Br. J. clin. Pharmac. (1981), **12**, 235–246

METFORMIN KINETICS IN HEALTHY SUBJECTS AND IN PATIENTS WITH DIABETES MELLITUS

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1 The kinetics of metformin were studied after i.v. and oral administration in four healthy subjects and after oral administration in twelve maturity onset (Type II) diabetic patients.

2 After i.v. administration most of the dose was rapidly eliminated but with a mean 'terminal' $T_{\frac{1}{2}}$ of 4 h measured up to 12 h in plasma and of 16 h measured up to 60 h from the urinary excretion rate. On average, 80% of the dose was recovered as unchanged drug in the urine with none detected in the faeces.

3 After single oral doses (0.5 and 1.5 g), maximum plasma concentrations and urinary excretion rates were observed at about 2 h with urinary recoveries of unchanged drug of 35–50% and faecal recoveries of about 30%. Urinary recoveries were significantly lower after the higher dose. Absolute oral bioavailability was 50–60% of the dose.

4 Deconvolution analysis showed that after a short lag-time, the available oral dose was absorbed at an exponential rate over about 6 h. Implications for the design of prolonged release dosage forms are discussed.

5 Plasma metformin concentrations measured throughout the seventh and fourteenth days of continuous 0.5 g twice daily treatment were accurately predicted from single dose data, although a discrepancy between observed and predicted trough levels reflected the existence of a slow elimination phase. Implications of the latter for a gradual accumulation of metformin in peripheral tissues and a possible association with lactic acidosis are discussed.

6 Renal clearance of metformin was highly correlated with creatinine clearance. However, a weaker relationship between total oral clearance of the drug and creatinine clearance suggests that the latter may not always be a reliable indicator of potential metformin accumulation owing to variability in absorption and possibly non-renal clearance of the drug,

Introduction

Following the restrictions placed upon the prescribing of phenformin (phenylethylbiguanide) in some countries, and its removal from the market in others, metformin (N^1, N^1-dimethylbiguanide) and buformin (N^1-butylbiguanide) are now the most commonly prescribed oral hypoglycaemic drugs of the biguanide class. Metformin has been recommended as the drug of choice because the risk of developing lactic acidosis during treatment is less than that resulting from the use of phenformin (British Medical Journal, 1977; Phillips, Thomas & Harding, 1977; Bergman, Boman & Wiholm, 1978).

In spite of its widespread use, little is known about the pharmacokinetics of metformin. Two recent papers have described the kinetics in normal man (Sirtori *et al.*, 1978; Pentikäinen, Neuvonen & Penttilä, 1979) and in one of these (Sirtori *et al.*, 1978) special emphasis was placed upon the relationship between impairment of renal function and the resulting slowing of metformin clearance. The literature is deficient in information concerning the kinetics of metformin in patients with diabetes mellitus.

In this paper we describe the pharmacokinetics of metformin administered via the oral and intravenous routes in normal subjects and in patients with diabetes mellitus.

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0306–5251/81/080235–12 $01.00

Methods

Protocol

Three groups of subjects were studied (Table 1).

Group I consisted of four healthy male volunteers who were given single intravenous and oral doses of metformin HCl on separate occasions at least 2 weeks apart, according to a cross-over design. The intravenous dose was 0.25 g given by constant-rate infusion over the course of 15 min and the oral doses were 0.5 g and 1.5 g, respectively, in the form of Glucophage® tablets from a single batch. The intravenous solution and tablets were analysed and found to contain between 98 and 100% of the stated dose. The oral doses were taken with breakfast. Drug concentrations were measured in serial samples of whole blood, plasma, urine and faeces. Blood samples, obtained by venepuncture without stasis, were collected up to 12 h (i.v. study) and 24 h (oral study); urine samples were collected up to 72 h and faecal samples to 5 days.

The purpose of these experiments was to assess: (I) the recovery of unchanged drug; (II) the rate and extent of oral bioavailability of metformin; (III) any dose-dependence in its kinetics and (IV) the distribution of the drug between plasma and blood cells.

Group II consisted of four newly diagnosed maturity onset (Type II) diabetic patients. They received a single 1.0 g oral dose (as Glucophage® tablets) followed 3 days later by 0.5 g (p.o.) twice a day. The drug was taken with meals as is normally advised.

Metformin concentrations were determined in serial plasma samples up to 24 h and in serial urine samples up to 72 h after the first dose and in plasma samples during days 7 and 14 of continuous twice daily dosing.

The purpose of this experiment was: (I) to compare metformin kinetics in the patients with that in healthy subjects (Group I); (II) to assess the accumulation of the drug and the degree to which this could be predicted from single dose data.

Group III was composed of eight maturity onset (Type II) diabetic patients four of whom were taking chlorpropamide (Table 1). They were all given a single 1.0 g oral dose in the form of Glucophage® tablets. Metformin concentrations were measured in serial plasma samples up to 24 h and in serial urine samples up to 72 h.

The purpose of this experiment was to assess the relationship between metformin kinetics and renal function. Combining the data from all three groups gave information about metformin clearance over a range of creatinine clearance from 47 to 179 ml min^{-1}. (Table 1.)

These studies were approved by the local hospital Ethics Committee.

Drug analysis

Concentrations of unchanged metformin were meas-

Table 1 Clinical details of normal subjects and diabetic patients

Group	*Subject*	*Age (years)*	*Sex*	*Weight (kg)*	*Height (cm)*	*Cl_{CR}[a] ($ml\,min^{-1}$)*	*Other[b] drugs*
I	1	34	M	66	108	113	—
	2	30	M	68	178	106	—
	3	30	M	64	175	145	—
	4	36	M	83	178	179	—
II	5	62	M	95	173	120	—
	6	68	M	74	160	85	M, N
	7	70	F	68	152	86	N
	8	46	M	90	179	168	—
III	9	70	M	73	168	51	P, C
	10	67	M	58	168	97	—
	11	68	F	78	173	85	M
	12	81	F	57	155	47	C
	13	73	F	64	127	57	A, C
	14	57	M	84	176	116	M
	15	70	M	81	168	72	C
	16	59	M	82	184	107	—

a creatinine clearance, determined by the Jaffé method using an Autoanalyser.

b A = atenolol; C = chlorpropamide; M = α-methyldopa; N = Navidrex K; P = prochlorperazine

ured using a specific gas chromatographic method (Lennard *et al.*, 1978). Coefficients of variation of the assay were ±9% and ±5% at 50 ng ml^{-1} and 2 μg ml^{-1}, respectively. All samples were assayed in duplicate.

Plasma binding

The binding of metformin in plasma samples from healthy subjects, spiked with drug concentrations of 0.1 and 10 μg ml^{-1} was determined using the Dianorm® equilibrium dialysis apparatus (Weder, Schildknecht & Kesselring, 1971). Samples were dialysed for 3 h at 37°C against phosphate buffer, pH7.4, using 1.0 ml half-cells and a cellulose acetate membrane.

Pharmacokinetic analysis

Intravenous administration (Group I) Post-infusion plasma drug concentrations (C_{post}) were fitted by a triexponential equation:

$$C_{post} = \sum_{i=1}^{3} C_i^1 . e^{-\lambda_i t} \quad (1)$$

Initial estimates of the coefficients C_i^1 and λ_i were obtained graphically by the method of residuals. The values were then refined using the Gauss-Newton iterative procedure incorporated in a modification of the IGPHARM package (Gomeni & Gomeni, 1978). Experimental data points were weighted according to the square of their reciprocal values. Assessment of the goodness of fit of computed data to observed data was based on plots of weighted residuals against time and the coefficient of determination (Boxenbaum, Riegelman & Elashoff, 1974).

Values of the coefficients C_i^1 were corrected to those expected following an instantaneous bolus injection (C_i) using equation 2:

$$C_i = C_i^1 \left(\frac{\lambda_i \tau}{1 - \varepsilon^{-\lambda_i \tau}} \right) \quad (2)$$

where τ is the infusion time.

Total plasma clearance (Cl) was calculated from:

$$Cl = \frac{D}{AUC} \quad (3)$$

where D is the dose and AUC is the area under the plasma drug concentration-time curve extrapolated to infinite time and given by:

$$AUC = \sum_{i=1}^{3} \frac{C_i}{\lambda_i} \quad (4)$$

Renal clearance (Cl_R) was obtained using equation 5:

$$Cl_R = \frac{Ae(12)}{AUC(12)} \quad (5)$$

where Ae(12) is the amount of unchanged drug excreted in the urine up to 12 h and AUC(12) is the area under the plasma drug concentration-time curve up to 12 h and given by:

$$AUC(12) = AUC - \frac{C(12)}{\lambda_3} \quad (6)$$

where C(12) is the estimated plasma drug concentration at 12 h after a bolus injection.

The fraction of the dose excreted as unchanged drug (fe) was calculated from:

$$fe = \frac{Ae(72)}{D} \quad (7)$$

where Ae(72) is the urinary recovery of unchanged drug at 12 h.

The volume of distribution at pseudoequilibrium during the terminal log-linear phase (V) was calculated from:

$$V = \frac{Cl}{\lambda_3} \quad (8)$$

Urinary excretion rates were also fitted by a triexponential equation using non-linear least squares regression with weighting by the square of reciprocal values.

Oral administration

(a) *Single dose (Groups I–III)* Plasma drug concentration-time curves were fitted graphically by a triexponential equation with one negative and two positive terms in a similar manner to the i.v. data. When subjected to non-linear least squares regression analysis the solutions for many of the data sets converged on an equation consisting of a negative and a positive exponential term plus a constant term. The latter reflected the slow disappearance of metformin between 12 and 24 h and the lack of data points between these times. In view of this deficiency in data collection an approximate 'terminal' $T_{\frac{1}{2}}$ is reported, based upon the initial graphical estimates.

Oral bioavailability was calculated in two ways, using plasma data (F_p) by equation 9 and using urine data (F_{ur}) by equation 10:

$$F_p = \frac{[AUC(12)_{po}].D}{[AUC(12)].D_{po}} \quad (9)$$

where D_{po} in the oral dose and $AUC(12)_{po}$ is the area under the plasma drug concentration-time curve up to 12 h after the oral dose calculated by the trapezoidal rule. D and AUC(12) refer to intravenous administration, as above.

$$F_{ur} = \frac{[Ae(72)_{po}].D}{[Ae(72)].D_{po}} \quad (10)$$

where $Ae(72)_{po}$ and $Ae(72)$ are the urinary recoveries of unchanged drug at 72 h after oral and i.v. administration, respectively.

Oral clearance (CL_{po}) was calculated from:

$$CL_{po} = \frac{D_{po}}{AUC_{po}} \quad (11)$$

The fraction of the oral dose unabsorbed as a function of time was calculated by deconvolution of the corresponding i.v. and oral plasma drug concentration *v* time data using both the Point-Area Method (Vaughan & Dennis, 1978) and a linear interpolation method analogous to the Loo-Riegelman procedure (Loo & Riegelman, 1968). It was found possible to describe the fraction unabsorbed data accurately by assuming a short lag-time followed by a monoexponential input of the available fraction of the dose. Using this input function to drive the disposition function derived from the i.v. data, the plasma drug concentrations observed after oral administration were recovered satisfactorily, thereby providing a check on the deconvolution routines.

(b) *Multiple dosing (Group II)* Plasma drug concentrations during days 7 and 14 of continuous treatment in Group II patients were predicted from their initial dose data by application of the Superposition Principle (Wagner, 1975).

The area under the plasma drug concentration-time curve extrapolated to infinite time after the initial dose in each subject was compared to the areas under the curves during days 7 and 14.

The latter were calculated by the trapezoidal rule. These areas should be identical if the kinetics of the drug are linear and steady-state has been reached during continuous dosing.

Statistical analysis

A paired *t*-test was used to assess differences in the urinary and faecal recovery of metformin at the two dose levels in Group I subjects. Pearson product moment correlation coefficients were calculated to assess the strength of linear correlations between metformin and creatinine clearances.

Statistical significance was assumed when P was < 0.05.

Results

Intravenous administration (Group I)

Plasma metformin concentrations decreased rapidly after the end of infusion and fell below the limit of the assay after 12 h (Figure 1). Over this period the data were accurately described by equation 1. Values of the parameters of equation 1 are listed in Table 2, as are values of clearance and volume of distribution. The 'terminal' half-life over the period of observation ranged from 2.5 to 7.0 h, with an harmonic mean of 3.8 h.

The urinary excretion rate of the drug could be measured up to 60 h and the half-life calculated from the latter part of these data ranged from 13–34, with an harmonic mean value of 16 h (Table 2, Figure 1).

An average of 79% of the dose was recovered as unchanged drug in the urine after 72 h, 95% of this total appearing in the first 8 h (Figure 2). Renal clearance was about four times the creatinine clear-

Table 2 Pharmacokinetic parameters describing the disposition of metformin in Group I subjects after intravenous administration of 0.25 g metformin HCl

Parameter	*Subject*					
	1	*2*	*3*	*4*	*Mean*[b]	*s.d.*
C_1(μg ml^{-1})[a]	22.99	3.33	13.27	10.46	12.51	8.14
C_2(μg ml^{-1})[a]	3.91	2.85	2.52	2.04	2.83	0.79
C_3(μg ml^{-1})[a]	0.442	0.081	0.372	0.104	0.245	0.18
λ_1(h^{-1})	27.17	4.26	6.68	4.85	10.74	11.00
λ_2(h^{-1})	1.079	0.649	1.033	0.815	0.894	0.20
λ_3(h^{-1})	0.225	0.129	0.276	0.098	0.182	0.083
$T_{\frac{1}{2}}z$(plasma) (h)[c]	3.08	5.39	2.51	7.04	4.50	2.10
$T_{\frac{1}{2}}z$(urine) (h)[d]	14.2	12.9	14.9	34.2	19.0	10.11
Cl (ml min^{-1})	657	718	721	728	706	33
fe	0.737	0.839	0.818	0.763	0.789	0.047
Cl_R(ml min^{-1})	462	600	578	537	544	61
V(l)	175	333	156	443	276	136

a as metformin HCl
b arithmetic mean
c 'terminal' half-life determined up to 12 h
d 'terminal' half-life determined from urinary excretion rate up to 60 h

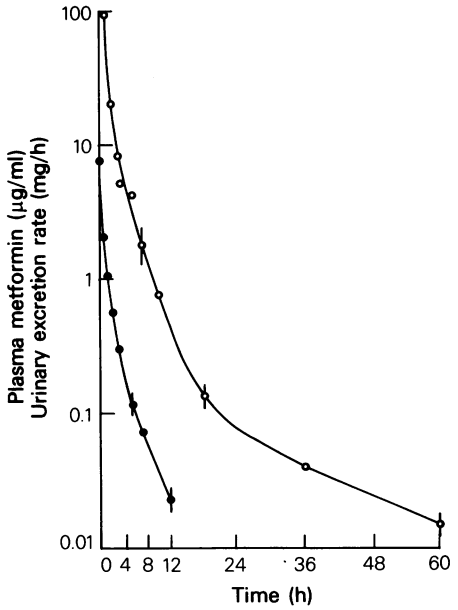

Figure 1 Decay of mean plasma concentrations (● μg/ml) and urinary excretion rate (○, mg/h) of metformin (as HCl) post-i.v. infusion of 0.25 g over 15 min in Group I subjects (bars indicate ± s.d.).

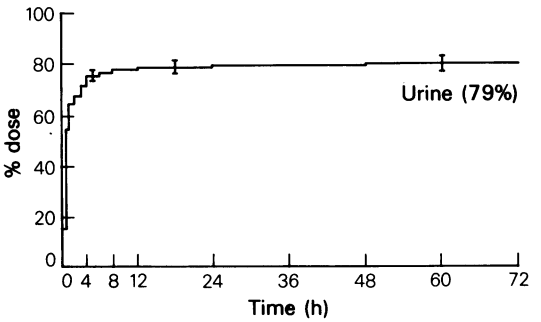

Figure 2 Cumulative mean urinary excretion of metformin after 0.25 g i.v. in Group I subjects (bars indicate ± s.d.).

ance (Tables 1 and 2). No metformin was detected in faecal samples.

Oral administration

(a) *Single dose (Groups I–III)* Although peak plasma metformin concentrations were slightly higher and peak urinary excretion rates were lower in the patients of Groups II and III than in the subjects of Group I, when normalized for dose, the kinetic profiles in plasma and urine were similar (Figure 3, Tables 3, 5, 6).

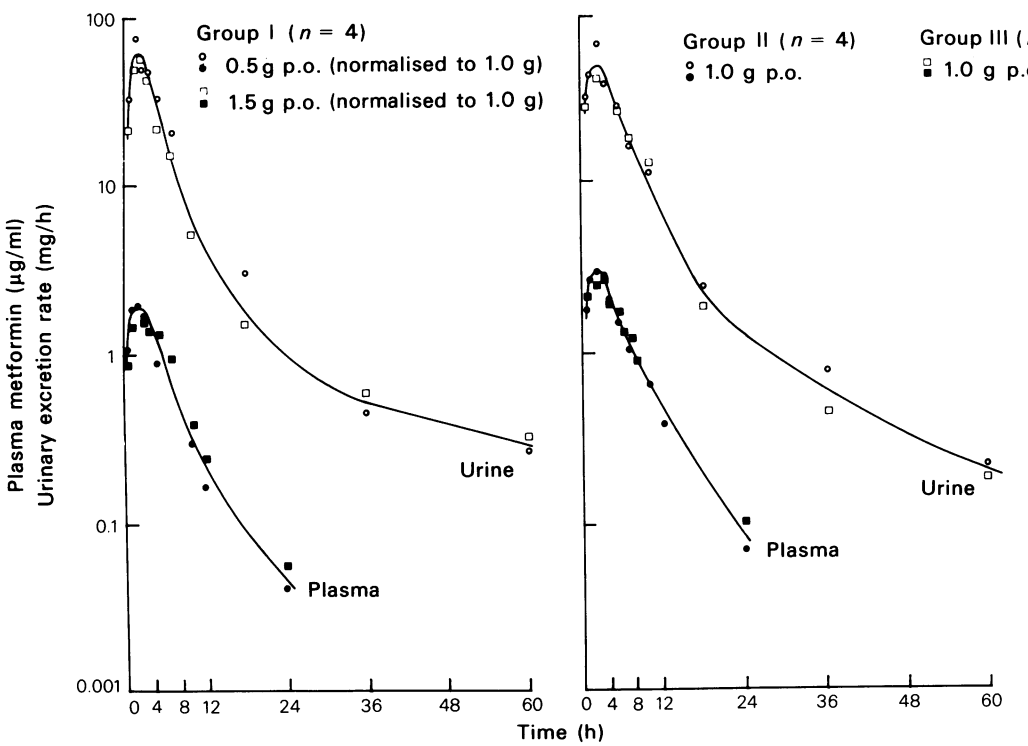

Figure 3 Comparison of mean plasma concentrations and urinary excretion rates after oral administration of metformin HCl in healthy subjects and diabetic patients.

Table 3 Parameters describing the kinetics of metformin after oral administration to Group I subjects

Parameter	*Subject*											
	1		*2*		*3*		*4*		*Mean*		*s.d.*	
Dose (g)	*0.5*	*1.5*	*0.5*	*1.5*	*0.5*	*1.5*	*0.5*	*1.5*	*0.5*	*1.5*	*0.5*	*1.5*
t_{max}(h)[a]	2.5	2.0	2.5	1.5	2.0	1.0	2.0	1.5	2.2	1.5	0.3	0.4
C_{max}(μg ml^{-1})[b]	0.59	3.37	1.30	3.18	1.29	4.03	0.91	1.81	1.02	3.10	0.34	0.93
$AUC(24)_{po}$(μg ml^{-1}h)	4.52	18.61	7.91	24.86	8.47	20.70	5.96	9.42	6.71	18.40	1.82	6.52
fe_{po}[c]	0.316	0.288	0.510	0.433	0.595	0.423	0.562	0.373	0.496	0.379	0.125	0.066
fe_F[d]	0.204	0.210	0.190	0.213	0.250	0.447	0.434	0.448	0.269	0.329	0.113	0.136
F_p	0.34	0.45	0.63	0.75	0.69	0.57	0.54	0.24	0.55	0.50	0.15	0.21
F_{ur}	0.43	0.39	0.62	0.52	0.73	0.52	0.74	0.49	0.63	0.48	0.14	0.06
Cl_R(ml min^{-1})	382	316	550	387	486	445	683	929	525	519	125	278
CL_{po}(ml min^{-1})	1843	1343	1053	1006	984	1208	1398	2654	1319	1552	393	347
$T_{\frac{1}{2}Z}$(plasma) (h)[e]	7.54	5.33	4.90	5.40	4.10	5.00	5.20	8.20	5.43	5.98	1.47	1.49
$T_{\frac{1}{2}Z}$(urine) (h)[f]	—	23	20	20	20	20	—	16				

a = Time of maximum plasma drug concentration

b = Maximum plasma drug concentration (as metformin HCl)

c = Fraction of dose excreted in urine as unchanged drug

d = Fraction of dose excreted in faeces as unchanged drug

e = 'Terminal' half-life determined up to 24 h

f = 'Terminal' half-life approximated from urinary excretion rate between 36–60 h.

Other symbols as defined in the text.

Table 4 Absorption lag times (t_{lag}) and rate constants (ka) in Group I subjects[a]

Subject	Dose (g)	t_{lag} (h)	ka (h^{-1})	r^2
1	0.5	0.20	0.259	0.993
	1.5	0.00	0.379	0.994
2	0.5	0.22	0.317	0.994
	1.5	0.40	0.351	0.993
3	0.5	0.45	0.296	0.992
	1.5	0.25	0.368	0.997
4	0.5	0.47	0.293	0.996
	1.5	0.33	0.430	0.999
Mean±s.d.	0.5	0.33±0.14	0.291±0.024	
	1.5	0.24±0.17	0.382±0.034	

a A monoexponential equation was fitted to a plot of the differences between the bioavailability (F_p) and the fraction absorbed as a function of time. The r^2 values refer to the regression of the log transformed data *v* time; the lag time was taken as the intercept on the time-axis.

Peak plasma drug concentrations and urinary excretion rates were observed at about 2 h in all Groups. Plasma data collected up to 24 h indicated a 'terminal' half-life of 4–8 h, whereas urinary excretion rates measured up to 60 h disclosed the presence of a further elimination phase with a half-life of about 20 h.

After the 0.5 g dose the mean total recovery of unchanged metformin in Group I subjects was 77% of the dose, of which 50% appeared in the urine and 27% in the faeces (Figure 4, Table 3). Following the 1.5 g dose the mean total recovery was 71%, of which 38% was in the urine and 33% in the faeces (Table 3). The difference between the urinary recoveries at the two dose levels was statistically significant ($P < 0.05$).

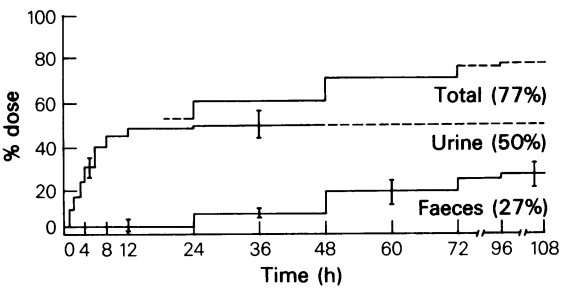

Figure 4 Cumulative mean urinary and faecal excretion of metformin after 0.5 g p.o. in Goup I subjects (bars indicate ± s.d.).

Estimates of oral bioavailability showed good agreement using plasma data and urinary recoveries and averaged 50–60% of the dose (Table 3).

Renal clearances after oral dosage were similar to those observed after intravenous administration (Tables 2 and 3).

Deconvolution analysis showed that most of the oral absorption of metformin takes place over 6 h. Beyond this time the absorption rate is negligible

Table 5 Parameters describing the kinetics of metformin after oral administration of the initial 1.0 g dose to Group II subjects

Parameter	Subject 5	6	7	8	mean	s.d.
t_{max}(h)	2.0	3.0	2.5	1.0	2.1	0.8
C_{max}(h)	3.54	3.36	4.20	1.89	3.25	0.97
$AUC(24)_{po}$($\mu g\,ml^{-1}h$)	16.67	26.43	24.75	11.22	19.77	7.11
fe_{po}	0.482	0.372	0.266	0.403	0.381	0.089
Cl_R($ml\,min^{-1}$)	344	217	178	548	322	166
Cl_{po}($ml\,min^{-1}$)	1000	630	673	1485	947	394
$T_{\frac{1}{2}}z$(plasma)(h)	5.00	4.70	5.60	5.85	5.25	0.61

Table 6 Parameters describing the kinetics of metformin after oral administration of 1.0 g to Group III subjects

Parameter	Subject 9	10	11	12	13	14	15	16	Mean	s.d.
t_{max}(h)	2.0	3.0	3.0	3.0	2.0	3.0	2.0	1.0	2.4	0.7
C_{max}($\mu g\,ml^{-1}$)	4.76	3.02	6.10	2.00	2.53	1.79	2.74	2.99	3.24	1.46
$AUC(24)_{po}$($\mu g\,ml^{-1}h$)	32.22	29.73	33.75	19.32	18.28	15.87	25.55	24.01	24.84	6.68
fe_{po}	0.395	0.350	0.330	0.181	0.291	0.322	0.382	0.388	0.347	0.070
Cl_R($ml\,min^{-1}$)	192	183	173	155	259	328	235	269	224	58
Cl_{po}($ml\,min^{-1}$)	517	561	494	863	912	1050	652	694	718	203

(Figure 5). The two methods of deconvolution used gave similar results and only those obtained with the Point-Area method are reported. Representative data for one subject illustrating how the drug input profile may be described by a short lag-time plus a monoexponential phase operating upon the bioavailable fraction of the dose are shown in Figure 6. Table 4 lists the lag-times and input rate constants obtained at each dose level in the four subjects of Group I. The difference between the input rate constant at the two dose levels was significant ($P < 0.05$).

In the patients of Groups II and III urinary recoveries of unchanged metformin averaged 38% and 35% of the 1.0 g dose, respectively (Tables 5 and 6).

(b) *Multiple dosing (Group II)* Overall agreement between observed and predicted plasma drug concentrations on days 7 and 14 of continuous dosage was excellent (Figure 7). In individual subjects the ratio of the area under the curve during a day of continuous treatment to that under single dose data ranged from 0.92–1.06 for day 7 and from 1.05–1.22 for day 14. Nevertheless, observed trough concentrations on continuous dosing were about 95% higher than predicted, reflecting the existence of an additional elimination phase or phases undetected from 24 h single dose plasma data. It was also evident that accumulation was still proceeding slowly at 14 days since the trough levels at this time were higher than those at 7 days (Figure 7).

Plasma binding

Metformin was not bound to plasma protein.

Distribution of metformin between plasma and blood cells

A consistent finding was that although blood drug concentrations were initially lower than those in plasma, they crossed over at about 8 h and subsequently remained much higher. Figure 8 shows representative data from an individual subject. A 'terminal' half-life of 17 h in blood was similar to that recorded from urinary excretion rate data.

In vitro experiments with blood samples spiked with metformin indicated that the value of the drug blood/plasma concentration ratio is time-dependent rather than concentration-dependent.

Metformin clearance and renal function

On combining data from all three Groups a highly significant linear correlation was observed between the renal clearances of metformin and creatinine (Figure 9a). However, the relationship between total oral clearance of the drug and creatinine clearance was much weaker (Figure 10).

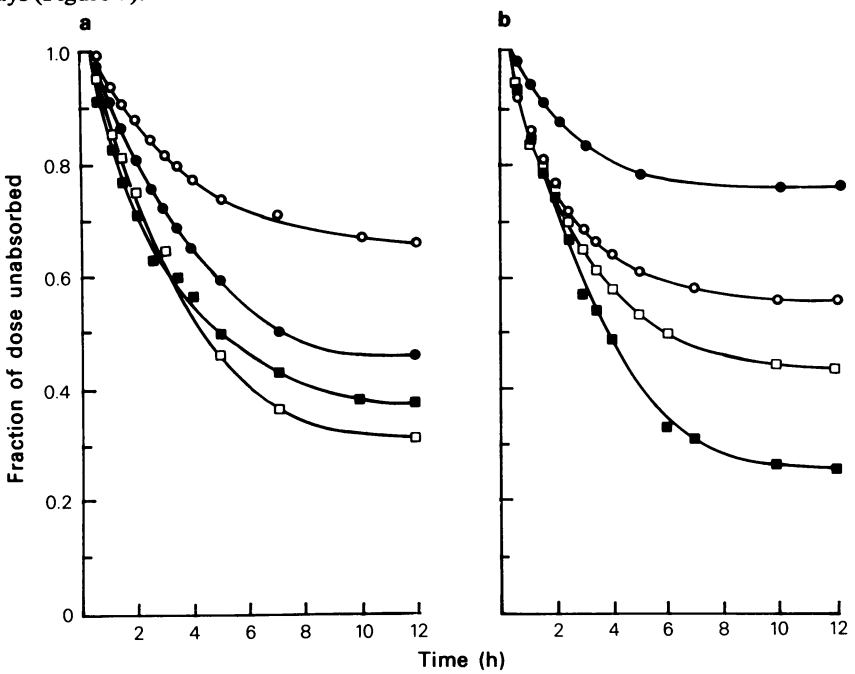

Figure 5 Fraction of oral dose remaining to be absorbed as a function of time in Group I subjects, after (a) 0.5 g dose and (b) 1.0 g dose. ○ subject 1, ● subject 2, □ subject 3, ■ subject 4.

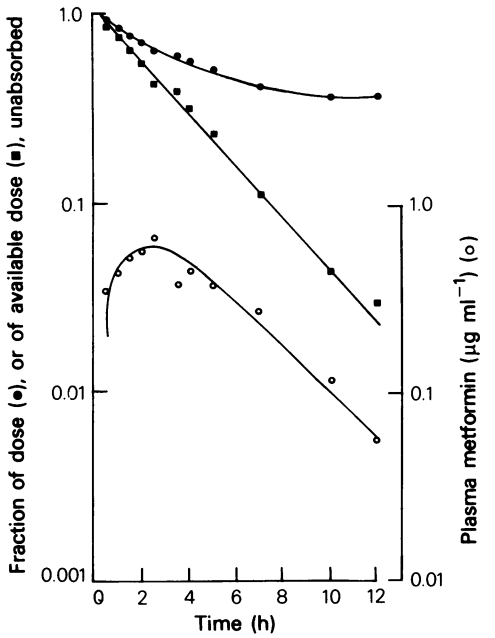

Figure 6 Plasma concentrations of metformin and its rate of absorption after an oral dose of 0.5 g in subject 2. (The smooth line drawn through the plasma data was obtained by combining the fitted input function and the disposition function from corresponding i.v. data.).

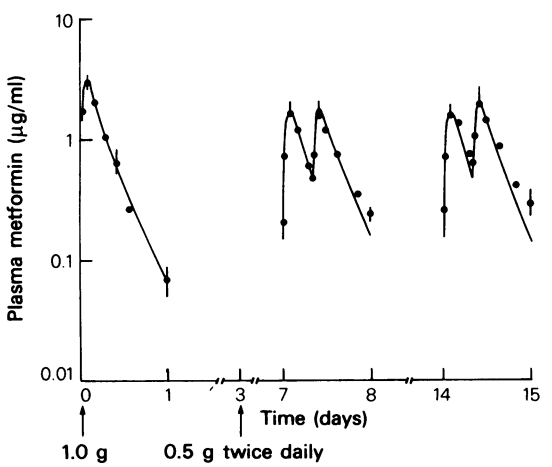

Figure 7 Plasma concentrations of metformin (as HCl) after the first dose and during days 7 and 14 of continuous treatment in Group II patients (bars indicate ± s.d.). ● observed, — predicted values.

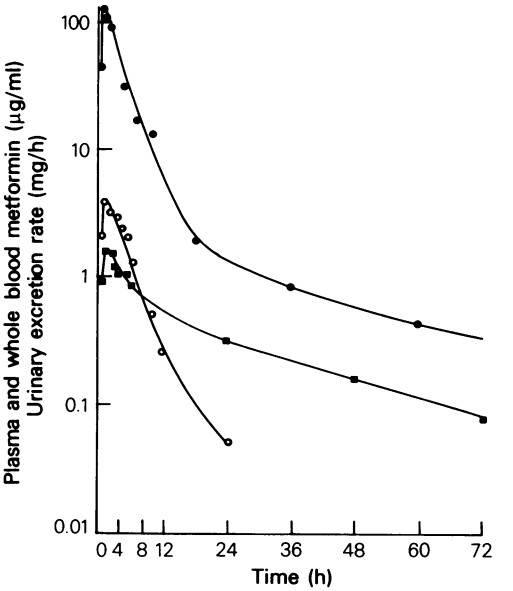

Figure 8 Plasma (○) and whole blood (■) concentrations and urinary excretion rate (●) of metformin after 1.5 g p.o. in subject 3.

Discussion

Apart from the work reported here two other groups have studied the kinetics of metformin after intravenous administration to normal subjects (Sirtori *et al.*, 1978; Pentikäinen *et al.*, 1979). A comparison of the findings is summarized in **Table 6**. There are some discrepancies between clearance and half-life values which, in part, may be related to differences in sampling periods and in curve-fitting procedures. The most important difference is seen when figures for the fraction of the dose recovered unchanged in the urine (fe) are compared. Using [^{14}C]-labelled metformin Pentikäinen *et al.* (1979) recovered all of the dose as intact drug in the urine whereas we did not account for 20% of the dose and must presume that this represents drug which has been metabolised. These observations are difficult to reconcile, firstly because animal studies have failed to detect any metabolites of the drug (Beckmann, 1969) and secondly because Pentikäinen *et al.* (1979) appear to have established, by thin-layer autoradiography, that all of the radiolabel in their urine samples was in the form of metformin. Nevertheless, our findings are supported by those of Sirtori *et al.* (1978). Although they concluded that metformin is not metabolised, inspection of their data reveals that mean renal clearance was only 77% of mean total plasma clearance (Table 7), in accordance with our results. Incubation of our

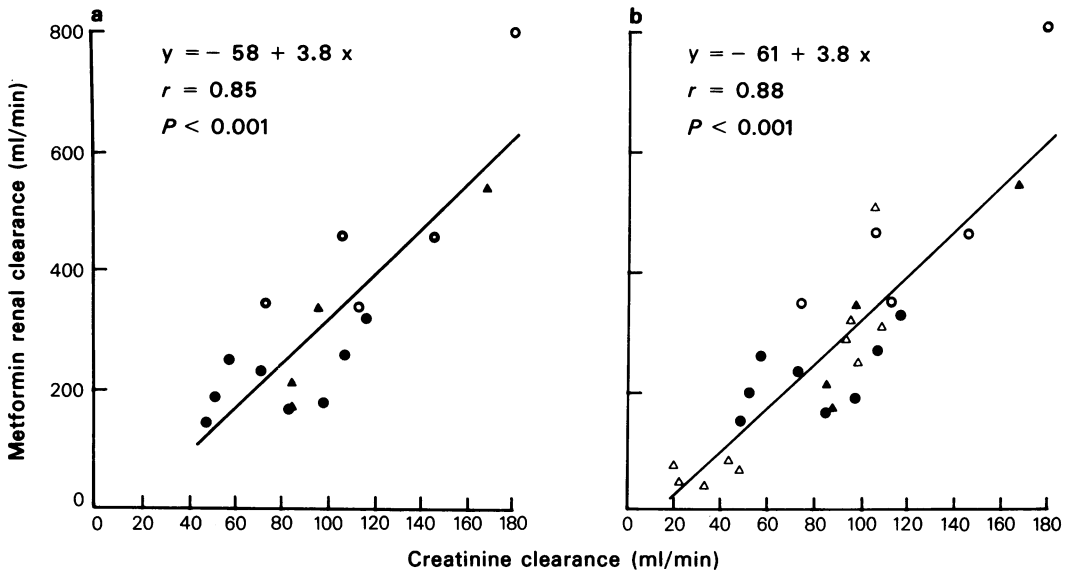

Figure 9 Relationship between the renal clearance of metformin and creatinine clearance (a) Data from this study (O Group I subjects – mean values for the two oral doses; ▲ Group II patients; ● Group III patients). (b) As (a) but including data (Δ) reported by Sirtori *et al.* (4).

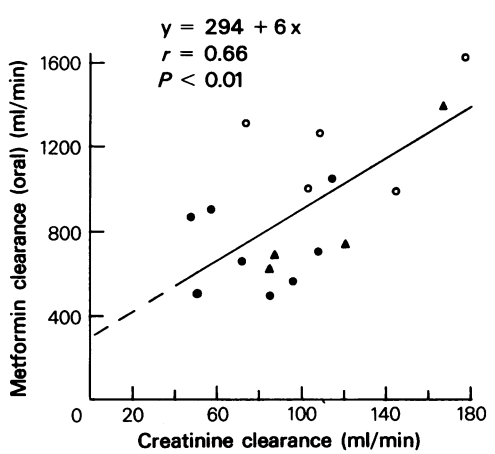

Figure 10 Relationship between oral clearance of metformin and creatinine clearance (symbols as in Figure 9).

urine samples with a glucuronidase-sulphatase mixture failed to increase the yield of metformin, indicating that simple conjugates were not formed.

Since no drug was recovered in the faeces after intravenous administration net secretion of metformin from blood into the gut lumen was negligible. Therefore, faecal recoveries of about 30% of an oral dose must represent unabsorbed drug. The estimated oral bioavailability of 50–60% agrees with the findings of others (Sirtori *et al.*, 1978; Pentikäinen *et al.*, 1979) and the difference between faecal recovery and bioavailability may reflect pre-systemic metabolism of drug.

Lower urinary recoveries and higher faecal recoveries after the 1.5 g compared to the 0.5 g oral dose in Group I subjects (Table 3) suggest that increasing dosage is accompanied by a decrease in the absorption of metformin. A similar conclusion was made by Noel (1979) who found that the fraction of the dose recovered in the urine fell from 0.86 to 0.42 as the dose was raised from 0.25 g to 2.0 g.

A longer plasma half-life after oral administration compared to that observed after intravenous administration (Tables 2 and 3) indicates that slow absorption of metformin rate-limits its disposition over a significant period of time; an observation also made by Pentikäinen *et al.* (1979). The calculations indicating that the majority of the dose which is going to be absorbed has done so by about 6 h (Figure 5) have implications for the design of prolonged-release dosage forms of the drug. These are usually intended to release metformin at a constant rate over about 6–12 h. Clearly, if absorption of the compound is largely confined to the upper part of the intestine, as our data might suggest, we would predict poor bioavailability for these preparations (present authors, unpublished observations).

Assuming that the dosage interval (τ) is longer than the beginning of the log-linear phase of elimination of drug from the plasma, accumulation of drug in plasma during repeated administration can be predicted from equation 12:

Table 7 A comparison of three studies of the intravenous kinetics of metformin in normal subjects (mean values ± s.d.)

	This study	*Pentikäinen et al. (1979)*	*Sirtori et al. (1978)*
Assay method[a]	GC-EC	^{14}C	GC-MS
Number of subjects	4	3	5
Age (years)	33 ± 3	38 ± 2	45 ± 9
Dose (g metformin HCl)	0.25	0.5	1.0
Infusion time (min)	15	5	rapid
Sampling time (plasma) (h)	12	12	8
Sampling time (urinary excretion rate) (h)	60	40	—
Cl (ml min^{-1})	706 ± 33	459 ± 10	441 ± 89
Cl_R (ml min^{-1})	544 ± 61	454 ± 81	335 ± 46
$T_{\frac{1}{2}}$(z)(plasma) (h)	4.50 ± 2.10	1.74 ± 0.20	1.52 ± 0.13
$T_{\frac{1}{2}}$(z)(Urine) (h)	19.0 ± 10.1	9.29 ± 0.83	—
fe	0.789 ± 0.047	0.999 ± 0.008	0.766 ± 0.178[b]
fu[c]	1.0	1.0	1.0

a GC-EC = gas chromatography with electron-capture detection
^{14}C = liquid scintillation counting of radiolabel
GC-MS = mass fragmentography

b There is a discrepancy between this figure calculated from individual data and the mean of 0.86 quoted by the authors

c Fraction of drug unbound in plasma

$$R_{ac} = \frac{1}{1-2^{-\varepsilon}} \qquad (12)$$

where R_{ac} is the ratio of the trough plasma drug concentration at steady-state during repeated administration to the concentration at τ h after a single dose and ε is the ratio of τ to the half-life. A usual dosage regimen of 0.5 g every 8 h and a half-life of 5 h (Table 5) gives a value of 1.5 for the accumulation ratio of metformin. This estimate is not materially altered if more complex equations are used (Gibaldi & Perrier, 1979) incorporating a further elimination phase with a $T_{\frac{1}{2}}$ of about 20 h, as indicated from the urine data. The contribution of this slow component of elimination to plasma drug accumulation is small. However, as pointed out by Gonda & Harpur (1980), relatively slow rises in trough plasma drug concentrations may reflect much more dramatic increases in the accumulation of drug in tissues. Thus, accumulation in the peripheral 'tissue' compartment of a two-compartment open system is given by equation 13:

$$R'_{ac} = {}^{1}/[(1-\varepsilon^{-\lambda_1^{\prime}\tau})\,(1-\varepsilon^{-\lambda_2^{\prime}\tau})] \qquad (13)$$

where $\lambda_1^{\prime}$ and $\lambda_2^{\prime}$ are the exponents describing the biexponential decay of plasma drug concentration. Assuming values of 0.231 h^{-1} and 0.0346 h^{-1}, respectively (corresponding to half-lives of 3 h and 20 h), from an inspection of mean plasma and urinary excretion rate data, equation 13 predicts an accumulation ratio in the 'tissue' compartment (R'_{ac}) of about 5 for metformin given every 8 h. Accordingly, if the site at which metformin initiates lactic acidosis is located in a tissue which acquires the drug slowly, plasma concentrations of the drug may not be sensitive predictors of toxicity. This may partially account for the poor correlation found by Irsigler, Kritz, Regal & Kaspar (1979) between serum biguanide levels and raised blood lactate concentrations in diabetic patients.

A slow association of metformin with blood cells indicated by the increasing blood : plasma drug concentration ratio with time (Figure 8) may serve as a model of the rate of cellular uptake of the drug in other tissues.

The primary role played by the kidney in the clearance of metformin is in accordance with the clinical finding that impaired renal function is a significant risk factor for lactic acidosis associated with metformin therapy (Assam, Heuclin, Caneval, Bismuth, George & Girard, 1977). Renal clearance values for the drug well in excess of creatinine clearance implicate tubular secretion of this highly ionised compound as a major mechanism of urinary excretion.

Age will be a factor in the correlation observed between the renal clearance of metformin and creatinine clearance (Figure 9a) since age and renal function covary. However, the direct correlation between metformin renal clearance and the ages of our subjects was weaker ($r = 0.76$) than that between metformin renal clearance and creatinine clearance ($r = 0.85$). Furthermore, Sirtori *et al.* (1978) studied

patients with more severe renal impairment than ours and their data support a strong correlation between metformin renal clearance and creatinine clearance (Figure 9b).

Assuming that renal function is a major determinant of the accumulation of metformin, a decrease in creatinine clearance should be accompanied by a parallel increase in the average amount of drug in the body at steady-state during continuous administration and a greater increase in the minimum amount of drug in the body at the end of a dosage interval. However, other factors may partially offset these changes. These include the possibility that the absorption of metformin may be lower in patients with renal failure. Certainly, it is clear that if total oral clearance of metformin, a more appropriate predictor of accumulation than its renal clearance, is plotted against creatinine clearance a much weaker correlation is observed (Figure 10). Therefore, we suggest that, at least in patients with moderate renal impairment, creatinine clearance may not always be a reliable indicator of potential metformin accumulation owing to variability in absorption, and, possibly, non-renal clearance of the drug.

We thank Rona Laboratories for financial support.

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(Received September 5, 1980)