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Bioavailability of gliclazide from some formulation tablets

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Abstract

Diabezid, from Jelfa, and diabrezide, from Molteni, tablets are bioequivalent as well as producing pharmacokinetic parameters typical for classic gliclazide oral formulations ($C_{max} = 3.4–4.1$ mg l^{-1}, $t_{max} = 3.5–4.6$ h, $t_{0.5} = 5.2–6.5$ h). In contrast, diaprel tablets, from Servier, seem to be a sustained release formulation and is not bioequivalent to the above tablets. It produces a long tablet disintegration time (58 min) and the dissolution of gliclazide in 0.1 mol l^{-1} HCl (9.04 mg l^{-1} (11.3%) at 4 h and 37°C) as well as in serum C_{max} (0.7 mg l^{-1}) are poor. In contrast with the Jelfa tablets, the Servier tablets do not demonstrate any hypoglycemic effect in healthy volunteers.

Keywords: Gliclazide; Bioavailabilty; Tablets; Volunteers; Serum; Release in vitro; Hypoglycemic effect; Humans

1. Introduction

Gliclazide, 1-(3-azabicyclo(3.3.0)oct-3-yl)-3-*p*-tolylsulphonylurea is an oral hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Its common proprietary names are diabrezide, diamicron, diaprel, diabezid etc. It is readily absorbed from the gastro-intestinal tract and extensively metabolized in the liver by hydroxylation, *N*-oxidation and oxidation to a number of inactive metabolites. Approximately 60–70% of a dose is excreted in the urine with less than 5% as unchanged drug. Approximately 10–20% of the dose is eliminated in the faeces as metabolites. It is protein human plasma bound in 85–95%. Its plasma half-life is 6–14 h (Moffat, 1986; Reynolds, 1993). After a single oral dose of 80 mg to 23 subjects, peak plasma concentrations of 0.7–4.9 mg l^{-1} were attained in about 4 h (Cambell et al., 1991).

In this study, bioavailability of three kinds of 80 mg gliclazide tablets (diabezid from PF Jelfa, diabrezid from Molteni and diaprel from Servier) was followed in volunteers. To explain some differences in their bioavailabilty, the time of disinte-

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gration of diaprel and diabezid tablets and their rate of release of gliclazide were also examined and as their hypoglycemic effect was determined in humans. Bioavailability data of diaprel (Servier, Poland) and diabezid (Jelfa, Poland) tablets were not published at this time.

2. Materials and methods

2.1. Materials

Product samples identified as diabezid tablets 80 mg (DB_1), lot number 10794p, diabezid tablets 80 mg (DB_2), lot number 10395p as well as diaprel tablets 80 mg (DP), lot number 3 L 0761 and diabrezide tablets 80 mg (DBR), lot number 299 were received from Jelfa, Jelenia Góra, Poland, Servier Poland and Molteni, Italy, respectively. A gliclazide authenthic sample, lot number 136 (99.8%) was purchesed from Orgasynth, France. An internal standard—glibenclamide—was obtained free of charge from Pharmaceutical Works, Polpharma, Starogard Gdański, Poland. BioMerieux's reagents (France) were used for the volunteers' serum glucose level determinations.

2.2. Subject selection

Ten each of normal adult, non-smoking, male and female volunteers between 20 and 36 years (mean 24.9 ± 5.9) and between 20 and 37 years (mean 26.0 ± 6.0) weighing on average 65.2 ± 9.5 and 69.5 ± 10.2 kg were selected for participation in the above investigations for DB_1 versus DP and DB_2 versus DBR, respectively. The volunteer subjects were selected after completing a thorough history and physical examination, and after a normal laboratory examination. The laboratory tests consisted of the following: hematology, serum chemistry and urinalysis. All subjects were presented with full details of the investigation, both verbally and in written form, prior to providing written informed consent. The investigations were approved by Human Investigations Ethical Committee at the University of Medical Sciences in Poznań.

2.3. Study design

The study was of a non-blinded, open-label, single dose, double-way crossover design. All subjects were randomly assigned a drug assignment number from 1 to 10, which was used throughout the study period. Dosing periods were separated by at least a two weeks washout period. The subjects were required to fast for at least 10 h prior to the timing of the dose. On each of two treatment days, subjects were instructed to present in the study facility. At 'zero hour' the subjects were assigned to a phlebotomist for the purpose of collecting a 5 ml blood sample. The assigned tablet was swallowed with 200 ml water. All subjects abstained from food until the 4-h blood specimen was obtained when a standardized low fat lunch was provided. Regular meals were resumed after the 12-h blood sample was obtained. Following drug administration, venous blood samples (5 ml) were obtained (in Serum Gel tubes, S/4.7 ml, Sarstedt Monovette, Germany) from the subject's right or left antecubital fossa at the following times: immediately before administration of gliclazide and 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 9.0, 12.0 and 24 h after administration. Within 30 min following blood withdrawal, the samples were centrifuged. The separated plasma samples were frozen in plastic vials at -20°C and labeled with the subjects I.D. number, the drug assignment number, treatment day and time of sampling. The red blood cells were discarded.

Serum samples were quantitated first for gliclazide by an HPLC procedure published elsewhere (Główka and Hermann, 1997) and a second sample simultaneously (DB_1 and DP volunteers only) for their glucose level by an enzymatic methodology from a French company ready for test use (bioMerieux). Serum glucose was oxidised to hydrogen peroxide, which was conjugated with phenol and 4-aminoantipyrine in the presence of peroxidase to a colour quinonoimine, whose absorbance was read at 505 nm in an Clinilab apparatus.

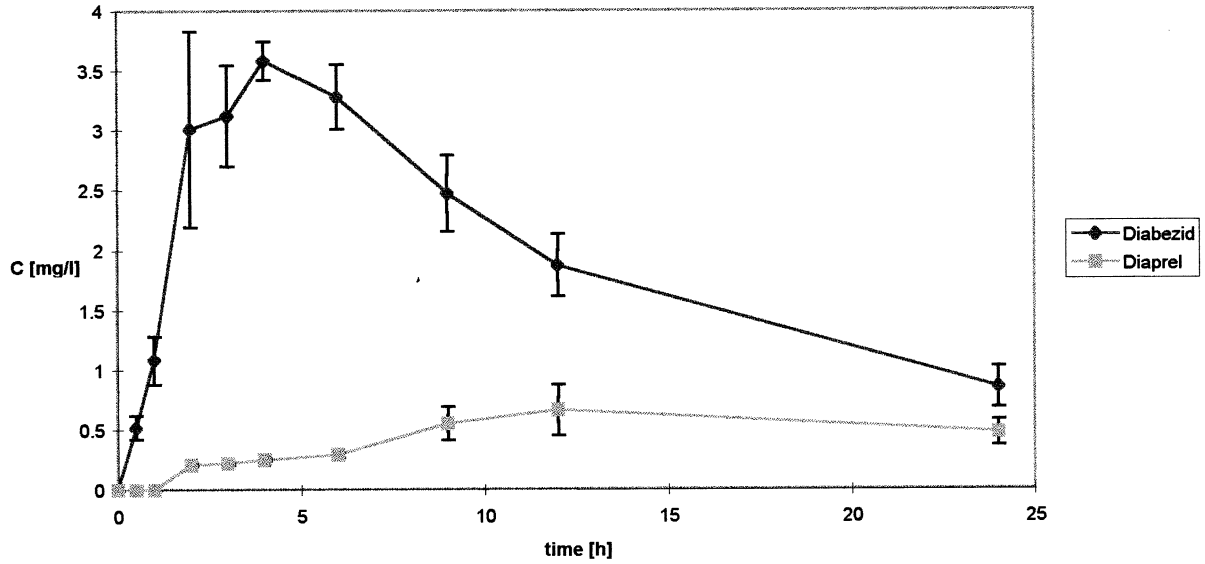

Fig. 1. Mean serum gliclazide concentrations after the crossover administration of a diabezid Jelfa tablet and a diaprel Servier tablet to 10 volunteers.

2.4. Pharmacokinetic analysis

The analytical results of the plasma specimens were used to calculate the following: elimination rate constant (K, h^{-1}), half-life time ($t_{0.5}$, h), area under the plasma concentration–time curve ($AUC_{0\rightarrow\infty}$, mg h l^{-1}), time to peak plasma concentration (t_{max}, h), peak plasma concentration (C_{max}, mg l^{-1}) and extent of bioavailability (EBA, %). TOPFIT 2.0 software (Gustav Fischer, Stuttgart, 1993) was used for calculation of the above pharmacokinetic parameters. Statistical significance of gliclazide and glucose plasma variations in the different formulations investigated was tested according to an ANOVA test by the Excel 4.0 program.

2.5. Gliclazide dissolution test from tablets

The dissolution test was performed in a rotating disk apparatus at 100 rpm in 0.1 mol l^{-1} HCl medium at 37 ± 0.5°C according to FP V (Wieniawski, 1993). The yield (mg l^{-1}) of release of gliclazide from each of 12 tablets was measured at time intervals of 15 min over a period of 4 h from the start of the experiment. The absorbance of the dissolution medium at 230 nm was taken by means of a UV–vis spectrophotometer Specord M 40 (Carl Zeiss, Jena). Each 1 ml sample withdrawn from the dissolution apparatus was diluted with 2 ml 0.1 mol l^{-1} HCl prior to reading against a blank solution of 0.1 mol l^{-1} HCl in 1 cm silica cells. The concentrations of gliclazide released from a tablet were then calculated using the absorbance coefficient of gliclazide determined ($A^{1\%}_{1\ cm} = 446$ (100 ml g^{-1} cm $^{-1}$)).

3. Results and discussion

3.1. Pharmacokinetic analysis

The serum gliclazide concentrations (C) following the administration of a tablet to each volunteer were well characterized by the difference in two exponentials (Figs. 1 and 2):

$$C = Be^{-\lambda_2 t} - Ae^{-\lambda_1 t} \quad (1)$$

In Eq. (1), A and B are the corresponding zero-time intercepts, λ_1 and λ_2 are the apparent first-order fast and slow disposition rate constants, and t is the time. The averaged gliclazide serum data

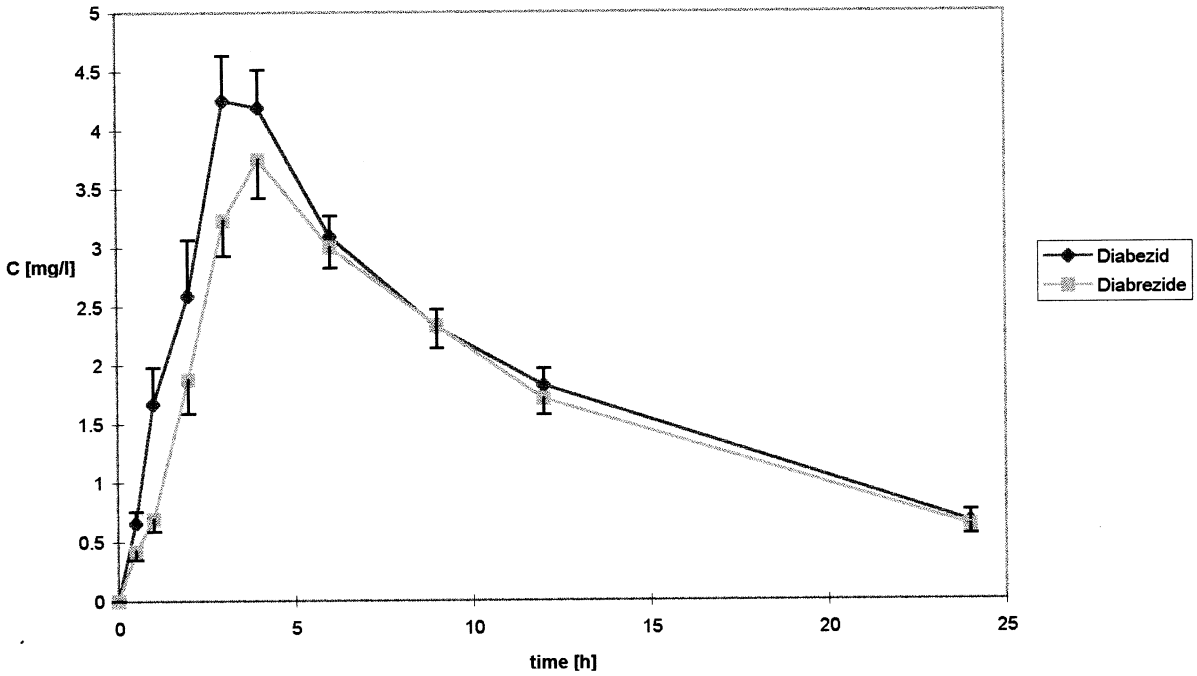

Fig. 2. Mean serum gliclazide concentrations after the crossover administration of a diabezid Jelfa tablet and a diabrezide Molteni tablet to 10 volunteers.

and their S.E.M.s as well as the above bioavailability parameters are given in Table 1 for DB_1 and DP tablets and in Table 2 for DB_2 and DBR tablets.

The p-values, which are with respect to the ANOVA test used, would indicate that only in the case of 24 h serum data the tablets DB_1 and DP are statistically equivalent. The other serum data and all bioavailability parameters are significantly different (Table 1). Peak serum C (C_{max}) of diabezid Jelfa tablets (4.1 mg l^{-1}) is in accordance with a reference data (Cambell et al., 1991). In contrast, serum levels produced on administration of supposedly equivalent diaprel tablets are very low ($C_{max} = 0.69$ mg l^{-1}). It seems to us that the DP tablets can be recognized as a slow release preparation. However, that information is not provided by the manufacturer (Servier Poland) in the available booklet (Diaprel®), where C_{max} is specified as 6–8 mg l^{-1}. It should be mentioned that in all subjects except one the plasma gliclazide levels following oral administration of a tablet of either Jelfa (diabezid) or Molteni (diabrezide) were equivalent (Table 2) and in accordance with the literature on human data for a single 80 mg gliclazide tablet administration (Cambell et al., 1991). Also, all but one of the biovailability parameters of the Jelfa and Molteni tablets were not significantly different (Table 2). The only statistically different parameter was the time to maximum concentration (t_{max}), which is shorter (3.48 h) for DB_1 than for DBR (4.61 h). Therefore, the extent of bioavailability of the Jelfa tablets is insignificantly higher (113.4%) if compared to the Molteni tablets (Table 2). The above tablets can be considered as bioequivalent. In contrast to the above, the Jelfa tablets and Servier Poland tablets examined are not bioequivalent. They are different tablets if their drug delivery system is considered. According to our information some excipients are different in the DP tablets. Either Gummi Accaciae or polyvinylpyrrolidone is used as a binding agent in the Servier and Jelfa tablets, respectively. In addition starch is formulated in the Jelfa tablets to shorten their disintegration time. The above for-

mulation excipients could be responsible for the different serum profiles of the Jelfa and Servier tablets.

3.2. Dissolution studies of gliclazide from DB_1 and DP tablets in vitro

The disintegration time of the tablets examined in 0.1 mol l^{-1} HCl medium at 37°C was as follows: 8.58 and 12 min for DB, DP and DBR tablets, respectively (Table 3).

The dissolution time was also in accordance with the above pattern. It means that the yield of gliclazide released under the above medium conditions was greatest at 4 h for the Jelfa (75.5 mg l^{-1}) and Molteni (60.45 mg l^{-1}) tablets and lowest for the Servier tablets (9.07 mg l^{-1}) (Table 3). The results obtained under the in vitro conditions comply very well with pharmacokinetic studies in man. The Jelfa tablets deliver a statistically higher amount of gliclazide to the systemic circulation than the Servier tablets, because the rate of release of that drug is over 8-fold greater in the HCl medium. However, the Jelfa tablets produce insignificantly higher C_{max} value than the Molteni tablets, and their gliclazide yield of release is only by 15 mg l^{-1} greater in vitro at 4 h (Tab. 3).

Table 1
Mean serum concentrations of gliclazide from 10 subjects after the crossover administration of DB_1 and DP tablets and suitable pharmacokinetic and bioavailability parameters

Time (h)	Concentrations (mg l^{-1})		ANOVA test
	DB_1	DP	
0.5	0.52 ± 0.10	<0.20	—
1.0	1.08 ± 0.20	<0.20	—
2.0	3.01 ± 0.82	0.21 ± 0.01	$p<0.034$
3.0	3.12 ± 0.42	0.22 ± 0.01	$p<0.001$
4.0	3.58 ± 0.16	0.25 ± 0.01	$p<0.001$
6.0	3.28 ± 0.27	0.29 ± 0.02	$p<0.001$
9.0	2.47 ± 0.32	0.55 ± 0.14	$p<0.001$
12.0	1.87 ± 0.26	0.66 ± 0.21	$p<0.002$
24.0	0.85 ± 0.17	0.47 ± 0.11	NS
Parameters			
$AUC_{0\rightarrow\infty}$ (mg h l^{-1})	47.36 ± 4.08	10.97 ± 2.69	$p<0.001$
C_{max} (mg l^{-1})	4.56 ± 0.63	0.69 ± 0.21	$p<0.001$
t_{max} (h)	4.10 ± 0.44	13.80 ± 1.74	$p<0.001$
$t_{0.5}$ (h)	9.90 ± 0.82	17.50 ± 1.74	$p<0.002$
EBA (%)	431.7	—	—

Values are mean ± S.E.M.

Table 2
Mean serum concentrations of gliclazide from 10 subjects after the crossover administration of DB_2 and DBR tablets and suitable pharmacokinetic and bioavailability parameters

Time (h)	Concentrations (mg l^{-1})		ANOVA test
	DB_2	DBR	
0.5	0.66 ± 0.10	0.42 ± 0.07	NS
1.0	1.67 ± 0.31	0.69 ± 0.10	$p<0.016$
2.0	2.59 ± 0.47	1.88 ± 0.29	NS
3.0	4.25 ± 0.38	3.23 ± 0.30	NS
4.0	4.19 ± 0.32	3.75 ± 0.33	NS
6.0	3.09 ± 0.18	3.00 ± 0.18	NS
9.0	2.32 ± 0.15	2.33 ± 0.19	NS
12.0	1.82 ± 0.15	1.71 ± 0.14	NS
24.0	0.66 ± 0.09	0.63 ± 0.08	NS
Parameters			
$AUC_{0\rightarrow\infty}$ (mg h l^{-1})	49.42 ± 4.04	43.59 ± 3.60	NS
C_{max} (mg l^{-1})	4.12 ± 0.28	3.44 ± 0.25	NS
t_{max} (h)	3.48 ± 0.20	4.61 ± 0.25	$p<0.003$
$t_{0.5}$ (h)	6.46 ± 1.05	5.23 ± 0.67	NS
EBA (%)	113.4	—	—

Values are mean ± S.E.M.

3.3. Hypoglycemic effect of DB_1 and DP tablets in humans

The action of the Jelfa tablets is reflected in a reduction of blood glucose levels in volunteers from 89.6 ± 11.2 mg dl^{-1} at zero time to 70.8 ± 10.5 mg dl^{-1} after 3 h from administration. No significant glucose reduction level was observed in the above volunteers after administration of the Servier tablets within the period of examination (Table 4).

However, it should be taken into consideration that the Servier tablets do not demonstrate any hypoglycemic effect in healthy volunteers. It is claimed that the Servier tablets demonstrate a unique and safe profile of clinical action with good general tolerability if compared to other

Table 3
Disintegration time of gliclazide tablets and its dissolution from them in 0.1 mol l^{-1} HCl at 37°C

Tablets	Disintegration time (min)	Dissolution of gliclazide at different times	
		0.25 h	4.00 h
DB_1	8.0	50.94 ± 0.49	75.50 ± 0.52
DP	58.0	0.00	9.04 ± 0.35
DBR	12.0	11.90	60.45

Values are mean ± S.E.M.

sulphonylureas (Kobayashi et al., 1984; Ishibashi and Takashina, 1990; Palmer and Brogden, 1993; Harrower, 1994; Tessier et al., 1994). The prevalence of hypoglycemic symptoms was significantly higher in patients treated with glyburide than in patients treated with gliclazide ($p < 0.01$) or chlorpropamide ($p < 0.05$) (Jennings et al., 1989). It is worth mentioning that elderly diabetic patients' fasting blood glucose (approximately 11 mmol l^{-1}) has been decreased to an average 8.5 mmol l^{-1} after 1 month treatment with gliclazide tablets (Servier, Montreal, Canada) (Tessier et al., 1994).

4. Conclusion

Diaprel 80 mg tablets (Servier, Poland) are a sustained release formulation as a result of a high tablet disintegration time (58 min) and a very low gliclazide dissolution from a tablet (9.07 mg l^{-1} at 4 h at 37°C). They produce very low maximum serum levels of gliclazide in healthy volunteers (0.66 mg l^{-1} at 12 h) and show no change in their serum glucose. However, it does not mean that these tablets should not develop a hypoglycemic effect in diabetic patients. The manufacturer (Les Laboratoires Servier, Poland) does not provide suitable information on these tablets as a sustained release formulation. On the contrary, they provide pharmacokinetic parameters characteristic for a classic gliclazide oral formulation ($C_{max} = 6–8$ mg l^{-1}, $t_{max} = 2–3$ h, $t_{0.5} = 10–12$ h). However, the above data are typical for the Jelfa as well as for the Molteni tablets. It should be mentioned that the only pharmacokinetic parameter which differs between the DB and DBR tablets is their t_{max}, which is significantly shorter for the DB (3.48 h) than for the DBR tablets (4.61 h) as a result of 1.25-fold greater gliclazide dissolution at 4 h (Tables 2 and 3). It is not up to us to decide which tablets are best for the treatment of NIDDM. It is clear that the DB and DBR tablets are bioequivalent but they are different from the DP tablets. A diabetologist should specify the indications for the use of suitable gliclazide tablets available on the market.

Table 4
Mean glucose serum levels from 10 subjects after the crossover administration of DB_1 and DP tablets as a function of time

Time (h)	DB_1 (mg dl^{-1})	DP (mg dl^{-1})	ANOVA test
0.0	89.6 ± 3.5	81.6 ± 2.0	NS
0.5	78.2 ± 3.5	87.7 ± 3.2	$p < 0.05$
1.0	68.7 ± 4.0	81.9 ± 2.3	$p < 0.01$
2.0	71.1 ± 3.9	82.4 ± 1.7	$p < 0.01$
3.0	70.8 ± 3.3	83.4 ± 4.1	$p < 0.03$
4.0	86.0 ± 5.5	91.2 ± 5.8	NS
6.0	82.6 ± 5.5	77.6 ± 5.4	NS
9.0	79.5 ± 5.6	85.9 ± 5.6	NS
12.0	91.6 ± 6.5	83.4 ± 1.8	NS
24.0	89.5 ± 2.9	91.2 ± 6.2	NS

Values are mean ± S.E.M.

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