ABSOLUTE BIOAVAILABILITY OF GLIMEPIRIDE (AMARYL®) AFTER ORAL ADMINISTRATION

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SUMMARY

Twelve healthy fasting male volunteers received a single 1.0 mg dose of glimepiride either as an intravenous injection over one minute or as a tablet. Blood and urine samples were taken before drug administration and afterwards for up to 24 hours (blood) and 48 hours (urine) to determine serum and urinary concentrations of glimepiride and its hydroxy- and carboxy-metabolites (M1 and M2). There were no statistically significant differences between mean serum pharmacokinetic parameters for the oral and intravenous formulations either with glimepiride or M1. Mean urinary recovery of M1 plus M2 was 50% of the dose for the glimepiride tablet and 51% for the intravenous injection. The absolute bioavailability of the tablet formulation was 107% ($AUDC_{glimepiride}$), 109% ($AUDC_{M1}$) and 97% (urinary recovery). The tablet formulation of glimepiride is completely bioavailable and was safe and well tolerated in healthy volunteers.

KEY WORDS

pharmacokinetics, absolute bioavailability, glimepiride, healthy volunteers

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INTRODUCTION

Glimepiride (Amaryl®) is a new oral hypoglycaemic agent of the sulphonylurea class /1/. As with other sulphonylureas, the drug appears to lower plasma glucose levels by stimulating the release of insulin from the pancreas, which is dependent on functioning beta cells in the pancreatic islets /2/. When administered orally to healthy volunteers in increasing doses of up to 8.0 mg, the minimum dose for hypoglycaemic effect was observed at 0.5 mg /3/. Single doses of up to 2.0 mg, given intravenously to healthy volunteers, and oral doses of between 1 and 32 mg daily in patients with non-insulin dependent diabetes mellitus were well tolerated /3-5/.

After oral and intravenous administration, approximately 50% of the drug is recovered in the urine as the sum of the two main metabolites, hydroxy-glimepiride (M1) and carboxy-glimepiride (M2) /5,6/. Pharmacology studies in animals have shown M2 to have no hypoglycaemic effect in either rats or rabbits, and the pharmacological activity of M1 in rats was three times less than that of glimepiride. In animal toxicology studies, both metabolites were well tolerated /7/.

The aim of this study was to determine the absolute bioavailability of the 1.0 mg tablet formulation of glimepiride in healthy fasting volunteers.

METHODS

This open-label, randomised single dose study, with a two period cross-over design and a seven day washout period between treatments, was conducted at a single centre, the Medizinische Universitätsklinik, Vienna, Austria.

Healthy male volunteers, aged between 18 and 40 years, with normal physical examinations and normal ECGs, chest X-rays and laboratory values, were considered for entry into the study. Inclusion criteria required subjects to have a normal oral glucose tolerance test in the last six months and a body weight within + 10% and – 15% of normal weight according to Broca (Broca's formula for normal weight = height in cm – 100).

Subjects who had a serious medical disease in the four weeks prior to the study or who had the presence or history of gastrointestinal, hepatic or renal disease which could interfere with drug pharmacology

were excluded from the study, as were subjects known to be abusing alcohol or who had a hypersensitivity to sulphonylureas or a related compound. Subjects were also excluded from the study if they were receiving, or had received prior to the start of the study, any treatment which could interact with glimepiride or the assessment of its bio-availability.

The trial protocol was approved by the local ethics committee. All volunteers gave their written consent to participate in the trial.

Treatment

On entry into the study, subjects were randomised to receive a single 1.0 mg dose of glimepiride either as an intravenous injection or as a tablet. On the day before dosing, food and fluid intake were standardised in order to obtain a standard baseline situation across all volunteers. On the morning of the dosing days, the subjects reported to the Clinical Pharmacology Unit after an overnight fasting period of 12 hours. Thirty minutes prior to drug administration, an indwelling cannula was fixed into a suitable vein and was left in place for up to 12 hours after medication. The total amount of blood withdrawn for the trial including the safety pharmacology was about 350 ml. For the intravenous dosing, 1.0 mg of glimepiride was injected over one minute into a vein in the arm contralateral to the one used for blood sampling. The tablet was administered with 150 ml of water. No food was permitted until 10 hours after medication, at which time a standardised meal was served. The subjects drank 125 ml of water hourly up to 10 hours after dosing; fluid intake was then unrestricted. The subjects remained seated for the first four hours after dosing.

Assessments

Blood samples were taken before administration of glimepiride and 5, 10, 15, 20, 30, 40, 50 minutes, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours afterwards.

Total urine output was collected before administration of glimepiride and afterwards at the following time intervals: 0-2, 2-4, 4-8, 8-12, 12-24 and 24-48 hours.

Serum and urinary concentrations of glimepiride and the two main metabolites, M1 and M2, were determined by high-performance liquid chromatography (HPLC) /8/.

Clinical chemistry, haematology and urinalysis tests were performed at screening, before the first dose and 24 hours after the second dose of glimepiride. Monitoring of vital signs (blood pressure and heart rate) was carried out before medication and 30 minutes, 1, 2, 3, 4, 6, 8, 10 and 24 hours after medication. Twelve-lead ECGs were performed at screening and at the end of the study. Any adverse events which occurred during the trial were noted and, for safety purposes, blood glucose concentrations were regularly measured by the hexokinase method for up to 24 hours after drug administration.

Data analysis

The following model-independent pharmacokinetic parameters for glimepiride and its metabolite M1 in serum were calculated: maximum serum concentration (C_{max}), time to peak concentration (t_{max}), area under the concentration time data completed by extrapolation (AUDC), terminal half-life ($t_{1/2\,z}$) and total clearance (CL).

Urinary recovery of the metabolites M1 and M2 was expressed in mg and as a percentage of the dose. The latter was calculated as the sum of the excreted metabolites M1 and M2 after molecular weight correction.

The determination of absolute bioavailability was based on the AUDCs for glimepiride and metabolite M1 and the relative cumulated urinary recovery of M1 and M2. Absolute bioavailability was calculated as the point estimates of the geometric means for the individual ratios of oral to intravenous data expressed as a percentage. Conventional 90% confidence intervals were calculated /9/.

RESULTS

Twelve healthy white male volunteers participated in the study. Mean age of the subjects was 28 years (range 20-40), mean weight 78 kg (72-88) and mean height 184 cm (172-199). All subjects received both the oral and intravenous formulations and completed all the examinations.

Profiles of the mean serum concentrations for the parent compound and metabolites M1 and M2 are plotted in Figure 1. The mean pharmacokinetic parameters (± SD) for glimepiride and M1 are given in Table 1. There were no statistically significant differences between the oral and intravenous formulation for either glimepiride or M1. No

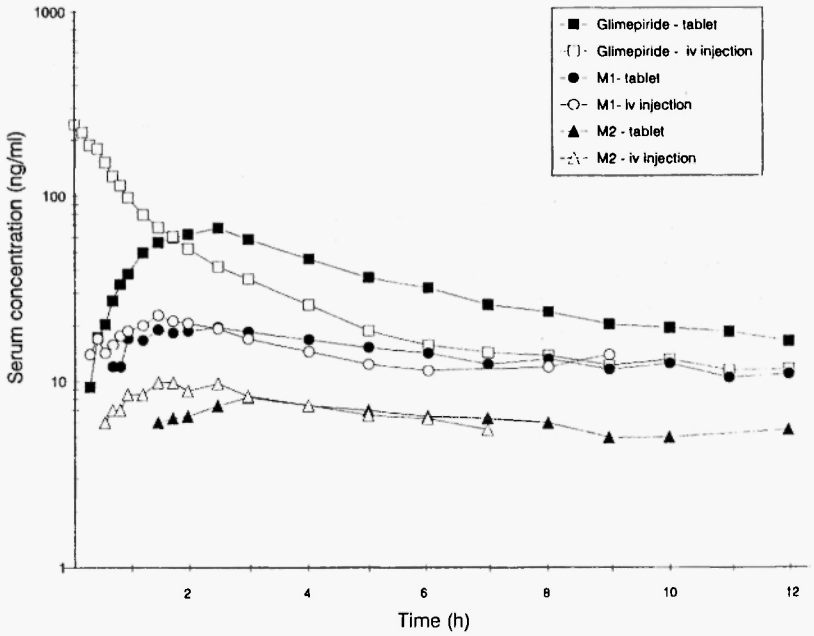

Fig. 1: Mean serum concentrations (ng/ml) of glimepiride, M1 and M2, after tablet and intravenous (iv) injection.

TABLE 1
Pharmacokinetic parameters in serum [mean (± SD)]

	Glimepiride		Metabolite M1	
Parameter	**Tablet**	**Intravenous**	**Tablet**	**Intravenous**
C_{max} (ng/ml)	88 (± 21)	243 (± 33)*	20 (± 6)	24 (± 5)
t_{max} (h)	2.7 (± 1.4)	*	3.9 (± 1.9)	1.6 (± 0.4)
AUDC (ng*h/ml)	449 (± 248)	412 (± 184)	134 (± 46)	115 (± 39)
$t_{1/2,z}$ (h)	3.1 (± 1.2)	3.4 (± 2.0)	3.3 (± 1.2)	2.7 (± 1.0)
CL (ml/min)	45 (± 16)	48 (± 20)	143 (± 48)	175 (± 94)

* First sample taken 5 minutes after start of injection

pharmacokinetic parameters were calculated for M2 since most of the serum concentration values were below or close to the detection limit.

Unchanged glimepiride was not detectable in the urine of any of the subjects after the oral dose. After intravenous administration, six subjects showed levels of up to 72 ng/ml in the urine collection period 0-2 hours. In these six subjects, this urinary recovery of unchanged glimepiride ranged from 0.1% to 0.4% of the dose administered. Mean urinary recovery (± SD) of M1 and M2 is shown in Table 2. Mean urinary recovery of the sum of M1 and M2 after molecular weight correction expressed as a percentage of the dose was 50 (± 7)% for the glimepiride tablet and 51 (± 5)% for the intravenous injection (Figure 2).

Table 3 shows the absolute bioavailability of the tablet formulation to be 107% based on $AUDC_{glimepiride}$, 109% based on $AUDC_{M1}$ and 97% based on urinary recovery.

One subject experienced dizziness, paleness and sweating 75 minutes after receiving the intravenous injection of glimepiride 1.0 mg. The symptoms were moderate and lasted for 30 minutes. The subject's blood glucose was 2.8 mmol/l (normal range: 3.61 - 5.55 mmol/l) one hour after the intravenous injection of glimepiride and 3.4 mmol/l 30 minutes later; no countermeasures were necessary. No other adverse events were reported.

There were no clinically important or drug-related changes in either vital signs or laboratory tests for any of the subjects.

Mean blood glucose levels following the oral formulation remained within normal ranges for all time points. For the intravenous formulation, mean blood glucose was slightly below the normal range between 40 and 90 minutes after the injection, and within normal ranges at all other time points.

TABLE 2
Urinary recovery (mg) of metabolites M1 and M2 [mean (± SD)]

	M1		M2	
	Tablet	**Intravenous**	**Tablet**	**Intravenous**
Urinary recovery	0.38 (± 0.10)	0.37 (± 0.06)	0.14 (± 0.06)	0.17 (± 0.05)

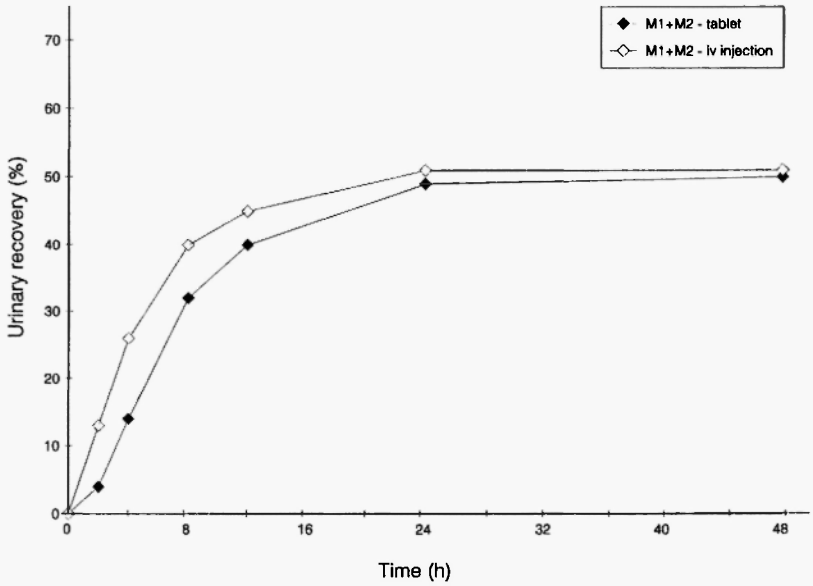

Fig. 2: Mean urinary recovery of the sum of M1 and M2 as a percentage of glimepiride dose (after molecular weight correction).

TABLE 3
Absolute bioavailability calculated as ratios of oral to intravenous data

Parameter	Point estimate (%)	90% confidence interval (%)
$AUDC_{glimepiride}$	107	87-130
$AUDC_{metabolite\ M1}$	109	92-129
Urinary recovery	97	93-102

DISCUSSION

In this single dose study of healthy male volunteers, there were no statistically significant differences between the mean pharmacokinetic parameters of the oral and intravenous formulations either for glimepiride or its metabolite M1. No calculations were done for M2 since most of the values were below or close to the detection limit.

Unchanged glimepiride was not detectable in the urine after the oral tablet formulation. Although unchanged glimepiride was recovered in the urine from six subjects following intravenous administration, the levels were negligible (between 0.1% and 0.4% of the dose administered). Mean urinary recovery of the sum of M1 and M2 expressed as a percentage of the dose was 50 (± 7)% for the tablet formulation and 51 (± 5)% for the intravenous injection. Absolute bioavailability for the tablet formulation, calculated as the ratio of oral to intravenous data, was 107% based on $AUDC_{glimepiride}$, 109% based on $AUDC_{M1}$ and 97% based on urinary recovery. These data, therefore, confirm the complete bioavailability of the tablet formulation of glimepiride, and this represents an advantage for glimepiride over other sulphonylureas.

One subject experienced moderate hypoglycaemic symptoms 75 minutes after the intravenous injection of glimepiride, and these symptoms lasted for only 30 minutes and required no countermeasures. No other adverse events were reported during the study and there were no clinically important or drug-related changes in either vital signs or laboratory tests for any of the subjects.

In conclusion, the 1.0 mg tablet formulation of glimepiride is completely bioavailable, and glimepiride was safe and well tolerated in healthy volunteers.

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