dosage form, affect the absorption of metformin HCl in man

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The pharmacokinetics of four single-dose treatments of the metformin administered orally (as the HCl salt) were compared in 24 healthy subjects: 500 mg and 850 mg tablets and 850 mg solution fasting and 850 mg tablet with food. Solution and tablet formulations are bioequivalent. Bioavailability of a 500 mg tablet is 14% greater than that of an 850 mg tablet. Compared with the fasting state, bioavailability is 24% lower, and the peak concentration delayed about 37 min when an 850 mg tablet is administered with food.

Keywords metformin pharmacokinetics food interaction dose-proportionality dosage form

Introduction

Metformin, a biguanide antihyperglycaemic agent, has been widely used for the treatment of diabetes for more than three decades [1, 2]. Pharmacokinetic studies show that it is rapidly eliminated by the kidney [3–5] and its metabolism and plasma protein-binding are negligible [4, 5]. Gastrointestinal absorption of metformin is slow and incomplete when administered as a solution or rapidly dissolving tablet [3–7].

We evaluated factors that may influence the absorption (or elimination) of metformin: dosage level, dosage form, and food. Because in a few patients bioavailability decreased with increasing dose [4, 6], we studied the pharmacokinetic linearity of two commonly used doses of metformin HCl, 500 and 850 mg. We compared the pharmacokinetics of tablet and solution formulations of metformin HCl because of confounding results in an earlier study [7]. Metformin is recommended to be taken with food to decrease gastrointestinal symptoms, but the impact of food on extent and rate of absorption is unknown.

Methods

Study design

A four-way randomized, crossover, open-label investigation was conducted in 24 consenting healthy male subjects, ages 21–35 years weighing within 10% of normal for height and frame, at the Drug Studies Unit, University of California San Francisco, and was approved by the Committee on Human Research. Each subject was randomized to receive one of four treatment sequences: ABCD, BCDA, CDAB or DABC (six subjects per sequence), in which A was a 500 mg tablet, B an 850 mg tablet, and C an 850 mg/100 ml solution, each administered after an overnight fast. D was an 850 mg tablet taken 5–10 min after a high-fat high-calorie breakfast. Treatments were administered with 240 ml (Treatment C 140 ml) of water and separated by at least 1 week.

Venous blood was drawn just before drug administration and at 0.25, 0.50, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h thereafter. Harvested plasma was assayed for metformin. Urine (~20 ml) was obtained just before each treatment and during the following intervals relative to the dose: 0–4, 4–8, 8–12, 12–16, 16–24, 24–36, and 36–48 h. Samples were frozen (−20° C) until analysed.

Drug analysis

Metformin in plasma and urine was quantitated by high performance liquid chromatography [8], using

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Parameter	500 mg tablet fasting (Treatment A)	850 mg tablet fasting (Treatment B)	850 mg solution fasting (Treatment C)	850 mg tablet fed (Treatment D)	Statistically significant difference*
C_{max} (μg ml^{-1})	1.75±0.11†	1.58±0.08	1.50±0.08	0.97±0.04	A B B C D
t_{max} (h)	2.75±0.17	2.77±0.14	2.49±0.14	3.38±0.27	D B A C
AUC (μg ml^{-1} h)	11.47±0.61†	10.07±0.56	9.59±0.57	7.65±0.32	A B C D
k (h^{-1})	0.153±0.011	0.133±0.009	0.147±0.011	0.142±0.009	A C D B
$t_{1/2}$ (h)	5.10±0.36	5.76±0.40	5.26±0.36	5.54±0.53	B D C A
CL/F (ml min^{-1})	1025±48	1183±63	1243±64	1508±57	D C B A
V_{area}/F (L)	451±43	575±41	559±43	712±63	D B B C A
Ae (mg)	385±12.8†	329±17.6	323±14.9	276±11.1	A B C D
CL_R (ml min^{-1})	598±27	573±32	605±26	633±33	D C A B

* Treatments over same line do not differ significantly.
† Normalized to 850 mg.

propylbiguanide as the internal standard. The limit of quantitation was 10 ng ml^{-1} for plasma and 4 μg ml^{-1} for urine. Coefficients of variation for interday and intraday were $<10\%$ for all assays.

Pharmacokinetic analysis

Using standard non-compartmental methods, estimates of peak plasma concentration (C_{max}), time of C_{max} (t_{max}), extrapolated area-under-the-curve (AUC), terminal rate constant of elimination (k), terminal half-life ($t_{1/2}$), clearance/bioavailability (CL/F), volume of distribution/bioavailability (V_{area}/F), total amount of drug excreted in the urine (Ae), and renal clearance (CL_R) were obtained [9]. AUC was estimated using the linear trapezoidal rule when concentrations were ascending and the log-linear trapezoidal rule when descending. Subjects whose Ae was unevaluable (due to missing samples) were excluded from that analysis (three subjects/treatments), and CL_R was estimated by dividing the sum of the Ae values for the evaluable intervals of collection by the sum of the AUC for the respective intervals. Calculations for the 500 mg treatment that depend on dose were normalized to 850 mg.

Statistical analysis

Differences in parameter estimates between treatments were tested using ANOVA and Ryan-Einot-Gabriel-Welsch Multiple F Test (α value = 0.05). Bioequivalence of the (850 mg) tablet formulation to solution (reference) was defined as estimated 90% confidence intervals of the ratio (test/reference) of C_{max} and of AUC that are within 80 to 125%.

Results

There was no significant difference ($P<0.05$) in any pharmacokinetic parameter estimate of metformin between Treatments B and C, and no significant difference among all treatments with respect to CL_R, k, or $t_{1/2}$ (Table 1; Figure 1). The 90% confidence intervals of the ratio of C_{max} and of AUC for Treatment B:C were (0.99, 1.14) and (0.99, 1.12), respectively, indicating bioequivalence. On average, treatment A had a 14% larger AUC, 17% larger Ae (normalized for dose), and 13% smaller CL/F than Treatment B. Treatment D

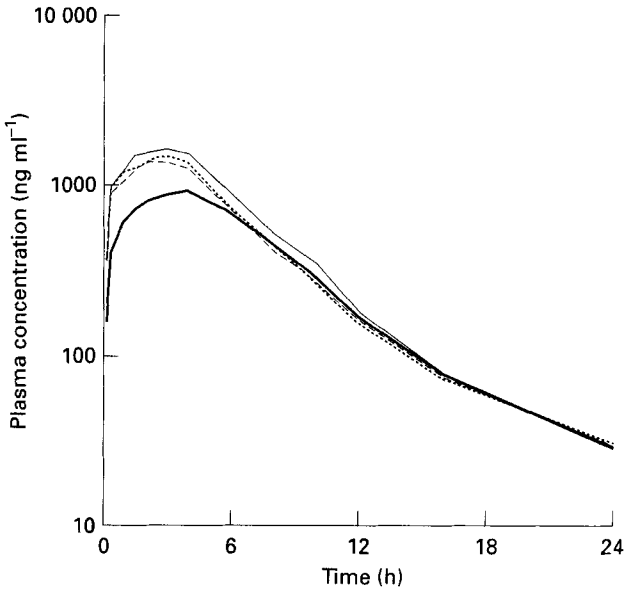

Figure 1 Mean metformin plasma concentration vs. time curves in 24 healthy subjects after oral administration of metformin HCl as a 500 mg tablet (—), an 850 mg tablet (···) and 850 mg solution (– – –) in the fasting state, and as an 850 mg tablet (——) in the fed state. Error bars have been omitted for clarity.

excretion of unchanged drug during the first 24 h ranged from 41.5% (Treatment D) to 57.3% (Treatment A) of the dose. Only minor adverse reactions (i.e. headaches, diarrhoea, nausea, and anorexia) occurred.

Discussion

Because metformin is eliminated almost exclusively by the kidney (i.e. CL_R is $\geqslant 90\%$ of CL) [3–5], the ratio of Ae/Dose (range 42–58%) is an estimate of absolute bioavailability and its values are consistent with previous reports [3–6].

The smaller CL/F with 500 mg compared with 850 mg was probably due to a higher F because CL_R did not differ significantly and Ae (normalized for dose) was significantly greater. Incomplete absorption of metformin and its dose-disproportionality [4, 6] may be related to physicochemical properties that limit its permeability [7], increasingly so as it moves down the small intestine [10] (it is largely ionized in the gut and is nonlipophilic). Less likely, a saturable transport process may exist [6].

Contrary to the findings of Pentikäinen [7], in which AUC (but not other measurements) was greater with the solution than with the tablet, we found that these formulations of metformin HCl are bioequivalent. This finding is expected because the tablet is completely dissolved within 1 h [7].

Metformin HCl is recommended to be taken with meals because gastrointestinal side-effects occur in about 30% of patients [2, 11]. We showed that concurrent food intake decreases the rate and extent of metformin HCl tablet absorption. We cannot determine whether food decreases the dissolution of the tablet or some other aspect of the absorption process because food was not given with the solution. The clinical benefit of administering metformin with food to decrease benefit seems to outweigh the potential disadvantage in the average person.

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(*Received 21 August 1995, accepted 28 March 1996*)