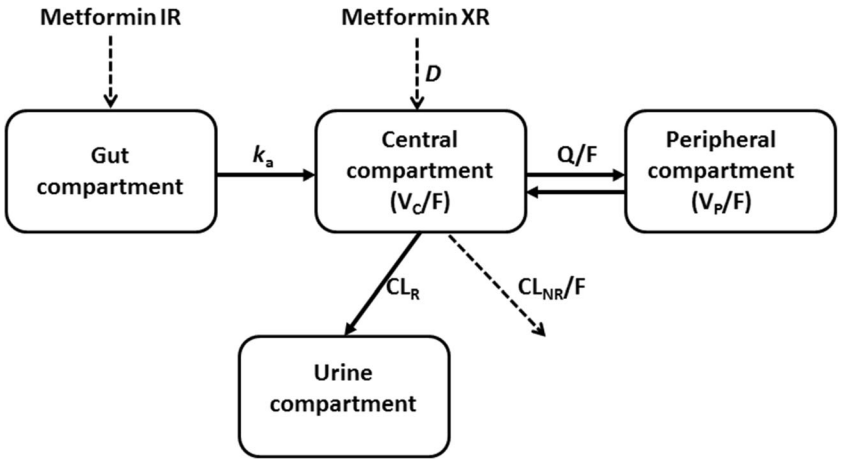

Fig. 2 The final two-compartment model of metformin describing first-order absorption for metformin immediate release (IR) and zero-order absorption for metformin extended release (XR), where k_a is the first-order absorption constant and D is the duration of infusion. CL_R is the renal clearance, CL_{NR}/F is the non-renal clearance, Q/F is the inter-compartmental clearance, V_C/F is the apparent central volume of distribution and V_P/F is the apparent peripheral volume of distribution

sample collection. The combined additive and proportional residual models (mixed error models) were described as

$$C_{ij} = C\left(1 + \varepsilon_{pij}\right) + \varepsilon_{aij} \quad (2)$$

where C_{ij} is the j^{th} measured observation for the i^{th} individual and ε_{pij} and ε_{aij} are the proportional and additive residual random errors, respectively, for the i^{th} individual and the j^{th} measurement. ε_{pij} had a normal distribution of N(0, ${\sigma_1}^2$) and ε_{aij} had a normal distribution of N(0, ${\sigma_2}^2$), where σ_1 and σ_2 represent the standard deviations for the proportional and additive residual error, respectively.

A time-dependent error model [13] was also tested for study 3 due to the missing dosage history. This was investigated as a step function for the plasma concentrations, whereby a different error model was tested for the pre-dose samples, compared to the 2-h post-dose samples.

Covariate model

Covariates for CL_R, CL_{NR}/F and V_C/F were screened by inspecting scatter plots of empirical Bayes estimates (EBEs) against characteristics of patients (age, sex, weight, lean body weight [14]) and between studies. The equation used for calculating lean body weight was as follows [14]:

$$\mathrm{LBW(male)} = \frac{9.27 \times 10^3 \times \mathrm{WT}}{6.68 \times 10^3 \times 216 \times \mathrm{BMI}} \quad (3)$$

$$\mathrm{LBW(female)} = \frac{9.27 \times 10^3 \times \mathrm{WT}}{8.78 \times 10^3 \times 244 \times \mathrm{BMI}} \quad (4)$$

where WT is total body weight (kg) and BMI is the body mass index (kg/m^2).

Creatinine clearance was tested as a covariate for all clearance parameters and was calculated using the Cockcroft-Gault equation (CL_{CR}) [15] with either total body weight or lean body weight [14, 16]. Creatinine clearance was also calculated directly from the urine output/plasma concentration (UV/P, Eq. 5, CL_{UCR}) and was tested as a covariate for CL_R.

$$\mathrm{CL_{UCR}} = \frac{\mathrm{Creatinine_{urine}}\left(\mu\mathrm{mol}/\mathrm{L}\right)}{\mathrm{Creatinine_{serum}}\left(\mu\mathrm{mol}/\mathrm{L}\right)} \times \frac{\mathrm{Volume_{urine}\ (mL)}}{\mathrm{Time\ (hours)} \times 60} \quad (5)$$

Stepwise covariate modelling was utilized to select significant covariates and included the forward selection (OFV ≤3.84 points, $P < 0.05$, d.f. = 1) and backward elimination of potential covariates (OFV ≤6.63 points, $P < 0.01$, d.f. = 1).

Model evaluation

The models were evaluated by inspecting diagnostic plots and prediction-corrected visual predictive checks (VPCs, n = 1000). The VPC of the final model was evaluated by comparing the 10th, 50th and 90th percentiles of the observations to the corresponding 10th, 50th and 90th percentiles of the simulations (n = 1000) [17]. A non-parametric bootstrap (n = 1000) stratified by study was used to evaluate the uncertainty of all pharmacokinetic parameter estimates in the final model to obtain the 95% confidence interval for all parameters, as described previously [18].

Dosing simulations

The final model with residual variability and parameter uncertainty was used to simulate 1000 concentration-time profiles at steady-state doses of 500 mg IR and at CL_{CR} of 30, 60, 90 and 120 mL/min. The model-derived $AUC_{0\text{-}\tau}$ was used to investigate the relationship between drug exposure and CL_{CR}. Relationships between CL_{TOTAL}/F, CL_R and CL_{CR} were also investigated.

Results

Patients

A total of 66 patients with T2DM were investigated (Table 1). In study 1, data collection stopped prematurely for two patients taking metformin XR once daily. For these two patients, serial plasma and urine samples were only collected up until 12 and 8 h post dose, respectively. There were no significant differences in the HbA1c values and plasma lactate concentrations between the three studies (Table 1).

Pharmacokinetics

A total of 327 observations from the 66 patients were used for population pharmacokinetic analyses. Over a dosage interval (study 1), the median recovery of metformin in the urine was 49% (19–75%, range) of the dose. The dataset was best described using a two-compartment model with first-order absorption for IR and zero-order absorption for XR. Inter-individual variability (IIV) was added on to the CL_{NR}/F, CL_R, V_C/F and F parameters, and covariance of CL_{NR}/F and CL_R were accounted for in the model. The inclusion of IIV for F reduced the IIV of CL_{NR}/F from 172 to 69%.

A mixed error model was used to describe the residual error for the plasma concentrations of metformin. The model was further improved by using different error models for the urine output for subjects from study 3 (study 1 and study 2 vs study 3, ΔOFV −24.2). A mixed residual error model best described the residual error for the urine concentrations for studies 1 and 2, while an additive residual error best described the residual error for study 3. A time-dependent error model was investigated for study 3, but it did not improve the model predictions.

Despite the lack of dosing information for study 3, there was good agreement between observed and predicted concentrations (without the inclusion of the pre-dose data points) and the eta and epsilon shrinkage was low (<30%), suggesting that the assumptions regarding the times of last doses were valid.

The CL_{CR} using lean body weight was found to be the most significant covariate for CL_R and reduced IIV from 45 to 22% ($P < 0.01$, Eq. 6):

$$CL_{CR}\left(L/h\right) = \left(\frac{140-\text{Age (years)} \times \text{LBW}(kg)}{\text{Serum creatinine}\left(\frac{\mu mol}{L}\right) \times 0.814}\right) \times 0.06 \quad (6)$$

CL_{CR} estimated using Cockcroft-Gault and with lean body weight resulted in a lower OFV than CL_{UCR}. Lean body weight reduced the IIV for V_C/F by 4%, but it was not significant at $P < 0.01$ following backwards elimination of the covariate. Other body size descriptors (total body weight, lean body weight) were not significant covariates for any of the pharmacokinetic parameters. The final model equation for CL_R is as follows (Eq. 7):

$$CL_R = \theta_{CLR} \times \left(CL_{CR}/2.7\right) \times e^{\eta_{CLR}} \quad (7)$$

where θ_{CLR} is the mean population value for CL_R, CL_{CR} was centred to the median population value of 2.7 L/h (45 mL/min) and η_{CLR} is the IIV for CL_R.

The final model showed good agreement between the observations and the model predictions (Fig. 3) and good agreement between the observations and the model simulations (Fig. 4). Due to the limited number of urine samples collected in the 0- to 12-h post-dose period, wide 95% confidence intervals were observed for the accumulated urine output (Fig. 4). All population pharmacokinetic parameter estimates and their precision are summarized in Table 2. A large residual error was observed for the urine concentrations from study 3, which may be due to the patients' variable compliance to the study protocol.

At metformin doses of 500 mg IR, there was a proportional increase in drug exposure with reduced renal function (Table 3). The CL_R of metformin increased approximately in proportion to CL_{CR}. The median ratio of CL_R to CL_{CR} was 6.6 (5.1–8.8, 5–95%), and the median ratio of CL_{TOTAL}/F to CL_{CR} was 13 (9–36). The CL_{NR}/F was much smaller than CL_{TOTAL}/F and did

Table 1 Patient characteristics by study

Parameter	Study 1	Study 2	Study 3	Total
N	16	5	45	66
Age (years)	64 (40–79)	73 (64–80)	69 (51–79)	68 (40–80)
Weight (kg)	84 (67–165)	80 (60–127)	99 (64–156)	99 (60–165)
Body mass index (kg/m^2)	29 (25–45)	31 (23–42)	33 (23–49)	32 (23–49)
Lean body weight (kg)	60 (43–87)	60 (44–72)	65 (41–80)	63 (41–87)
HbA1c (%)	7.0 (5.5–14.5)	7.1 (5.8–10.1)	6.5 (5.1–8.6)	7.0 (5.5–14.5)
Lactate (mmol/L)	1.7 (1.0–2.9)	0.9 (0.8–3.0)	1.7 (0.6–3.7)	1.7 (1.0–2.9)
Creatinine clearance (mL/min)	75 (24–112)	26 (14–38)	44 (28–75)	46 (15–112)

Values are expressed as median (range)

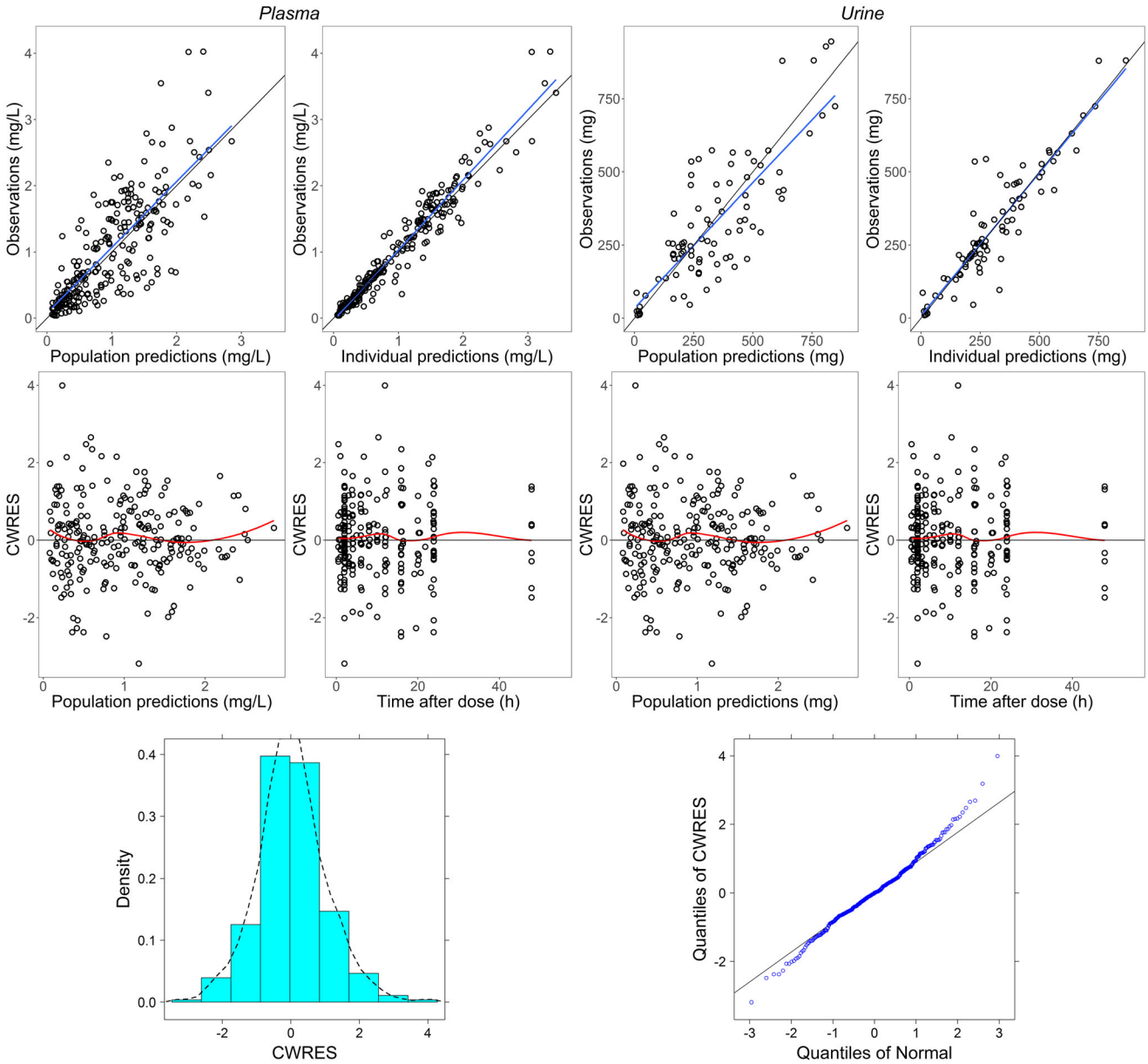

Fig. 3 Diagnostic plots of the final model. The plots of observations against population predictions and individual predictions were plotted with the line of identity (*black*) and a linear regression line (*blue*). Plots of conditional weighted residuals (CWRES) were plotted with a locally weighted scatterplot smoothing curve (*red*) (colour figure online)

not change with renal function (Table 3). Target doses of metformin (while maintaining median C_{max} < 5 mg/L, [6]) can be reached using the dosing algorithm (Eq. 8):

$$\text{Dose}\left(\text{mg}\Big/\text{day}\right) = \frac{\text{CL}_{\text{CR}}}{3} \times 100 \quad (8)$$

This dosing algorithm was used to simulate concentration-time profiles by CL_{CR} (Fig. 5). Since the maximum recommended XR dose of metformin is 2000 mg, this dose was used for dosing simulations at CL_{CR} of 60 to 90 mL/min. Using this dosing algorithm, median $AUC_{0–12}$ for metformin ranged from 18 to 26 mg/L/h (Table 3). Similarly, the median $AUC_{0–24}$ for metformin XR ranged from 38 to 51 mg/L/h. Therefore, this dosing algorithm provided a consistent drug exposure across a range of renal function as well as maintaining the median C_{max} to be below 5 mg/L (Table 3).

Discussion

It is well accepted that metformin doses should be reduced in patients with impaired renal function because the major mode of elimination is urinary excretion of the unchanged drug.

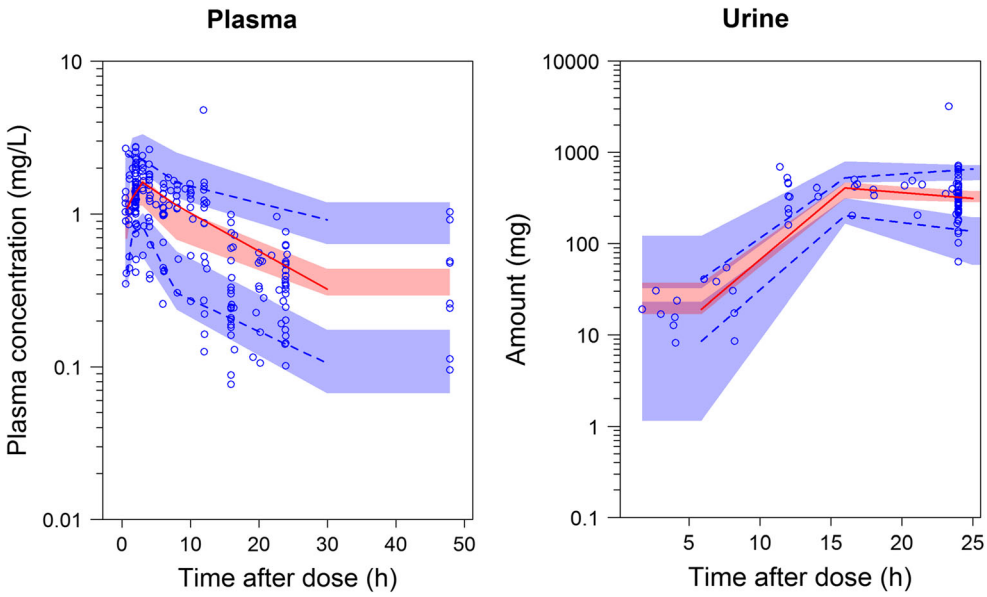

Fig. 4 Visual predictive checks (VPCs) of metformin concentrations in plasma (*top*) and cumulative amount excreted in urine (*bottom*). The lines represent the 10th, 50th and 90th percentiles of the observations, and the *shaded areas* represent 95% confidence intervals of the simulated concentrations of the 10th, 50th and 90th percentiles

This study provides further support for a dose-proportional reduction in metformin doses with the decline in kidney function. Based on the recommendation to keep metformin C_{max} below 5 mg/L [5, 6], we have proposed a dosing algorithm to estimate appropriate doses by renal function. The maximum recommended daily dose of metformin is 3000 mg for IR and 2000 mg for XR [19]. In our simulations, daily doses of 2000 mg XR were used for CL_{CR} of 60 to 90 mL/min (XR only). If higher doses are required, patients should be switched from metformin XR to metformin IR, provided that they do not experience gastrointestinal side-effects [19]. For metformin IR, median $AUC_{0–12}$ was 18 to 26 mg/L/h, which is similar to $AUC_{0–24}$ for metformin XR (38 to 51 mg/L/h) for patients with CL_{CR} from 15 to 90 mL/min. However, the ranges of peak plasma concentrations and AUC values are very wide (Table 3) and we therefore suggest that the plasma concentrations should be measured in order to optimize dosage with this important drug.

This is the first population pharmacokinetic model of metformin to describe the relationship between CL_R, CL_{NR}/F and drug exposure in patients with T2DM and kidney disease, and CL_{CR} estimated using Cockcroft-Gault and with lean body weight was a significant covariate for CL_R. Unlike our previous model [6], body weight was not a covariate for V_C/F. This is likely due to the high shrinkage for V_C/F (37%), which may have hidden the true covariate relationship with weight [20]. The median value of F in our study was 49 with (range, 19 to 75%). This result was similar to the values of 55 ± 19% (mean ± SD) [12].

There are limited and conflicting results on the non-renal clearance of metformin. Previous studies on the urinary recovery of metformin after the reference intravenous injection have reported either complete recovery [21] or 80% recovery in the urine, with no metformin recovered in the faeces [12]. By comparison, our pharmacokinetic analysis indicates that the CL_{NR}/F is much smaller than CL_R. Further studies are required to investigate whether a non-renal elimination pathway exists for metformin in man. In rats, the metabolism of metformin was suggested due to the reduced half-life of metformin by cytochrome P450 enzymes and lengthened by inhibitors of these enzymes, but no corresponding study has been conducted in man [22].

The ratio of CL_R and CL_{TOTAL}/F with CL_{CR} were higher than estimated previously. In our review of the pharmacokinetics of metformin, the ratio of CL_R to CL_{CR} was 4.0 ± 1.5 [7] compared to a median value of 6.6 (5 to 95% range 5.1 to 8.8) in the present studies. Further, the ratio of the CL_{TOTAL}/F in our review was 10.7 ± 3.5 which is considerably lower than the ratio 13.1 (5 to 95% range 9.3 to 36.5) in the present studies. The reasons for the contrast are unclear, but many patients included in our previous review either did not have T2DM or were administered single doses of metformin. By contrast, all patients in the present study were dosed with metformin in the long term for their T2DM. Furthermore, the wide range of CL_{TOTAL}/CL_{CR} in the present study is probably due to the large inter-patient variation of F.

There were some limitations to the present study. The shrinkage on V_C/F was high due to the sparse collection of pharmacokinetic time-points for studies 2 and 3, which may have masked the true covariate effect of weight for V_C/F. Additionally, there were a limited number of urine samples collected over the dosage interval and all urine collections were assumed to be complete. Study 1 was conducted entirely in the research centre while patients enrolled in study 2 were required to report the times of last void and patients from study 3 collected their 24-h urine at home. Poor compliance to the study protocol would contribute to the variability in the estimate of urinary recovery.

Table 2 The population parameter estimates and the median parameter values (5–95%) of the non-parametric bootstrap replicates of the final pharmacokinetic model

Parameter	Estimate (RSE %)	Median (5–95%)
Structural parameters		
CL_{NR}/F (L/h)	1.6 (65)	1.2 (0.1–3.1)
CL_R (L/h)	17 (7)	17 (16–19)
V_C/F (L)	123 (22)	118 (71–179)
V_P/F (L)	335 (42)	336 (180–1038)
Q/F (L/h)	13 (29)	12 (7.3–19)
k_a (1/h)	0.51 (30)	0.47 (0.28–1.1)
D (h)	9.6 (8)	9.6 (7.4–14.4)
F	0.55 (FIX)	–
Inter-individual variability (IIV)		
CL_{NR}/F (CV%)[a]	69 (49)	83 (25–206)
CL_R (CV%)	22 (21)	22 (14–30)
V_C/F (CV%)	36 (23)	36 (18–54)
F (CV%)	29 (16)	28 (18–36)
Residual error model		
Proportional error, plasma (CV%)	20 (43)	20 (13–26)
Additive error, plasma, SD (mg)	0.05 (118)	0.05 (0.001–0.09)
Proportional error, urine, studies 1 and 2 (CV%)	6.7 (93)	6.4 (0.0007–11.9)
Additive error, urine, studies 1 and 2, SD (mg)	24 (70)	23 (8–36)
Additive error, urine, study 3, SD (mg)	112 (35)	109 (71–140)

RSE is the percentage calculated as standard error divided by mean estimate

CL_{NR}/F non-renal clearance, *CL_R* renal clearance, *V_C/F* central volume of distribution, *V_P/F* peripheral volume of distribution, *Q/F* apparent inter-compartmental clearance, *k_a* first-order absorption, *D* duration of infusion, *F* bioavailability

[a] Correlation coefficient, $IIV_{CLNR/F} \sim IIV_{CLR} = 0.119$

Potential compliance issues for study 3were accounted for using a separate residual error model for the urine concentrations. This error model revealed a large additive residual error for study 3, which significantly improved the model and indicated poor compliance to urine collection at home.

Conclusion

We have described the CL_R, CL_{NR} and AUC of metformin in patients with varying degrees of renal function. We have proposed a dosing algorithm that can be used to reduce metformin

Table 3 Dosing simulations of metformin IR (twice daily) and metformin XR (once daily) doses at various stages of kidney function

	15 to 30 mL/min	30 to 60 mL/min	60 to 90 mL/min	90 to 120 mL/min
IR				
Dose (mg/12 h)	250	500	1000	1500
$AUC_{0–12}$ (mg/L/h)	19 (11–30)	20 (14–31)	26 (17–38)	18 (12–28)
C_{max} (mg/L)	1.4 (0.6–2.1)	1.5 (0.9–2.7)	2.3 (1.2–4.3)	1.8 (1.0–3.4)
CL_R (L/h)	9 (6–13)	17 (12–24)	29 (20–41)	40 (28–58)
CL_{NR}/F (L/h)	1.6 (0.5–4.8)	1.6 (0.5–4.8)	1.5 (0.5–4.6)	1.6 (0.5–4.8)
XR				
Dose (mg/day)	500	1000	2000[a]	
AUC_{0-24} (mg/L/h)	38 (22–59)	41 (27–63)	51 (34–73)	
C_{max} (mg/L)	1.5 (0.8–2.7)	1.9 (1.1–3.5)	2.7 (1.5–4.9)	
CL_R (L/h)	9 (6–13)	17 (12–25)	29 (21–42)	
CL_{NR}/F (L/h)	1.6 (0.5–5.3)	1.5 (0.5–4.8)	1.6 (0.5–5.0)	

Median (5–95%)

[a] Two thousand milligrams is the maximum recommended daily dose for XR. Dosage with IR tablets is recommended if higher doses are required

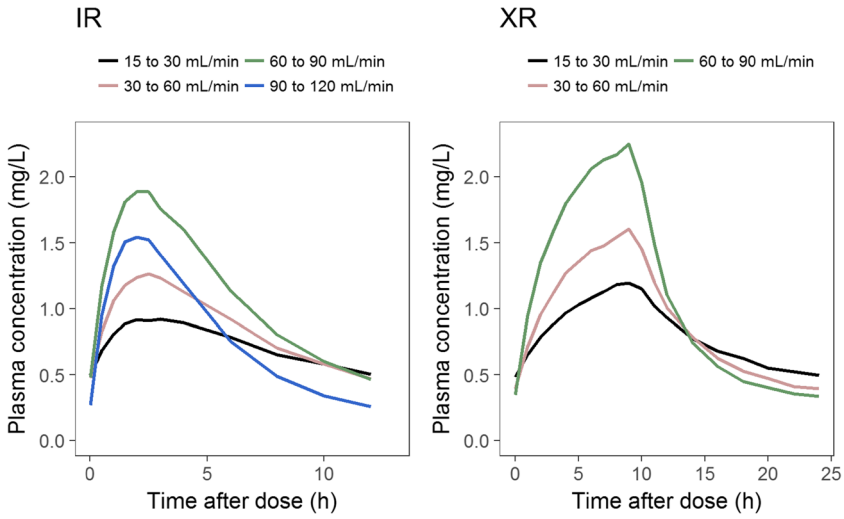

Fig. 5 Simulated median plasma concentrations of metformin for CL_{CR} of 15 to 30 mL/min, 60 to 90 mL/min and 90 to 120 mL/min (IR only) at daily doses of 500 mg, 1000 mg, 2000 mg (maximum XR dose) and 3000 mg, respectively

doses proportionally with kidney function to maintain C_{max} below 5 mg/L and to achieve a consistent drug across a range of renal function. CL_R was well estimated; however, further studies are required to obtain reliable estimates of CL_{NR}/F and F.

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Contributions JKD designed and conducted studies 1 and 2, analysed the data, built the model and wrote the manuscript. MK conducted study 3, analysed the data and contributed to the manuscript. SSK and CMK provided advice on the population model and interpretation of the results. GG was involved in detailed discussions on the clinical significance of the results with JKD. All authors reviewed the manuscript and approved the final version of the manuscript.

Compliance with ethical standards Informed consent was obtained from all individual participants included in the study. Studies 1 and 2 were approved by the Human Research Ethics Committee at St. Vincent's Hospital and University of New South Wales, Sydney (08209/SVH08/035; 09280/SVH09/080), and were registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000908932). Study 3 was approved by the Ethics Committee of the University Medical Center Groningen (Almelo, The Netherlands; METc 2013.178).

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Competing interests The authors declare that they have no conflicts of interest.

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