Bio-availability of three formulations of glibenclamide

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Summary

Eighteen healthy men participated in a double-blind, randomised, crossover study to compare the bio-availability of three 5 mg formulations of glibenclamide. The products compared were Daonil (Hoechst), Glycomin (Lennon) and Melix (Lagamed). Volunteers received a continuous intravenous infusion of glucose at a rate of 0,25 g/kg/h for 10 hours. Two hours after commencement of this infusion medication was given orally with 200 ml of a 10% (m/v) glucose solution. The subjects also drank 200 ml of the glucose solution hourly for 5 hours after medication. Blood samples were taken up to 22 hours after medication for radio-immunoassay of glibenclamide as well as for measurement of glucose concentrations. The following kinetic variables were calculated; maximum concentration, time to maximum concentration, terminal half-life, areas under the serum concentration-time curves, relative total clearance, total mean time and relative volume of distribution. Daonil and Glycomin were bio-equivalent, but important differences were demonstrated between these two formulations and Melix. This study method necessitates close surveillance of volunteers in order to detect and treat hypoglycaemia.

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Glibenclamide belongs to the sulphonylurea group of oral hypoglycaemic agents, lowering blood glucose by stimulating the secretion of insulin from the β-cells of the pancreatic islets.[1]

Glibenclamide is readily absorbed from the gastro-intestinal tract. It is excreted in faeces and, as metabolites, in urine and is bound to plasma proteins to the extent of 99%. Peak serum concentrations are reached in 4 hours.[2]

Subjects and methods

Eighteen healthy men (aged between 18 years and 36 years; weight between 65 kg and 94 kg) were enrolled to participate in a double-blind, randomised, cross-over study to compare the bio-availability of three formulations of 5 mg glibenclamide tablets: Daonil (Hoechst; batch No. 339 BI), Glycomin (Lennon; batch No. M816320) and Melix (Lagamed; batch No. 87394). The subjects were randomly allotted to the treatments. Each subject received each treatment once and the trial periods were separated by a drug-free interval of 7 days.

Volunteers had to be normal on physical examination and their haematological, clinical chemistry, urinalysis and electrocardiographic test results had to be satisfactory in order to be included in the study. Volunteers refrained from taking any medication, alcohol or caffeine and from participation in strenuous exercise as from 1 week before commencement of the study until its conclusion. On profile days, food and fluid intake were standardised in order to minimise intra- and inter-individual variation.

The study was carried out in conformance with the recommendations for clinical trials in man, as set out in the Declaration of Helsinki (Venice Amendment, 1983) and permission was obtained from the Ethics Committee of the University of the Orange Free State. Each volunteer signed an informed consent form.

On the mornings of profile days, volunteers reported to the clinic after an overnight fast. Indwelling venous cannulas were positioned, one in each arm, and subjects received a continuous intravenous infusion of glucose at a rate of 0,25 g/kg/h for 10 hours. This was administered as a 20% (m/v) intravenous solution. Two hours after commencement of the glucose infusion the appropriate formulation of glibenclamide was administered orally with 200 ml of a 10% (m/v) solution of glucose.[3] After medication they drank 200 ml of this solution hourly on the hour for 5 hours. Food intake was not permitted until 8 hours after medication when a standardised meal was served. They remained in a recumbent position for 10 hours.

Blood samples for glibenclamide assay were taken before medication and at 0,5, 1, 1,5, 2, 2,5, 3, 3,5, 4, 4,5, 5, 6, 7, 8, 10, 12,5 and 22 hours after medication, and immediately centrifuged and stored at −20°C pending assay. A radio-immune method was used to measure serum glibenclamide concentrations.[4]

Plasma glucose values were determined for each of the blood specimens. If symptoms of hypoglycaemia occurred, additional glucose was given intravenously.

Results

The mean glibenclamide serum concentrations are shown in Fig. 1.

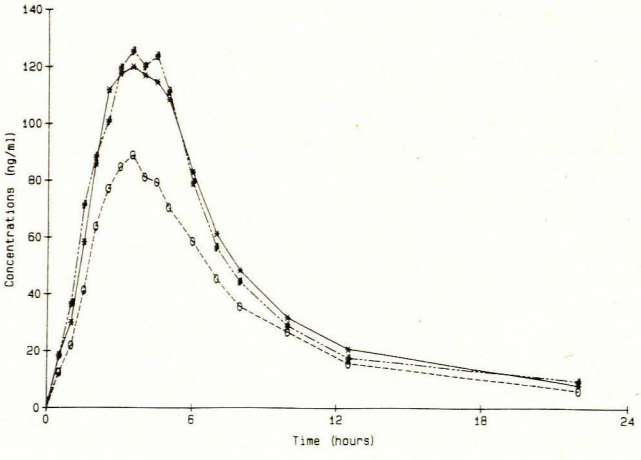

Fig. 1. Serum glibenclamide concentrations for Daonil ——X——; Glycomin -----≠-----; and Melix ——Θ——.

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The pharmacokinetic variables are reflected in Table I. The time to maximum concentration (T_{max}) and the maximum concentration (C_{max}) values were determined by inspection, whereas all the other pharmacokinetic variables were calculated by means of standard non-compartmental methods.

TABLE I. MEAN ± SD VALUES OF PHARMACOKINETIC VARIABLES

	Daonil	Glycomin	Melix
C_{max} (ng/ml)	156 ± 65	168 ± 61	112 ± 50
$T_{½}$ (h)	4,3 ± 1,5	4,2 ± 2,0	4,9 ± 1,2
T_{max} (h)	3,6 ± 1,4	4,1 ± 1,4	4,0 ± 2,1
AUC (0-12,5 h) (ng/h/ml)	779 ± 451	781 ± 388	560 ± 247
AUC (ng/h/ml)	937 ± 702	912 ± 490	690 ± 333
Cl-tot/f (ml/min)	112 ± 46	106 ± 33	139 ± 46
MT-vsys (h)	7,1 ± 1,9	7,3 ± 2,2	8,0 ± 1,8
V-sys/f (l)	47 ± 29	44 ± 16	64 ± 18

C_{max} = maximum concentration; T_{max} = time to maximum concentration; $T_{½}$ = terminal half-life; AUC (0 - 12,5 h) = area under the curve for the period 0 - 12,5 hours; AUC = total area under the curve; Cl-tot/f = relative total clearance; MT-vsys = total mean time; V-sys/f = relative volume of distribution in litres.

Symptoms associated with hypoglycaemia were observed in 12 subjects after medication with Daonil, in 11 after medication with Glycomin and in 4 after medication with Melix and were treated with additional intravenous glucose.

Statistical analysis

The variables C_{max} and AUC were subjected to an analysis of variance with subject, treatment and period as the main effects. Ninety-five per cent conventional confidence intervals were constructed for the ratio 'test reference' (expressed as a percentage) for each variable (Table II). The interpretation of the confidence interval for Glycomin/Daonil, for example, is that the true mean C_{max} of Glycomin lies (with 95% certainty) between 5% below and 21% above that of Daonil.

A frequency table is provided for values of T_{max} (Table III).

TABLE II. 95% CONFIDENCE INTERVALS FOR THE RATIOS (IN PERCENTAGE)

	Glycomin/ Daonil	Melix/ Daonil	Melix/ Glycomin
C_{max}	95 - 121	59 - 84*	54 - 78*
AUC	81 - 113	58 - 90*	59 - 92*

*Significant difference.

Discussion and conclusion

No serious side-effects were observed, although several of the volunteers experienced unpleasant symptoms owing to hypoglycaemia. It is imperative that if this method of glucose administration is used in studies of this nature, volunteers are closely monitored in order that hypoglycaemia is recognised and treated.

TABLE III. FREQUENCY FOR TIME TO MAXIMUM CONCENTRATION

Time interval (h)	Daonil	Glycomin	Melix
0,0 - 1,99	1	0	0
2,0 - 3,99	9	8	11
4,0 - 5,99	6	8	4
6,0 - 7,99	2	1	1
8,0 - 10,00	0	1	2
Total	18	18	18

Because differences of less than 20% are generally considered clinically irrelevant in bio-equivalence studies, it follows from our results that Glycomin may be considered bio-equivalent to Daonil. The probabilities that the true ratios with respect to C_{max} and AUC are within bio-equivalence ranges of 80 - 120% are very high at 0,95 and 0,98 respectively. However, the results in respect of the comparison between Melix and Daonil reveal that they cannot be considered bio-equivalent. The upper limits of confidence for the ratio Melix/Daonil are 84% and 90% for C_{max} and AUC. This means that, at its very best, the mean C_{max} and AUC of Melix are only 84% and 90% of that of Daonil but can also be as low as 59% and 58% respectively. The probability that the true ratios with respect to C_{max} and AUC are within the bio-equivalence range of 80 - 120% is very low at only 0,08 and 0,19 respectively. It is therefore clear that Melix cannot be considered bio-equivalent to Daonil with respect to the extent of absorption as measured by AUC. The fact that the two products also differed with respect to C_{max} is probably due to differences in the extent of absorption rather than the difference in the rate of absorption. In view of the differences in C_{max} and AUC values Melix can likewise not be considered bio-equivalent to Glycomin.

From a clinical point of view, it may therefore be stated that, according to the results of this study, Daonil and Glycomin may be expected to be equally efficacious in the management of diabetes mellitus, but that the same cannot be said of Melix.

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