REVIEW ARTICLE

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Clinical Pharmacokinetics of Metformin

Garry G. Graham,[1] *Jeroen Punt*,[1] *Manit Arora*,[1] *Richard O. Day*,[1] *Matthew P. Doogue*,[2] *Janna K. Duong*,[1] *Timothy J. Furlong*,[3] *Jerry R. Greenfield*,[4] *Louise C. Greenup*,[1] *Carl M. Kirkpatrick*,[5] *John E. Ray*,[1] *Peter Timmins*[6] and *Kenneth M. Williams*[1]

1 Departments of Pharmacology & Toxicology and Medicine, St Vincent's Clinical School, University of New South Wales, Sydney, New South Wales, Australia
2 Department of Clinical Pharmacology, Flinders Medical Centre, Adelaide, South Australia, Australia
3 Department of Nephrology, St Vincent's Hospital, Sydney, New South Wales, Australia
4 Department of Endocrinology and Diabetes Centre, St Vincent's Hospital and Diabetes and Obesity Research Program, Garvan Institute of Medical Research, Sydney, New South Wales, Australia
5 School of Pharmacy, The University of Queensland, Brisbane, Queensland, Australia
6 Biopharmaceutics Research and Development, Bristol-Myers Squibb Company, Moreton, UK

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Abstract

Metformin is widely used for the treatment of type 2 diabetes mellitus. It is a biguanide developed from galegine, a guanidine derivative found in *Galega officinalis* (French lilac). Chemically, it is a hydrophilic base which exists at physiological pH as the cationic species (>99.9%). Consequently, its passive diffusion through

cell membranes should be very limited. The mean ± SD fractional oral bioavailability (F) of metformin is 55 ± 16%. It is absorbed predominately from the small intestine.

Metformin is excreted unchanged in urine. The elimination half-life ($t_{½}$) of metformin during multiple dosages in patients with good renal function is approximately 5 hours. From published data on the pharmacokinetics of metformin, the population mean of its clearances were calculated. The population mean renal clearance (CL_R) and apparent total clearance after oral administration (CL/F) of metformin were estimated to be 510 ± 130 mL/min and 1140 ± 330 mL/min, respectively, in healthy subjects and diabetic patients with good renal function. Over a range of renal function, the population mean values of CL_R and CL/F of metformin are 4.3 ± 1.5 and 10.7 ± 3.5 times as great, respectively, as the clearance of creatinine (CL_{CR}). As the CL_R and CL/F decrease approximately in proportion to CL_{CR}, the dosage of metformin should be reduced in patients with renal impairment in proportion to the reduced CL_{CR}.

The oral absorption, hepatic uptake and renal excretion of metformin are mediated very largely by organic cation transporters (OCTs). An intron variant of OCT1 (single nucleotide polymorphism [SNP] rs622342) has been associated with a decreased effect on blood glucose in heterozygotes and a lack of effect of metformin on plasma glucose in homozygotes. An intron variant of multidrug and toxin extrusion transporter [MATE1] (G>A, SNP rs2289669) has also been associated with a small increase in antihyperglycaemic effect of metformin. Overall, the effect of structural variants of OCTs and other cation transporters on the pharmacokinetics of metformin appears small and the subsequent effects on clinical response are also limited. However, intersubject differences in the levels of expression of OCT1 and OCT3 in the liver are very large and may contribute more to the variations in the hepatic uptake and clinical effect of metformin.

Lactic acidosis is the feared adverse effect of the biguanide drugs but its incidence is very low in patients treated with metformin. We suggest that the mean plasma concentrations of metformin over a dosage interval be maintained below 2.5 mg/L in order to minimize the development of this adverse effect.

Type 2 diabetes mellitus has become an epidemic in the past several decades. Metformin, an oral antihyperglycaemic agent, is the most widely used drug in the treatment of type 2 diabetes. It is a biguanide which has supplanted phenformin, another biguanide (figure 1). These drugs were developed from galegine, a derivative of guanidine found in *Galega officinalis* [French lilac; goats rue] (figure 1).

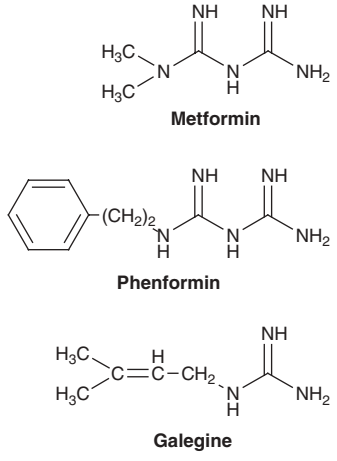

Fig. 1. Chemical structures of metformin, phenformin and the guanidine derivative, galegine, an active principle of the French lilac.

Unlike the sulfonylureas, metformin is rarely associated with hypoglycaemia or weight gain. Most commonly, patients maintain or even lose weight. The International Diabetes Federation and the American Diabetes Association and European Association for the Study of Diabetes both recommend that metformin be commenced as the first-line treatment in all newly diagnosed patients, regardless of age.[1,2] Questions about the cardiovascular safety of an alternative group of drugs, the glitazones, have further added to the status of metformin.

The purpose of this review is to summarize the pharmacokinetics of metformin. Passive diffusion of metformin through cell membranes is low because of the hydrophilic chemical nature of metformin but it is a substrate for several organic cation transporters (OCTs) and an aim of this review is to examine the significance of these transporters in the distribution, elimination and biochemical effects of metformin in man. A feature of the activity of metformin is the intersubject differences in its clinical response and up to about one-third of patients do not respond adequately to metformin. Consequently, we have sought to determine if genetic variants of the

transporters are responsible for intersubject variations in the pharmacokinetic parameters and clinical response of metformin. The relationship between the plasma concentrations of metformin and the most severe adverse effect, lactic acidosis, has also been reviewed. It should be noted that several aspects of the clinical pharmacokinetics of metformin, particularly the involvement of transporters, are unclear and further research is required.

1. Methods

1.1 Literature Searches

Data on the pharmacokinetics and pharmacodynamics of metformin were examined by searches on MEDLINE (1950 to 15 November 2010) and EMBASE (1988 to 15 November 2010). The keywords used were: 'metformin' together with 'pharmacokinetics', 'metabolism', 'half-life', 'pharmacodynamics', 'lactate', 'lactic', 'plasma', 'erythrocyte', 'transporter', 'OCT', 'MATE' or 'PMAT'. Papers were also obtained from the reference lists of research and review articles. Inclusion criteria were papers describing the pharmacokinetics of metformin as well as correlations between the pharmacokinetics or plasma concentrations of metformin and the blood concentrations of lactate and glucose. Recent results on cation transporters were obtained from databases of the National Center for Biotechnological Information (www.ncbi.nim.nih.gov/sites/entrez). Papers were included irrespective of the language. No study could be eliminated because of poor quality. Approved product information on metformin was also examined.

1.2 Statistics

All data are presented as mean ± SD. The population mean ± SD values of the renal clearance (CL_R) were calculated from the mean ± SD values from the several individual studies in subjects with good renal function using the methods of Sheiner et al.[3] (equation 1):

$$CL_R = \frac{\sum (N \bullet w \bullet CL_R)}{\sum (N \bullet w)} \quad \text{(Eq. 1)}$$

where N = number of subjects in the individual studies and w is the weight, an integer ranging from 1 to 3. In general, w was set at 3 when means of replicated studies had been published. Otherwise, w was set at 1. The population SD was estimated by the same general procedure. The mean and SD of the population values of the apparent clearance after oral administration (CL/F) and the ratios of CL_R and CL/F to creatinine clearance (CL_{CR}) were determined similarly.[3,4]

2. Physicochemical Properties

Metformin has acid dissociation constant values (pKa) of 2.8 and 11.5[5,6] and, therefore, exists very largely as the hydrophilic cationic species at physiological pH values. The pKa of 11.5 makes metformin a stronger base than most other basic drugs with less than 0.01% unionized in blood. Furthermore, the lipid solubility of the unionized species is slight as shown by its low logP value [log(10) of the distribution coefficient of the unionized form between octanol and water] of −1.43.[5] These chemical parameters indicate low lipophilicity and, consequently, rapid passive diffusion of metformin through cell membranes is unlikely. The logP of metformin is less than that of phenformin (−0.84) because two methyl substituents on metformin impart lesser lipophilicity than the larger phenylethyl side chain in phenformin (figure 1). More lipophilic derivatives of metformin are presently being investigated with the aim of producing prodrugs with better oral absorption than metformin itself. The dose of metformin is quoted as the hydrochloride salt (molecular weight 165.63) but all concentrations in biological fluids are expressed as the free base (molecular weight 129.16).

3. Pharmacokinetics after Intravenous Administration

Initially, the plasma concentrations of metformin decrease rapidly after intravenous dosage but it is difficult to quote a meaningful elimination half-life ($t_{½}$) because the time course of plasma concentrations of metformin follows a multiphasic pattern (figure 2a). The plasma concentration-time curve has been fitted by both biexponential[8] and triexponential functions.[7,9] The rapid initial decrease in plasma concentrations leads to the concentrations falling below the limit of assay by conventional high-performance liquid chromatography after about 12 hours. The mean terminal $t_{½}$ in plasma has been reported to range from 1.7 to 4.5 hours (table I) but these values do not represent the correct estimates of the terminal $t_{½}$ in plasma nor the $t_{½}$ during multiple dosage. The concentrations in urine are much higher than that derived from plasma and have been followed up for up to 72 hours (figure 2a). The terminal $t_{½}$ determined from the rate of excretion in urine is much longer than from plasma and ranges from about 9 to 19 hours (table I). A terminal $t_{½}$ of about 20 hours is supported from the determination of the plasma $t_{½}$ following cessation of multiple dosage regimens of metformin (section 4.1.2). The long terminal phase is due to a compartment that metformin enters and leaves slowly. This compartment includes erythrocytes (sections 4.1.2 and 5.3).

Despite the long terminal $t_{½}$, the bulk of the elimination of metformin occurs during the early phase. Thus, Tucker et al.[7]

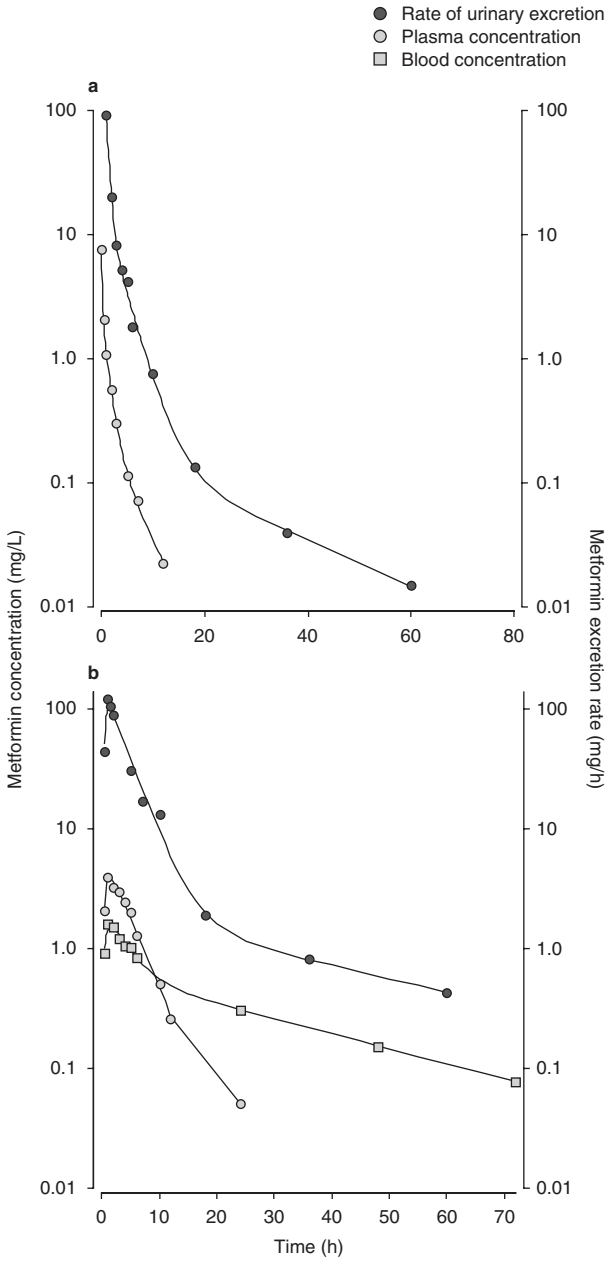

Fig. 2. (**a**) Time course of mean plasma concentrations and mean rate of urinary excretion of metformin following a short infusion (0.25 g over 15 min). (**b**) Time course of concentrations of metformin in plasma and in blood, and rate of urinary excretion of metformin in a healthy subject following an oral dose of 1.5 g. The prolonged elimination half-life from blood is due to the slow uptake and loss from erythrocytes. The data are from Tucker et al.[7]

found that, of the 79% recovered in urine, approximately 95% of this total urinary output of metformin was excreted in the first 8 hours after dosage.

The most clinically relevant $t_{1/2}$ of metformin is the $t_{1/2}$ over a dosage interval during long-term treatment. This is discussed in section 4.1.2.

4. Pharmacokinetics after Oral Administration

4.1 Immediate-Release Tablets

4.1.1 Single Doses

Peak plasma concentrations of metformin occur approximately 3 hours after dosage.[7] The peak plasma concentrations range from 1.0 to 1.6 mg/L after a 0.5 g dose, increasing to about 3 mg/L after a 1.5 g dose.[7] The plasma concentrations decrease rapidly after a single oral dose and, as is the case after intravenous dosage, the rate of urinary excretion can be followed for a longer time than the plasma concentrations and again indicates a terminal $t_{1/2}$ of about 20 hours (figure 2b).[7] Metformin is also taken up by erythrocytes (section 5.3) from which the $t_{1/2}$ of loss is also about 20 hours (figure 2b).[7,10]

The gastrointestinal absorption of metformin from the immediate-release tablets is incomplete and the bioavailability (F) shows some intrasubject as well as intersubject variability (figure 3). From published data on a total of 11 healthy subjects,[7,9] we estimate that the population mean value of F is 55 ± 16%. Absorption ceases at about 6–10 hours after administration irrespective of the amount of metformin that has been absorbed up to this time (figure 3). This is about the time taken for the passage of drugs through the stomach and small intestine.[11] Absorption from the stomach is likely to be negligible and it therefore appears that the absorption of metformin is confined very largely to the small intestine with negligible absorption also from the large intestine. This conclusion is confirmed by the administration of metformin solutions containing a gamma emitter which show that the plasma concentrations of metformin commence to decline when the drug starts to arrive in the large intestine.[12]

The faecal recovery of metformin is 20–30% of an oral dose.[7] As there is no metformin in faeces after intravenous dosage, the material in faeces must be unabsorbed material.[7] Furthermore, there must be no significant biliary or gastrointestinal secretion.

It is recommended that metformin should be taken with food to minimize gastrointestinal side effects, such as bloating, flatus and diarrhoea. A high-fat meal has been reported to decrease the bioavailability of immediate-release tablets of metformin by about 25%[13] although the effect of food is minimal with combination tablets of metformin with other anti-diabetic drugs.[14-16] The reduced absorption is unlikely to be clinically significant in most patients.

4.1.2 Multiple Doses

In healthy subjects, the mean plasma concentrations of metformin fluctuate between about 0.4 and 1.3 mg/L during

Table I. Pharmacokinetic parameters of metformin after intravenous administration

Parameter	Tucker et al.[7]	Pentikäinen et al.[9]	Sirtori et al.[8]
Patients (n)	4	3	5
Dose (g)	0.25	0.5	1.0
Duration of collection of blood samples (h)	12	10–12	8
$t_{½}$ in plasma (h)[a]	4.5 ± 2.1	1.74 ± 0.19	1.52 ± 0.29
$t_{½}$ in urine (h)[a]	19 ± 10	8.9 ± 1.2	
CL (mL/min)[a,b]	706 ± 33	473 ± 18	441 ± 89
% of drug excreted unchanged[a]	78.9 ± 4.7	99.9 ± 1.4	86
V_d (L)[a,b]	276 ± 136	69 ± 8	63 ± 17

a Values are expressed as mean ± SD.

b $t_{½}$ and V_d estimated from plasma concentrations during the later times after dosage.

CL = apparent total clearance; **$t_{½}$** = half-life; **V_d** = volume of distribution.

dosage with 1000 mg twice daily (figure 4).[17] The mean concentrations over a dosage interval (average steady-state concentrations [$C_{av,ss}$]) are 0.86 mg/L (table II). Figure 4 shows the mean time course of plasma concentrations fitted by a one-compartment model and first-order rate constants (i.e. constant $t_{½}$ values of absorption and elimination). There is only slight deviation from the concentrations predicted from this model and the actual plasma concentrations. The mean $t_{½}$ is about 5 hours in these subjects with good renal function (figure 4, table II). A similar mean $t_{½}$ of 5.7 hours was calculated from the data of Hong et al.[21] (table II). This study was conducted in diabetic patients with, on average, slightly impaired renal function (CL_{CR} 83 ± 23 mL/min), but the $t_{½}$ values are very similar to those in healthy subjects.

As judged from the overall plasma concentrations of metformin, there is no significant accumulation of metformin during multiple doses. Thus, the area under the plasma concentration-time curve (AUC) after twice-daily dosage for 4 days is very similar to that seen in the first day of dosage.[17] However, the trough concentrations are about 95% higher than predicted from the pharmacokinetic parameters on the first day of treatment.[7] The trough concentrations were even higher and the discrepancy between actual and predicted trough concentrations is even greater after treatment for another 7 days. The lack of agreement between the predicted and actual trough concentrations in plasma is undoubtedly due to the late slow elimination phase (section 3, figure 2). This late phase in plasma is clearly seen after termination of multiple-dose treatment with metformin.[19]

As discussed above, there is some intrasubject variation in the bioavailability of metformin. However, the variation is not great during multiple dosing, at least under the conditions of a controlled pharmacokinetic study in which the plasma concentrations of metformin were measured over four dosage intervals of 12 hours (figure 4).[17] The mean coefficient of variation of the AUC values in the individual subjects was only 13% (range 4–23%).

4.2 Sustained-Release Formulations

Sustained-release dosage forms of metformin have been prepared because of the short initial $t_{½}$ of metformin. Metformin is not, however, a good candidate for a traditional sustained-release dosage form because its absorption is limited largely to the small intestine (section 4.1). A widely used formulation overcomes this problem to some extent. This sustained-release tablet swells into a gel-like mass which is designed to slow passage through the pylorus and thereby prolong gastric residence.[17] Transit through the small intestine may also be slowed by the formation of this gel-like mass. The metformin is contained in polymer particles in the polymer-containing tablet matrix from which it dissolves slowly and then diffuses through the outer gel-like mass.

An osmotic sustained-release tablet has also been prepared.[22] After single doses, this product has very similar bioavailability to that seen during dosing with immediate-release and other sustained-release tablets.

4.2.1 Multiple Doses

During long-term dosing, the absorption of metformin is slowed considerably by the sustained-release formulation and maximum plasma concentrations are reached at about 7–8 hours as opposed to about 3 hours with immediate-release formulation and coinciding, approximately, with the transit time to the large intestine (figure 4). The values of CL/F increase slightly with increasing daily dose (table II), presumably due to decreased values of F.

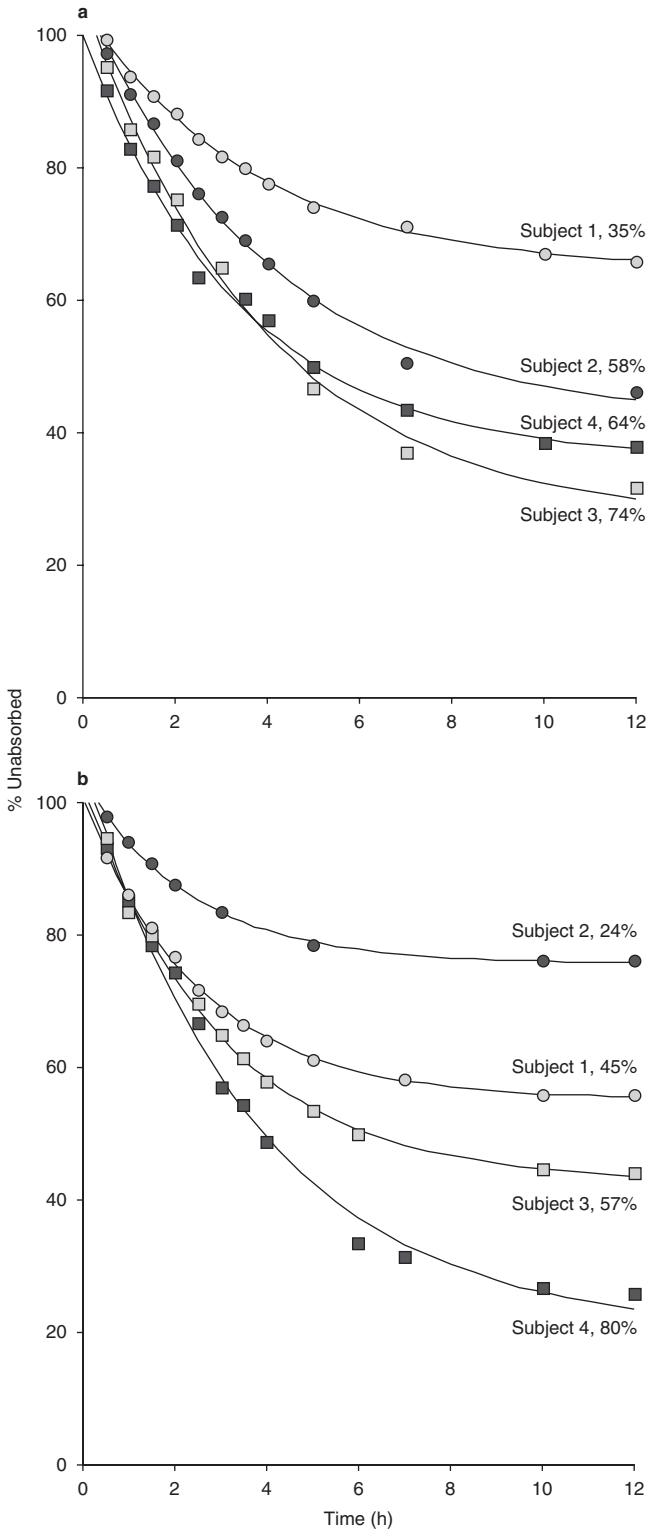

Fig. 3. Percentages of oral doses of metformin remaining to be absorbed as a function of time after (**a**) a 0.5 g dose and (**b**) a 1.0 g dose in four healthy subjects. The plots show the subject identification number and percentage of metformin absorbed. The percentage absorption of metformin is fairly consistent after the two doses in subject 1, 3 and 4 but dissimilar in subject 2. The data are from Tucker et al.[7]

At a dosage of 2 g as sustained-release tablets once daily, the plasma concentrations of metformin fluctuate from peaks of about 1.8 mg/L to troughs of about 0.16 mg/L (figure 4). The ratio of peak to trough plasma concentrations of metformin is greater with the sustained-release than with the immediate-release tablets. This is the result of the longer time between doses of the sustained-release tablets (typically 24 hours) than between doses of the immediate-release tablets (about 12 hours) [figure 4]. The lowering of blood glucose by metformin develops over at least 10 days[19,21] indicating that metformin has a long residence time in the liver or other effect compartments. Consequently, the greater fluctuation of plasma concentrations should not be clinically significant, as has been observed.[23]

Gastrointestinal intolerance occurs with both the immediate and sustained-release metformin but, on average, the sustained-release formulation is better tolerated.[24,25] As a result, patients often show improved gastrointestinal tolerance of metformin if changed from immediate-release to sustained-release metformin and the National Institute for Health and Clinical Excellence now recommends that sustained-release metformin should be trialled if gastrointestinal intolerance prevents continuation of the immediate-release preparation.[26] The sustained-release formulation also allows a once-daily dosing regimen which may lead to improved adherence.

4.3 Transporters and Absorption of Oral Metformin

Plasma membrane monoamine transporter (PMAT) may be the major transporter responsible for the uptake of metformin from the gastrointestinal tract. It is localized on the luminal side of enterocytes (figure 5).[27] OCT1 and OCT3 are also present in the small intestine although only low amounts of both transporters are present.[28,29] OCT3 is also localized in the brush border of enterocytes[30] and may therefore be, in part, a carrier of metformin into enterocytes. By contrast, OCT1 is localized in basolateral membranes and cytoplasm of enterocytes and may transport metformin into interstitial fluid.[30] OCT1 – and, possibly to a lesser extent, OCT3 – are transporters of metformin in the liver (sections 5.1 and 6.1) where they are present on the basolateral side of hepatocytes, indicating that they transport metformin into hepatocytes.

Genetic variants of OCT1 and OCT3 have been detected, many of which show lesser ability to transport metformin into model cells.[31,32] After oral dosage to healthy subjects, the plasma concentrations of metformin were slightly higher in heterozygotes with one of several variant OCT1 transporters than in persons with the normal (wild-type) OCT1. This indicates that the presently identified OCT1 variants do not lead

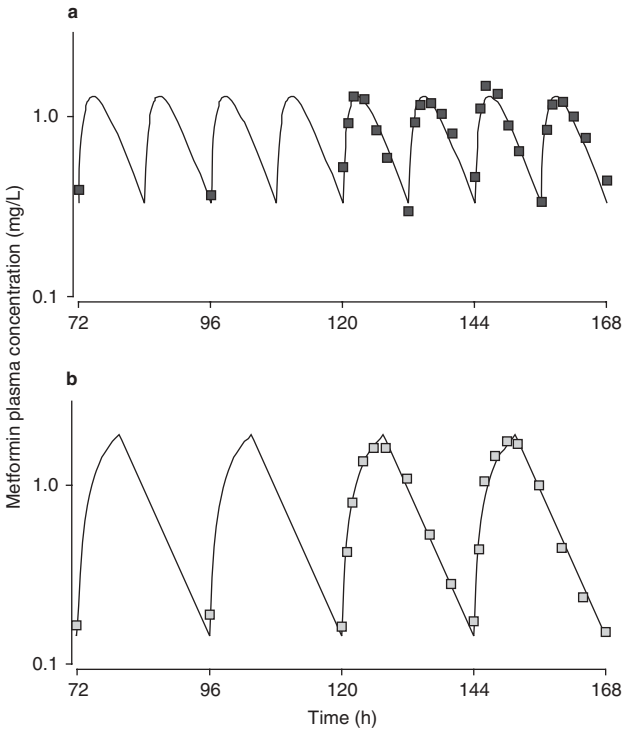

Fig. 4. Semilogarithmic plots of the time courses of mean plasma concentrations during multiple dosing with (**a**) immediate-release metformin 1000 mg (two 500 mg tablets) every 12 h, and (**b**) sustained-release metformin 2000 mg (four 500 mg tablets) once daily. The best-fit curves were determined by the use of the Kinetica software program (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The absorption kinetics are described by a constant half-life of absorption (first-order) and constant rate of absorption (zero-order) over 7.6 h, for the immediate-release and sustained-release tablets, respectively. A constant half-life was applied in both cases. The data are from Timmins et al.[17] in 14 to 16 healthy subjects.

to significantly decreased absorption.[31] A possible explanation is, as outlined in sections 6.1 and 7 and table III, that major changes may be seen only in homozygotes carrying poorly functioning transporters, but not in heterozygotes. An alternative explanation is that carriers, other than OCT1, may be transporting metformin out of enterocytes.

4.4 Concentrations of Metformin in the Small Intestine: Relevance to Action of Metformin

The peak concentrations of metformin in the jejunum are up to about 500 μg/g of tissue.[38] Although it may be difficult to wash out all the extracellular drug within the brush border, it does appear that the concentrations within the small intestine tissue are much higher than in other tissues or in plasma, raising the possibility that a significant site of action of metformin may be in the small intestine.[39] Modelling of the absorption of metformin through monolayers of a model cell line, Caco-2 cells, indicates that a substantial proportion of metformin may be absorbed through the paracellular route (between cells) although the model still allows high concentrations of metformin to develop within the cells.[40] Although Caco-2 cell monolayers are very useful in studying drug transport *in vitro*, the expression of OCTs, particularly the expression of OCT2 in Caco-2 cells,[30] makes Caco-2 cells different to normal enterocytes.

5. Distribution

Metformin is not bound to plasma proteins.[7] The volume of distribution (V_d) has been reported to range from 63 to 276 L after intravenous administration (table I). These values represent V_d over the last 8–12 hours after intravenous dosage (table I). Of greater significance is the apparent volume of distribution after oral administration (V_d/F) estimated during multiple dosing. During dosage with 2000 mg metformin daily, either as immediate-release or sustained-release tablets, V_d/F is approximately 600 L (table II). As approximately 50% is absorbed (section 4), the actual V_d during multiple dosage is about 300 L. This large V_d indicates that there is considerable tissue uptake of metformin.

The large V_d of metformin is confirmed by studies in mice and rats. After a single oral dose, concentrations up to seven times the serum concentrations are found in the kidneys, adrenal glands, pancreas and liver, with lesser amounts in lung, muscle and spleen.[41,42] The high concentrations in kidney are not necessarily due to uptake in kidney tissue and may be due, in part, to high concentrations of metformin in the urinary tract (section 6).

5.1 Transporters and Uptake by Liver

OCT1 and OCT3 are transporters of metformin in the liver. The greatly diminished hepatic uptake of metformin in OCT1-knockout mice indicates that OCT1 is the major transporter in mice.[33,43] It is widely presumed that this is also the case in man but the relative activities of OCT1 and OCT3 are still unknown in man.

Both OCT1 and OCT3 are present in highest levels on the sinusoidal membrane (basolateral side) of hepatocytes[32,44] and thus are located in a position for uptake of metformin from blood into hepatocytes (figure 4). They could also transport metformin in the reverse direction, i.e. from liver to blood. Both transporters are also present, at lower levels, in the cell membrane of cholangiocytes (epithelial lining cells of bile ducts)[44] where their function is unknown. Metformin is a substrate for OCT1[33,44-46] and OCT3[32,44] and the recently discovered and

Table II. Pharmacokinetic parameters of metformin during multiple-dosing regimens in healthy subjects (HS) or patients with type 2 diabetes mellitus (DM) with good renal function[a]

Dosage (mg)	n	C_{max} (mg/L)	$C_{av,ss}$ (mg/L)	CL/F (mL/min)	V_d/F (L)	$t_{½}$ (h)	Reference
Immediate-release							
HS, 250 mg bid	24	0.65 ± 0.11	0.35 ± 0.06	780 ± 139	NA	NA	18
DM, 850 mg tid	9	1.90 ± 0.63	1.35 ± 0.50	1118 ± 325	1952 ± 1519[b]	19.8 ± 15.9[b]	19
HS, 850 mg tid	9	2.01 ± 0.39	1.34 ± 0.35	1130 ± 457	1211 ± 690[b]	13.0 ± 7.8[b]	19
DM, 1000 mg bid	13	2.09 ± 0.56	1.23 ± 0.30	881 ± 215	NA	NA	20
HS, 1000 mg bid	15	1.32 ± 0.23	0.86 ± 0.19	1265 ± 274	559 ± 163	5.1 ± 1.0	17
DM, 850 mg bid[b]	12	NA	0.70 ± 0.06	1316 ± 113	648 ± 13.8	5.7 ± 1.3	21
Sustained-release							
HS, 500 mg od	16	0.60 ± 0.17	0.26 ± 0.08	1029 ± 325	463 ± 204	5.2 ± 1.6	17
HS, 1000 mg od	16	1.08 ± 0.26	0.52 ± 0.13	1033 ± 260	402 ± 123	4.5 ± 0.8	17
HS, 1500 mg od	15	1.44 ± 0.36	0.70 ± 0.17	1159 ± 287	481 ± 129	4.8 ± 0.5	17
HS, 2000 mg od	14	1.80 ± 0.29	0.85 ± 0.17	1271 ± 256	572 ± 175	5.2 ± 1.2	17

a Values are expressed as mean ± SD.

b V_d/F and $t_{½}$ are the pharmacokinetic parameters determined during the terminal log-linear phase elimination following termination of treatment and therefore do not represent the parameters over a dosage interval.

bid = twice daily; **$C_{av,ss}$** = average plasma concentration at steady state over a dosage interval; **CL/F** = total clearance after oral administration; **C_{max}** = maximum plasma concentration; **NA** = not available; **od** = once daily; **$t_{½}$** = elimination half-life; **tid** = three times daily; **V_d/F** = volume of distribution after oral administration.

very considerable variation in the hepatic expression of OCT1 may be of great significance in the clinical response to metformin because its major effect may be in the liver.[33] The large intersubject variation in the hepatic levels of OCT1 was detected by both the variation in the transporter protein (83-fold) and also in the corresponding messenger RNA (mRNA) [113-fold]. The importance of OCT1 expression may be important, as shown for imatinib. Low activity of OCT1 in mononuclear cells correlates with resistance to imatinib and requires higher than normal doses of the drug.[47]

As yet, the intersubject differences in the expression of OCT3 have only been detected by the 27-fold intersubject variation in the mRNA, and intersubject differences in the expression of OCT3 protein, although likely, have not been examined.[44]

These discoveries on variable expression of OCT1 and OCT3 have been made in normal sections of human livers taken at surgery. The patients were taking a variety of drugs and an influence of these drugs on the variation of OCT1 and OCT3 is possible. The levels of both OCT1 and OCT3 were lower in livers in patients with cholestasis than in livers in other patients although there was considerable overlap between the two groups.[44] The expression of OCT1 and OCT3 was also lower in patients carrying some variant transporters. As the clinical response to metformin shows considerable intersubject variation, it will be of great interest to determine if the variable response can be related to the hepatic expression of OCT1 or OCT3.

Multidrug and toxin extrusion transporter (MATE)-1 has been proposed to mediate the transport of metformin into bile canaliculus as it is present at this site and is a carrier of metformin.[48,49] However, metformin is not present in faeces after intravenous administration although it is present after oral dosage (section 4.1.1). The biliary excretion of metformin therefore appears insignificant in man although resorption in the biliary tract following initial secretion is possible. MATE1 is also present in the kidney where it probably transports metformin from kidney tubule cells into urine (section 6.1).

5.2 Organic Cation Transporters and Uptake of Metformin by Skeletal Muscle and Heart

Both OCT1 and OCT3 are expressed in skeletal muscle which may be a major site of action of metformin. The expression of mRNA of OCT3 is higher than that of OCT1 but the relative levels or activities of the two OCT proteins is unknown.[32] Several coding and intronic variants of OCT3 have been detected but the influence of these variants on the clinical response to metformin has not been determined. The actual uptake by skeletal muscle in man is not known but the concentration ratio is only about 1.5 in mice and, not surprisingly, is little reduced by OCT1 knockout.[45] As in skeletal muscle, the mRNA of OCT3 in heart is greater than mRNA of OCT1 but again, the relative activities of the two transporters are not known.[32]

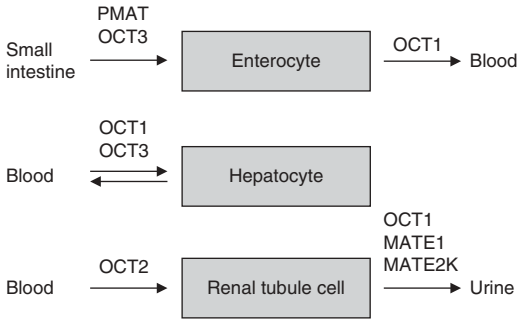

Fig. 5. Major known transporters involved in the absorption, hepatic uptake and urinary excretion of metformin. **MATE** = multidrug and toxin extrusion transporter; **OCT** = organic cation transporter; **PMAT** = plasma membrane monoamine transporter.

5.3 Uptake into Erythrocytes: Possible Value in Monitoring Dosage of Metformin

An unusual aspect of the pharmacokinetics of metformin is its slow uptake into erythrocytes (figure 2b). After single doses, the peak concentrations are much higher in plasma than in erythrocytes. The subsequent decline of concentrations in erythrocytes is much slower than in plasma and, after about 6 hours, the concentrations in erythrocytes exceed those in plasma. The mean terminal $t_{½}$ is about 20 hours in erythrocytes and is therefore very similar to the terminal $t_{½}$ of metformin in plasma and urine (section 4, figure 2b).[7,10] During long-term dosing, the concentrations in erythrocytes should fluctuate to a much lesser degree than in plasma.[10]

Monitoring the plasma concentrations of metformin is not standard clinical practice but it has been suggested that monitoring the concentrations in erythrocytes could assist the dosage optimization.[10] The relatively stable concentrations in erythrocytes should allow an evaluation of the exposure of patients to metformin over the previous 1 to 3 days. Erratic dosage times and intrasubject variation in the rate or extent of absorption should have lesser effects on the concentrations in erythrocytes than in plasma.

Two procedures have been used to measure the concentrations in erythrocytes. Robert et al.[10] assayed metformin in erythrocytes after centrifugation and washing the cells three times with normal saline. The alternative method is to measure the haematocrit (H) of the blood sample and to assay the concentrations in whole blood (C_b) and plasma (C_p). The concentrations in erythrocytes (C_e) is then calculated from equation 2:

$$C_e = \frac{C_b - (1 - H) \bullet C_p}{H} \qquad \text{(Eq. 2)}$$

5.4 Transport and Pharmacokinetics during Pregnancy and Lactation

Metformin is increasingly being used to treat gestational diabetes.[50-52] Metformin is carried across the placenta by transporters[53] and the concentrations in the fetus are only slightly lower than in the mother. Further, the plasma metformin concentrations are lower in pregnancy than in non-pregnant women if the dosage is not altered,[54,55] due to its greater CL_R which is the result of the higher glomerular filtration rate (GFR) during pregnancy.[56] CL_R and CL/F may be increased

Table III. Variants of organic cation transporters (OCTs) and renal clearance (CL_R) of metformin

Variant transporter, nucleotide, amino acid change	Uptake *in vitro* into cells expressing variant transporter (% of control)	CL_R of metformin in variants (% of control CL_R [95% CI] {n = no. of subjects in normal, variant groups})
OCT1 SLC22A1		
181C>T, Arg61Cys	7[33]	Heterozygotes (1 normal allele + 1 or more of 4 variant alleles)
1201G>A, Gly401Ser	100[33]	1 or 2 variant alleles, 95 [52, 138] {n = 8, 12}[31,34]a
1256delARG, Met420Del	30[33]	1 variant allele, 108 [99.5, 117] {n = 51, 48}[34,35]
1393G>A, Gly465Arg	3[33]	2 variant alleles, 121 [109, 134] {n = 51, 4}[34,35]
OCT2 SLC22A2		
808G>T, Ala270Ser	150,[36] 60[37]b	Heterozygotes (1 normal allele + 1 variant allele)
		95 [87, 103] {n = 113, 39}[34]
		Homozygotes {2 variant alleles}
		60 [46, 74] {n = 15, 10}[34]

a One subject was homozygous with respect to the variant transporter, Arg61Cys.

b Contrasting results may be due to differing cellular expression of variant transporter.

by about 50% during mid-pregnancy.[56] Increasing dosage during pregnancy and reducing dosage back to usual levels after delivery should be considered.[54]

There is minimal transport of metformin into milk with the estimated dose being less than 0.3% of the mother's dose even when calculated on the basis of their relative body-weights.[57]

5.5 Transport into Other Tissues

Both OCT1 and OCT3 are found in many tissues. OCT1 is located predominately in the liver with much lower concentrations in several other tissues.[44] The level of OCT1 mRNA is substantial in the adrenal gland although the expression is still much lower than in the liver. OCT3 is present in many tissues, apart from the liver, with the highest levels of the mRNA in the adrenal gland. The high levels of OCT1 and OCT3 in the adrenal gland are consistent with the substantial levels of metformin at this site.[41] In mice, MATE1 is found in many tissues, including A (glucagon-secreting) cells of the islets of Langerhans but not in B (insulin-secreting) cells.[58] As is the case in humans, high levels of MATE1 are also present in the adrenal cortex.[58] Correlations between the mechanism of action of metformin and its distribution in specific tissues requires examination.

6. Clearance

Excretion of unchanged drug in urine is the major mode of elimination of metformin. No metabolites of metformin have been found in urine[7,9,41] although different drug recoveries are reported in urine. Pentikäinen et al.[9] administered ^{14}C-labelled metformin intravenously and found 100% recovery of unchanged drug in urine (table I). By contrast, Tucker et al.[7] and Sirtori et al.[8] could not account for approximately 20% of the drug, using chromatographically based assays of unlabelled drug. No drug is, however, found in the faeces after intravenous dosage.[7,9] Thus, it is still possible that small proportions of doses of metformin may be metabolized or excreted by non-renal routes. Despite this uncertainty, it is clear that the CL_R of metformin is very high and is the major mode of elimination of metformin.[7] The estimated population mean (± SD) of CL_R is 507 ± 129 mL/min in subjects with good renal function (table IV).[7-9,14,19,35,36,59-61] Three factors probably contribute to its high CL_R:

(i) Metformin is a small molecule which is not bound to plasma proteins and, therefore, is readily filtered at the glomerulus.

(ii) Metformin is a substrate for several transporters in the kidney (section 6.1).

(iii) The low lipid solubility of metformin should lead to negligible passive resorption (section 2).

Table IV. Renal clearance (CL_R) of metformin in healthy subjects (HS) and patients with diabetes mellitus (DM). All doses were oral except where noted after the dose. All subjects and patients had good renal function

Dose	Subjects	n	No. of studies on each subject	CL_R (mL/min)	Reference
500 mg single dose	HS	5	1–2	446 ± 56	9
250 mg IV, 1000 and 1500 mg	HS	4	3	494 ± 110	7
1000 mg single dose	HS + DM	8	1	280 ± 127	7
1000 mg single dose	HS	5	1	597 ± 196	59
850, 1700 and 2550 mg single doses, 850 mg tid	DM	9	4	519 ± 205	19
850, 1700 and 2550 mg single doses, 850 mg tid	HS	9	4	521 ± 144	19
850 mg single dose	HS	6	1	636 ± 84	60
927 mg IV single dose	HS	5	1	335 ± 103	8
550 mg single dose	HS	12	1	395 ± 135	14
259 mg od	HS	7	1	527 ± 165	61
500 mg single dose	HS	103	1	533 ± 117	35
850 mg single dose	HS	14	1	441 ± 108	36
Population mean ± SD				**505 ± 129**	

IV = intravenous; **od** = once daily; **tid** = three times daily.

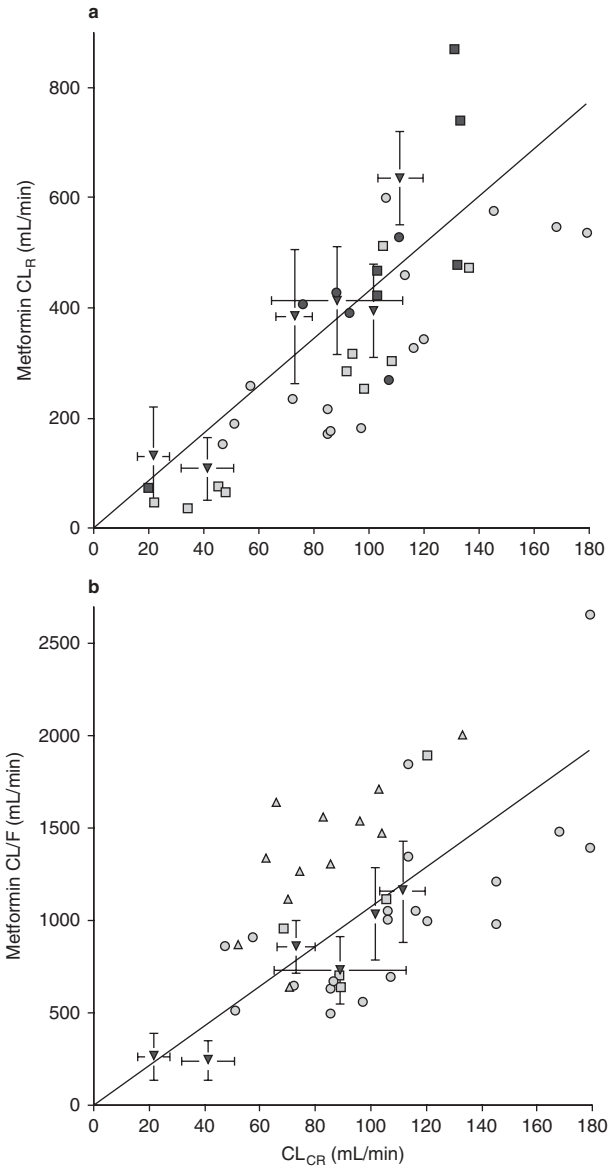

Fig. 6. (**a**) Relationship between renal clearance (CL_R) of metformin and the clearance of creatinine (CL_{CR}). The data are from Tucker et al.[7] (grey circles), Pentikäinen et al.[9] (black circles), Sirtori et al.[8] (grey squares) and Noel[59] (black squares) in individual subjects, and the mean ± SD data are from Sambol et al.[60] (black inverted triangles). The horizontal bars indicate the SDs of the CL_R. The correlation was significant ($r = 0.88$, $p < 0.001$). The line of best fit was calculated from the population mean ratio of the clearances (4.3). (**b**) Relationship between apparent clearance after oral administration (CL/F) of metformin and the CL_{CR}. The data are from individual subjects of Tucker et al.[7] (grey circles), Sirtori et al.[8] (grey squares) and Hong et al.[21] (grey triangles), and the mean ± SD data are from Sambol et al.[60] (black inverted triangles). The horizontal bars indicate the SDs of the CL_R. The correlation is significant ($r = 0.66$, $p = <0.01$). The line of best fit was calculated from the population mean ratio of the clearances (10.7).

As expected, the CL_R of metformin decreases approximately in proportion to decreasing renal function down to the lowest level of renal function measured, i.e. to a CL_{CR} of about 20 mL/min (figure 6a).[7-9,59,60] The ratio of the CL_R to the CL_{CR} is quite variable, 4.3 ± 1.5. In part, this variation may be due to the difficulty in collecting complete timed samples of urine for measurements of CL_R although careful measurements of the CL_R of metformin indicate that it varies little in individual subjects.[62] Intersubject differences in the tubular transport of metformin are likely and may also be due to either the presence of genetic variants or variable expression of the transporters (section 6.1).

Age is an independent variable which correlates negatively with the CL_R of metformin (i.e. for any particular value of CL_R, the CL/F of metformin decreased as age increased).[35,60] However, the influence of age is much smaller than the effect of CL_{CR}.

From measurements after single and multiple doses, the population CL/F is estimated to be 1140 ± 330 mL/min from data in subjects with good renal function (CL_{CR} >80 mL/min).[5,7,9,17-22,35,36,60,63] CL/F increases slightly with increasing multiple doses (table II), probably due to slightly decreasing fractional absorption (F). CL/F is higher than that of CL_R, as F is about 0.5 (section 4.1.1). Not surprisingly, a significant correlation is seen between the CL/F of metformin and the CL_{CR} (figure 6b). The population estimate of the ratio of the CL/F to the CL_{CR} is 10.7 ± 3.5.

The proportional relationship between both CL_R and CL/F with CL_{CR} indicates that the maximal dosage of metformin should be decreased in line with decreasing renal function. Many diabetic patients have impaired renal function and this is an important aspect of the control of metformin dosage. On the other hand, some patients have CL_{CR} well above the average of 120 mL/min and, not unexpectedly, the CL_R of metformin may be very high. For example, the data of Tzvetkov et al.[35] indicate that the mean CL_R is approximately 600 mL/min when the CL_{CR} is 150 mL/min. Higher dosages than usual may be considered in such patients if the clinical response to standard dosage is inadequate.

6.1 Renal Transporters

Several cation transporters are present in the kidney:
(i) OCT1, OCT2 and OCT3: OCT2 has been studied in most detail. It is located on the basolateral (blood) side of renal tubular cells and transports metformin into the proximal tubular lining cells (figure 5). OCT1 has been linked to the hepatic uptake of metformin (section 5.1) but has recently been detected in the apical membranes (luminal side) in the proximal and distal tubules [35] The site of OCT1 indicates that it is involved in the secretion of metformin although resorption is possible. OCT3 mRNA is also expressed in the kidney.[32]

(ii) MATE1 and MATE2K: MATE1 occurs in the brush border and probably transports metformin out of the tubule lining cells into urine. The transporter MATE2K, a splice variant of MATE2, is also present in the brush border and may be the major transporter of metformin into urine.[48,64]
(iii) PMAT has been recently detected in the podocytes in the glomerulus.[28,65] Its function in podocytes is not known.

The influence of four common low-activity variants of OCT1 on CL_R of metformin has been studied. Heterozygotes carrying only one of the four common variants show no significant changes in the CL_R but heterozygotes carrying two low-activity alleles have higher CL_R than normal subjects (table III). However, the number of subjects with two low-activity variants was only four and the percentage increase in CL_R was only 21% (table III), therefore further examination of this finding is required.

The intron variant, rs1867351, promotes the expression of OCT1 in lymphoblastoid cell lines but does not alter the CL_R of metformin in heterozygotes.[35]

Of the variants of OCT2, the Ala270Ser (rs316019, 808G>T) may be the most important because of the high frequency (10–15%) of this allele in several populations.[28] However, the results are inconsistent. Chen et al.[36] reported that CL_R and CL/F were higher in Caucasian and African-Americans heterozygotes carrying this variant than in normal homozygotes although there was considerable overlap of both clearances. However, Tzvetkov et al.[35] found no significant effect of the Ala270Ser transporter on CL_R in Caucasian heterozygotes while Song et al.[37] reported a lower clearance in a smaller number of heterozygous Korean subjects. Combining all the results on CL_R and ignoring possible racial differences in the expression of transporter variants, there is no significant difference between normals and heterozygotes carrying the variant Ala270Ser transporter.[34] Zolk[34] suggested that the lack of effect of the variant transporter in heterozygotes is due to the variant gene being recessive. To be consistent with the dominant/recessive hypothesis, a decreased CL_R should be seen in homozygotes carrying the variant OCT2 transporter, as is the case (table III). The CL_R is lower in two Asian groups of homozygotes carrying the variant Ala270Ser transporter than in normal homozygotes[37,66] but there are no data on the pharmacokinetics in homozygotes in Caucasian and African-American groups carrying the variant because of the rarity of such homozygotes.

The expression of OCT2 mRNA in human kidney varies over 100-fold.[67] As is the case with mRNA of OCT1 in the liver (section 5.1), it is likely that the variable mRNA leads to considerable intersubject variation in the expression of OCT2 protein and, potentially, in the CL_R of metformin. There is, however, no information on the levels of OCT2 protein in the human kidney. It is of note that the data on the expression of OCT2 mRNA may possibly be affected by the patients' cancers or treatment as the samples were obtained from apparently normal parts of kidney cortex taken from nephrectomized patients.[67]

Several coding variants of OCT3 have been detected[32] but several variants, even in homozygotes, have not significantly altered the CL_R of metformin.[68] Heterozygotes carrying one of several coding variants of MATE1 and MATE2K also did not alter the CL/F of metformin but, as yet, there is no information on the CL/F in homozygotes.[69]

6.1.1 Interactions Involving Cation Transporters

Cimetidine is a substrate for cation transporters and decreases the CL_R of a low daily dose of metformin (250 mg).[61] The inhibitory effect of cimetidine may be dependent upon the transporter variant. Thus, cimetidine (400 mg daily) decreases the CL_R of metformin to a mean of 48% in subjects containing the reference OCT2, to 32% in subjects who are heterozygous with respect to a variant (OCT2-270S) and to 19% of control values in homozygotes of the same variant.[66] Interaction by cimetidine through MATE1 is also possible.[70,71] Pyrimethamine inhibits MATE1 and MATE2K *in vitro*[72] but this potential interaction has not been examined in man.

Many drugs, like cimetidine, metformin and pyrimethamine, are basic – i.e. they are cationic to a greater or lesser extent at physiological pH. Consequently, other basic drugs, such as antihistamines, antidepressants and opioid analgesics, could possibly decrease CL_R of metformin. Conversely, metformin may decrease the CL_R of other basic drugs that are excreted largely unchanged (e.g. amphetamines).

Combination tablets of metformin with a variety other drugs have been formulated and there are studies on possible pharmacokinetic interactions with glyburide,[14] vildagliptin,[73] sitagliptin,[20] rosiglitazone[74] and *Ginkgo* extract.[75] The effects of these other drugs on CL/F of metformin or of metformin on CL/F of other drugs are, at most, small and not clinically significant. Aliskiren[76] (a direct renin inhibitor), memantine[18] (a drug used for Alzheimer's disease) and the antibacterial cephalexin[77] also have insignificant effects on the CL/F of metformin. Although several of these compounds (vildagliptin, sitagliptin, rosiglitazone and memantine) have basic nitrogen groups and exist, to some degree, as cations at physiological pH values and could be potential substrates for cation transporters, they do not exhibit significant interactions with metformin. A variety of basic drugs inhibit the *in vitro* uptake of metformin by HEK293 cells expressing OCT2 but of the several drugs tested, only fenfluramine and mexiletine, in addition to cimetidine,

were detected as interacting significantly with the uptake of metformin *in vitro*.[78] These drugs should be evaluated *in vivo*. This study of Zolk et al.[78] also indicated a general molecular structure of drugs which may inhibit OCT2 and, consequently, the CL_R of metformin.

6.2 Lactic Acidosis and Dosage of Metformin in Renal Impairment

The occurrence of lactic acidosis during treatment with metformin is of great clinical concern as the death rate is up to 50%. It is diagnosed when a patient has a blood pH <7.35 and plasma lactate concentrations >5.0 mmol/L.[79] Lactic acidosis was associated with the older biguanides, phenformin and buformin, and the product information (label) on metformin contains statements such as: ''Life-threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment. Other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g/day.'' It is therefore commonly stated that metformin should only be prescribed if patients' CL_{CR} or GFR is above a defined low limit. The problem for prescribers is that the statements on the limit are inconsistent and, furthermore, there is considerable doubt about these recommendations. The product information contains the statement that metformin should not be prescribed in patients with GFR values below 60 mL/min. Other references include both lower (30 mL/min[80]) and higher (90 mL/min[81]) limits. The higher limit was suggested to 'ensure an adequate margin of safety' but if this were the lower limit of GFR for the prescription of metformin, a large proportion of diabetic patients would not receive the drug. Recent surveys indicate that metformin is commonly prescribed for patients with estimated GFRs down to 30 mL/min[82] and, in small numbers of patients, at even lower CL_{CR}.[83]

Despite the warnings in the product information about the danger of lactic acidosis during treatment with metformin, there is still considerable discussion and question about metformin being a significant cause of lactic acidosis. A recent estimation of the incidence of lactic acidosis is 3.3 cases per 100 000 patient years of treatment with metformin.[84] It is of note that lactic acidosis also develops during treatment with the other major group of oral antihyperglycaemic drugs, the sulfonylureas, where the incidence of lactic acidosis was estimated as 4.8 per 100 000 patient years.[84] Furthermore, no case of lactic acidosis was recorded in clinical trials on metformin.[79] These trials included studies over more than 70 000 patient-years of metformin treatment but patient selection to exclude patients with risk factors for lactic acidosis and good patient care may well have contributed to the absence of this adverse effect in these clinical trials.

Although lactic acidosis is clearly uncommon during treatment with metformin, there is little doubt that high concentrations of metformin can cause lactic acidosis. First, acute overdoses taken with suicidal intent have caused lactic acidosis.[85-88] Furthermore, plasma lactate begins to increase when plasma metformin concentrations are greater than about 20 mg/L (150 μmol/L) in rats[45] and, in an excellent survey of reports of lactic acidosis in patients, Lalau and Race[89] recorded plasma concentrations of metformin of 20–107 mg/L (150–820 μmol/L) in 24 of 49 patients with lactic acidosis. An even greater proportion may have had plasma concentrations above 20 mg/L as the time between the development of the acidosis and the collection of plasma samples for the assay of metformin was not recorded well. Although the dosage of metformin is reduced in renal impairment in order to prevent lactic acidosis, it is notable that lactic acidosis may occur in patients whose renal function was previously normal.[90]

It now appears that most patients can take metformin safely for prolonged periods but, in a very small proportion of treated patients, lactic acidosis and renal impairment develop over a short time.[91] In many cases, the lactic acidosis has followed prolonged vomiting and/or diarrhoea.[90] We suggest that in these patients, dehydration might have caused acute renal failure, reduced CL_R of metformin and increased plasma concentrations of metformin when its dosage was continued. This may very well exacerbate, or even cause, the acidosis. Diabetic patients may be more prone to the development of lactic acidosis for a number of reasons, including their microvascular disease.

7. Genetic Variants of Transporters and Response to Metformin

Variation in the response of patients due to genetic variants of cation transporters has been sought because of the importance of transporters in the absorption, distribution and elimination of metformin and the considerable interpatient variation in the response of metformin. Several genetic variants of OCT1 show impaired transport of metformin into model cells *in vitro*.[28,46] Low-transporter-activity genetic variants include Arg61Cys (181C>T, single nucleotide [SNP] rs12208357), Gly401Ser (1201G>A, SNP rs34130495), Met420del (1256delATG, SNP rs72552763) and Gly465Arg (1393G>A, SNP rs34059508) [table III]. Met420del is the most common, with an allele frequency of 18.5% in Caucasian subjects although much lower in African Americans (2.9%) and an even lesser frequency in Japanese and Koreans.[28] All these non-synonymous genetic

variants are on exons and therefore lead to variations in the amino acid composition of OCT1.

At present, there is no clear cut major effect of the presence of these variants of OCT1 on the pharmacokinetics *in vivo* (section 5.1) or on the clinical response in patients expressing these variants. In the glucose tolerance test in individuals administered metformin, the increase in blood glucose was slightly greater in healthy subjects carrying one or two of these reduced function OCT1 variants than in subjects with the normal OCT1.[33] By contrast, fasting blood glucose of women with polycystic ovary syndrome was not influenced by the genes for up to three variants of OCT1, although total cholesterol and triglycerides in plasma decreased in patients with the reference genotype but not in carriers of the variants.[92] Furthermore, a recent study has found that the presence of two of these variants, Arg61Cys and Met420del (table III), did not impair the effect of metformin on blood glucose in diabetic patients.[93] In all three studies, almost all subjects carrying the variant genes were heterozygotes. Zolk[34] has suggested a recessive model (i.e. the presence of variants may only have a significant effect in homozygotes carrying the variant transporter) [table III]. In the liver, the utility of both OCT1 and OCT3 as transporters of metformin may decrease any effect of dysfunctional variants on the activity of either transporter alone and on the hepatic uptake of the drug. Furthermore, the variation in the expression of OCT1 and OCT3 in the liver may be a considerable cause of interpatient differences in the response to metformin (section 5.1).

Reduced antihyperglycaemic response to metformin has been found in patients carrying an intronic variant of OCT1 (A>C, SNP rs622342)[94] while there is a larger response in patients who have an intronic variant of the MATE1 (G>A, SNP rs2289669) transporter. In both cases, homozygotes carrying the variant genes have greater changes in the antihyperglycaemic response than is seen in heterozygotes.[95] Not surprisingly, there is an interaction between the response to metformin in patients carrying the two variants, such that the least beneficial effect on blood glucose was found in homozygotes for both the variant OCT1 and normal MATE1.[96] The blood glucose in this group actually increased during treatment with metformin. The CL_R of metformin is unaltered in patients carrying the MATE1 variant (G>A, SNP rs2289669), both in heterozygotes and homozygotes.[35] As both genetic variants OCT1 and MATE1 are in introns, the mechanism of the altered effect of metformin is not known. Possibilities include changes in the expression of the normal or variant transporters. Another intronic variant of MATE1 (C>T, SNP rs8065082) is possibly associated with a lesser progression of prediabetes to diabetes[97] but there has been no study on any influence on the pharmacokinetic parameters.

8. Conclusions

8.1 Therapeutic Plasma Concentrations of Metformin

The clinical effects of metformin develop slowly over several days of treatment at least[21] and the range of plasma concentrations over a dosage interval depends upon the formulation (figure 4, section 4.2) without any significant effect on the clinical response.[23] Consequently, we suggest that the $C_{av,ss}$ should provide the best correlate with the clinical effects of metformin, better than the trough or peak concentrations.

The plasma concentrations of metformin have been recorded in a number of studies (table V) with most emphasis on the concentrations which are not associated with lactic acidosis. We are presently developing pharmacokinetic programs for estimating the values of $C_{av,ss}$, from the plasma concentrations of metformin collected at various times after dosage. Our initial

Table V. Recorded or recommended plasma concentrations of metformin

Metformin dosage (g)	Plasma concentration (mg/L)	Comments	Reference
Various	C_{trough} up to 2.24	No correlation with plasma lactate	8
Various	$C_{av,ss}$ up to 1.5	Slight increase in plasma lactate with increasing plasma concentrations of metformin	98
Various	$C_{av,ss}$ up to 2.5	No correlation between plasma lactate and metformin	99
1 g immediate-release bid	C_{trough} 0.5 ± 0.4 C_{max} 1.6 ± 0.5		100
Not stated	0.6 ± 0.5	Recommended as normal concentration; presumably C_{trough}	91
Not stated	<5	Recommended; presumably C_{max}	101
3 g daily	$C_{av,ss}$ 1.4 ± 0.4	Calculated from CL/F of 1140 ± 330 mL/min	Present review

bid = twice daily; **$C_{av,ss}$** = average concentration at steady state over a dosage interval; **CL/F** = apparent clearance after oral administration; **C_{max}** = maximum plasma concentration; **C_{trough}** = trough plasma concentration.

finding is that 75 of 76 patients had achieved $C_{av,ss}$ values up to 2.5 mg/L.[99] No patient developed lactic acidosis and, tentatively, we propose this to be an upper level (table V).

Considering that the maximal recommended dose of metformin is 3 g in most countries, we have estimated the values of $C_{av,ss}$ from the mean population estimates of CL/F. For example, the mean population estimate of CL/F is 1140 ± 330 mL/min (section 6). Accordingly, the values of $C_{av,ss}$ at 3 g metformin HCl (= 2.34 g metformin base) daily are estimated to be 1.4 ± 0.4 mg/L (table V). These calculated values of $C_{av,ss}$ could, however, be slightly overestimated because the CL/F of metformin increases slightly as the dosage increases (table II, section 4). Overall, these estimated values of $C_{av,ss}$ are consistent with our tentative recommendation of a maximal value of $C_{av,ss}$ of 2.5 mg/L.

It should be emphasized that these recommendations about $C_{av,ss}$ have been made largely from considerations of toxicity due to lactic acidosis. Optimal concentrations for lowering blood glucose are unknown at this stage. Furthermore, careful monitoring of the plasma concentrations and correlations with the concentrations of both glucose (or glycosylated haemoglobin [HbA_{1c}]) and lactate are required in order to demonstrate the value of therapeutic drug monitoring.

8.2 Recommended Dosage Control of Metformin

The control and monitoring of the dosage of metformin are contentious areas. From the analysis in this review, we suggest that:

(i) as is generally recommended, metformin should be administered initially at a low rate in order to mitigate the adverse gastrointestinal effects. The doses should be increased to a maximum of 2.5–3 g daily in patients with good renal function although lower dosage may be sufficient.

(ii) again, as is common, the response of patients should be monitored by measurement of fasting levels of glucose and, most importantly, HbA_{1c}.

(iii) the dose of metformin should be individualized because of intersubject variation in the bioavailability, (section 4) CL_R and CL/F (section 6) and response (section 7). Initially, the maximum dose of metformin should be reduced proportionally to the reduction in CL_{CR} which can be estimated from the plasma concentrations of creatinine, the bodyweight and the age of the patient using, for example, the formulae of Cockcroft and Gault.[102] For example, the initial target dosage in a patient with a CL_{CR} of 60 mL/min (approximately 50% of normal GFR) should be a maximum of 1.5 g although, again, dosage should be commenced at a lower level. At 30 mL/min, a daily dose of 0.75 g daily should be the initial target dose. These recommendations are made because CL_R and CL/F of metformin are approximately proportional to the CL_{CR}, at least down to about 20 mL/min (figure 6). It is of note that the product information on metformin recommends that lower than normal doses should be used in patients with renal impairment but the doses are not specified. There are insufficient data to recommend routinely increasing the maximum dose with high CL_{CR} (>>120 mL/min), although there is the pharmacokinetic rationale to do so.

(iv) The plasma concentrations of metformin are not monitored in present clinical practice. However, we consider that this may be useful, particularly in patients with CL_{CR} below 60 mL/min in order to ensure that a safe dose is being administered. The blood samples would be best taken at about 8 hours after dosage with immediate-release tablets, or 4 or 16 hours after dosage with the sustained-release tablets as the plasma concentrations at these times approximate $C_{av,ss}$ (figure 4) Alternatively, the application of Bayesian methodology will allow an estimate of $C_{av,ss}$ which, we suggest, should not exceed 2.5 mg/L. Monitoring the plasma concentrations should also be valuable in patients who are failing to respond. Poor compliance or actual poor adherence to treatment may then be determined after careful discussion with the patients. Support for monitoring the plasma concentrations comes from the observation that the clinical response to metformin increases with increasing dose and, further, that a higher dose of metformin is required in patients with higher pretreatment fasting blood glucose levels.[103] The monitoring of plasma concentrations of metformin, however, requires clinical evaluation.

(v) The dosage of metformin must be suspended immediately if any features of acute renal failure develop. This recommendation follows from the high proportion of patients with acute renal failure who developed lactic acidosis (section 6). The dosage of metformin should be suspended in other states at high risk of acute renal failure and lactic acidosis, such as acute cardiac failure.

(vi) Any monitoring of plasma concentrations will require concurrent examination of blood glucose through fasting levels or by the measurement of HbA_{1c}. As discussed in section 5.1, low levels of transporters, such as OCT1, may require higher than normal dosage of metformin to produce an optimal response.

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Correspondence: Dr *Garry G. Graham*, Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Darlinghurst, NSW 2010, Australia. E-mail: g.graham@unsw.edu.au