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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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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:

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

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

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 ad-

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