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Comparison of the Pharmacokinetics of Glipizide and Glibenclamide in Man

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Summary. Four subjects received 5 mg ^{14}C-glipizide orally, 3 subjects 1 mg intravenously and 2 subjects 5 mg ^{14}C-glibenclamide orally. Plasma levels of radioactivity, and urinary and faecal excretion were measured. For both drugs the disappearance of radioactivity from plasma followed complex kinetics and the apparent half-lives increased steadily with time. The two sulfonylureas were extensively metabolized and were excreted in the urine as hydroxylated or conjugated metabolites. The effects of both drugs on blood glucose and immunoreactive insulin were comparable. The findings are compared with other published results.

Key words: Diabetes mellitus, sulfonylurea, glipizide, glibenclamide, pharmacokinetics, excretion

The pharmacokinetics of glibenclamide and glipizide, two potent "second generation" hypoglycaemic sulfonylureas, have been extensively studied during recent years (1-9). Their gastro-intestinal absorption, plasma half-life, volume of distribution etc. are compared in Tables 1 and 2. Although the majority of authors have agreed about the way in which the two compounds are metabolized, in general their calculated pharmacokinetic parameters have differed greatly. Therefore, it seemed appropriate to reconsider the interpretation of their data, including results obtained in the authors' laboratory, and to compare their pharmacokinetics with the pharmacological responses to both drugs.

Methods

Nine adult men and women were studied, who were hospitalized for various disorders; none had liver disease, renal insufficiency or a disturbance of carbohydrate metabolism. They gave informed consent to the studies.

The pharmacokinetics of glipizide was studied after oral administration of one tablet containing 5 mg ^{14}C-glipizide (specific activity 69 µCi/mg) to 4 subjects, or intravenous injection of 1 mg ^{14}C-glipizide (23 µCi/mg) in 3 patients. The behaviour of glibenclamide was studied in two subjects after oral administration of one tablet containing 5 mg ^{14}C-glibenclamide (8.7 µCi/mg).

The sulfonylureas were administered at 7.30 am, after 12 hours of fasting and bed rest. The patients continued to fast in bed until noon, when they received a normal meal. In the oral dose experiments, 1 mg glucagon was injected intravenously three hours after the administration of the drug in order to limit the hypoglycaemic response. Blood samples were collected between 0 and 48 hours, at the times indicated in Fig.1. All urines and faeces were collected for 4 days.

Glucose was determined by a modification of the o-toluidine method (10). Immunoreactive insulin was assayed by a modification of the double antibody method (11).

Total radioactivity was measured by counting 0.2 and 0.5 ml plasma in 10 ml Instagel (Packard), using a liquid scintillation counter *TRI CARB 3000* (Packard). Correction for quenching was made by a combination of internal (^{14}C-toluene) and external (channel ratio) standardisation.

Metabolites of glipizide and glibenclamide were determined by a combination of extraction and chromatographic methods (6, 9). The pH of the plasma samples was adjusted to 4.3 with acetate buffer, the solution extracted 4 times with 5 volumes methylene chloride, the organic phase separated by centrifugation and the solvent evaporated to dryness in a Rotavapor-EL (Buchi). The residue was taken up in methanol and the volume of the solution reduced under nitrogen prior to chromatography. The radioactivity of the aqueous phase was measured. It represented the unextractable metabolites of glipizide.

For thin-layer chromatography of methylene chloride extracts, silica gel was spread in 300 µ thick-layers using Desaga's manual apparatus. The plates were air dried and activated for 15 min at 120°C before application of the plasma extracts. Six solvent systems were used, but system C (6)

was found most satisfactory (benzene : glacial acetic acid : ethyl acetate : acetone 65:6:12:30). The radioactivity of the different fractions was measured by counting 5 mm wide bands scraped into 10 ml Bray's medium.

Paper chromatography of plasma extracts was also performed on Whatman No. 1 paper with a basic solvent system (butylacetate : isopropanol : H_2O: NH_3 in proportions of 30:50:15:5). The radioactivity of the peaks was measured by cutting 5 mm wide bands and counting in Bray's medium.

The separation methods permitted three constituents of *Total Radioactivity* to be distinguished: 1) non-metabolized *Sulfonylurea*, 2) metabolites *Extractable* by methylene chloride, and 3) *Unextractable* metabolites.

Total radioactivity in urine was measured in 0.5 and 1.0 ml samples. Correction for quenching was made by internal standardisation of all samples. Prior to extraction the urine was concentrated, if necessary, by adsorption on a column of XAD-2 resin and elution with methanol. The eluate was evaporated to dryness under reduced pressure. The residue was taken up in acetate buffer and extracted as described for plasma. The Unextractable radioactivity in all samples was measured using unconcentrated urine.

Total radioactivity of homogenized and lyophilized samples of faeces was determined after combustion in a sample Oxidizer (Packard).

Results

Plasma Levels

Maximal plasma concentrations of total glipizide radioactivity (380-560 ng/ml) were reached between 1.5 and 6 hours after oral administration. Gastrointestinal absorption was rapid in two subjects and was delayed in two others. For glibenclamide, maximal plasma concentrations (170-360 ng/ml) were observed at 3 hours.

The plasma concentration curves obtained after oral administration of both drugs showed a pronounced "nose effect" during the first hours, as can be seen in Fig.1, which illustrates typical examples presented on a semi-logarithmic scale. The "nose effect" is defined as a steep rise and fall of plasma concentration before and immediately after the peak value has been reached. Then the slope of the plasma concentration curve decreases gradually until a constant value is eventually reached, which is determined by the elimination processes.

The experimental data about total plasma radioactivity after oral and intravenous administration of the drugs could not be fitted to available computer programs designed for one or two compartment models (12). It is possible that the curves obtained after intravenous administration of glipizide could be resolved according to a three

Table 1. Absorption and blood levels after oral administration of glibenclamide (HB) or glipizide (K)

Reference		Dose	N	Lag time (hrs)	Absorption t 1/2	%	Max. levels ng/ml blood = b plasma = p	Time at max. levels hrs	Plasma concentrations at 24 h in % of max.	at 48 h in % of max. levels
Schmidt	(1)	5 mg HB-A	10	x	x	x	b 18 - 88	4 - 8	9.1	x
		10 mg HB-A	10	x	x	x	b 75 - 190	4 - 8	14.6	9.7
		5 mg HB-B	6	x	x	x	b 76 - 140	2 - 6	3.2	1.4
Rupp	(2)	5 mg HB	6	x	2^+	43^+	b 44 ± 7.1	2 - 4	x	x
Anderson	(3)	5 mg HB	4	x	x	x	x	2 - 6	x	x
Rupp	(4)	5 mg HB	6	x	x	84±9	p220 ± 94	2^+	4.5	x
Fucella	(5)	5 mg HB	2	0.5-1	x	~100	p~230$^+$	2 -2.5	x	x
Present results		5 mg HB	2	x	x	60-80	p170-360	3	5.5	2.1
Ambrogi	(6)	5 mg K	2	0.4-1	0.3-0.4	high	p~480$^+$	1.5-2	x	x
Taylor	(7)	5 mg K	10	x	0.5-1	x	p 800±100	1 - 3	x	x
Fucella	(5)	5 mg K	2	0.3-0.5	x	~100	p 550$^+$	0.7-1	x	x
Schmidt	(8)	5 mg K	6	x	x	~100	p 390-610	1 - 3	2.2	0.3
Present results		5 mg K	4	0-3	x	~100	p 380-560	1.5-6	2.5	0.2

Explanation of symbols: x : not published or not calculated
~ : approximate
b : blood levels (usually half of plasma levels)
$^+$: mean value
± : mean ± standard deviation
p : plasma levels
HB-A : glibenclamide preparation with a specific surface of 0.88 m^2/g
HB-B : glibenclamide preparation with a specific surface of 1,5 m^2/g

Table 2. Disappearance of glibenclamide (HB) and glipizide (K)

	Dose and route of administration	N	Vd (1)	t 1/2 fast hrs	t 1/2 slow hrs	% Excretion in urine 24 h	% Excretion in urine total	% Excretion in faeces total
Schmidt (1)	5 mg HB-A p.o.	10	-	-	-	25.5	27.6	-
	10 mg HB-A p.o.	10	-	-	-	17.6	24.9	-
	5 mg HB-B p.o.	6	-	-	-	40.1	42.7	-
Rupp (2)	1 mg HB i.v.	4	40	0.38	0.6	~53	54 ± 10	45 ± 9
	5 mg HB p.o.	6	41	5.0		21	23 ± 3	72 ± 4
Anderson (3)	5-10 mg HB p.o.	4	-	-	-	33.4	38	~50
Schultz (21)	1.13 mg HB i.v.	5	20.9	-	-	-	53	-
Rupp (4)	5 mg HB p.o.	6		2.1±0.7	10±2		50 ± 6	51 ± 7
Fucella (5)	5 mg HB p.o.	2	10.3	5.7		45.5	49	47.3
Present results	5 mg HB p.o.	2		1.9 to	16.0	28	35	42
Ambrogi (6)	5 mg K p.o.	2	5	2		82.7	83.7	15.0
Taylor (7)	5 mg K p.o.	10	-	2.7 ± 0.5		-	-	-
Fucella (5)	5 mg K p.o.	2	6.7	3.6		86.9	88.4	11.5
Schmidt (8)	1 mg K i.v.	3	11.1	0.6	3.6	62.6	64.8	-
	5 mg K p.o.	6	-	-	-	63.6	65.4	-
Present results	1 mg K i.v.	3	~20	0.6	3.7	66.7	68.3	~5.0
	5 mg K p.o.	4	-	2.6 to 7.0		65.8	67.9	~15.0

The values represent the means of available data

Explanation of symbols : - : not published or not calculated
± : mean ± standard deviation
~ : approximate value
Vd : volume of distribution
t 1/2 : plasma "apparent half-life" of elimination

HB-A : glibenclamide preparation with a specific surface of 0.88 m^2/g
HB-B : glibenclamide preparation with a specific surface of 1,5 m^2/g

compartment model. However, the smaller amount of radioactivity administered did not permit precise calculation of the slow half-life and the volume of the third "deep" compartment. As a consequence, it was not possible to deduce the parameters of the two other compartments. In the case of oral administration, the three compartment models did not lead to interpretable results.

Nevertheless, in order to be able to compare the present data with results reported by others, an attempt was made to determine graphically the disappearance rates from plasma of total radioactivity. For glipizide and glibenclamide given by mouth, the "apparent half-life" of total radioactivity in plasma increased with time, as shown in Table 3, an effect already noted after intravenous glipizide. The importance of this phenomenon is discussed below.

Glipizide and glibenclamide are extensively metabolized, mainly by hydroxylation of the cyclohexyl moiety of the molecule (2, 4, 6, 13). For glipizide a typical distribution of the different components of total radioactivity in plasma is shown in Fig.2. Up to 12 hours after oral adminis-

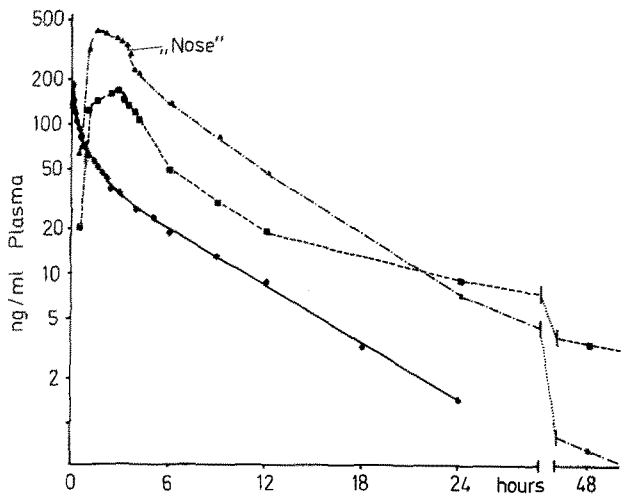

Fig.1. Plasma levels of total radioactivity after oral administration of 5 mg glipizide (-·-·-), 5 mg glibenclamide (------) or intravenous administration of 1 mg glipizide (———)

Table 3. "Apparent half-life" (in hrs) of total radioactivity at different times after administration of 5 mg glipizide p.o. (+), 1 mg glipizide i.v. (x) and 5 mg glibenclamide p.o. (')

Subject	Time interval 3-6	6-9	9-12	12-18	18-24	24-48
J.H.+	2.2	4.0	4.0	4.6		6.5
Cl.B.+	3.0	3.0	3.0	3.8		-
F.Z.+	-	3.5		3.5		8.5
M.A.+	-	3.1	4.1	4.5		6.0
Mean+	2.6	3.4	3.7	4.1		7.0
A.B.x	3.6	4.8	4.8	4.8		-
E.B.x	3.8	3.8	3.8	3.8	-	-
J.P.x	1.7	2.3	2.3	5.5	-	-
Meanx	3.0	3.6	3.6	4.7		
L.A.'	2.0	5.5	5.5	13.5		16.3
C.B.'	1.8	4.0	4.0	11.5		15.7
Mean'	1.9	4.8	4.8	12.5		16.0

tration the proportion of unchanged glipizide in plasma was about 85% of total radioactivity and with increasing time this value decreased slightly. At 12 hours the extractable metabolites amounted to about 13% of total activity. They chiefly represented metabolites with a similar chromatography behaviour as the cyclohexyl-hydroxylated derivatives of glipizide. The more hydrophilic unextractable metabolites were shown by enzymatic digestion most probably to be glucuronides and sulfate derivatives of glipizide; at 12 hours, they amounted to about 5% of the total activity.

For glibenclamide a precise separation of the three groups in the plasma was not feasible, due to the lower specific activity of the administered compound. However, the main chromatographic peak corresponded to unchanged glibenclamide and it could be separated from other constituents, probably the cyclohexyl-hydroxylated metabolites of glibenclamide.

Insulin Stimulation and Hypoglycaemic Effect

Table 4 shows the plasma levels of glucose and immunoreactive insulin (IRI) after oral administration of 5 mg glipizide or glibenclamide. Maximal plasma IRI levels were reached, 60 and 90 min after dosing, respectively 18 and 36 µU/ml for glipizide, and 8 and 50 µU/ml for glibenclamide. The lowest glucose levels occured at the same time or 30 minutes after the IRI peak. Blood sugar fell to 44 and 43% of pretreatment values after glipizide and to 69 and 39% after glibenclamide.

In the 2 patients who received glipizide, the IRI peak was observed 30 minutes before the maximal plasma level of sulfonylurea. The delay was longer after glibenclamide; it was 90 and 120 minutes, respectively. In the 4 subjects there was, therefore, a period during which IRI and glucose levels were returning to normal, while the sulfonylurea levels was still increasing.

The injection of 1 mg of glucagon was quickly followed by a rise of the blood sugar and the IRI level. This effect was similar in patients treated either with glipizide or glibenclamide.

Urinary Excretion

The urinary excretion of glipizide and glibenclamide occurred almost exclusively in the form of metabolites. Most of the radioactivity was excreted during the first 24 hours (Table 5). For glipizide the route of administration had no influence on the amount excreted in the urine, since 68.3 or 67.9% of the administered dose was found in the urine 4 days after oral or intravenous administration. After glibenclamide only 35% of the administered dose was recovered from urine

The distribution of the glipizide metabolites in the urines was similar in all subjects and was independent of the route of administration. Extraction of the urines with methylene chloride showed that the proportion of unextractable, i.e. hydrophilic metabolites was about 15% in the first portion (0-6 hours) and that it increased with time, reaching 40% between 24 and 48 hours. Chromatography of the extractable portion of the radioactivity showed that the main peak represented metabolites with the same Rf values as the 4-trans

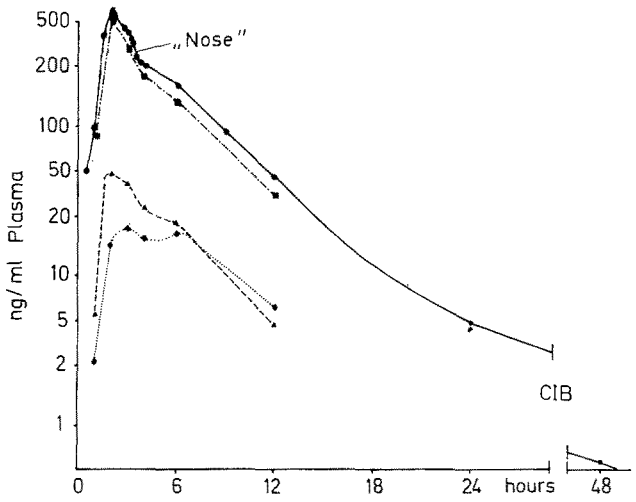

Fig.2. Plasma concentrations of glipizide and its metabolites (expressed in ng per ml) in 1 control subject following oral administration of a tablet, containing 5 mg of ^{14}C-glipizide. Total radioactivity (———), extractable glipizide (-·-·-·), extractable metabolites (- - - - -), unextractable metabolites (.....)

Table 4. Plasma glucose (G : mg %) and immunoreactive insulin (IRI : μU/ml) levels after oral administration of 5 mg glipizide or glibenclamide (time in minutes)

		0	30	60	90	120	165	180 1 mg glucagon i.v.	185	210	240
J.H.		89	86	69	38[a]	42	61	66	78	119	111
GLIPI.	IRI	2	5	18[b]	10+	8	2	4	34	20	14
Cl.B.	G	79	79	68	36[a]	39	73	73	94	123	71
GLIPI.	IRI	15	16	19	36[b]	17+	24	26	127	87	20
L.A.	G	95	93	80	56a	64	60	66	82	137	108
GLIBEN.	IRI	1	1	5	8[b]	2	1	10	20+	14	8
C.B.	G	100	92	80	61	39[a]	53	56	75	97	83
GLIBEN.	IRI	24	24	37	50[b]	39	29	23+	61	44	29

The two patients with slow absorption of glipizide are not shown on this table since the i.v. glucagon administration interfered with measurement of the hypoglycaemic action of the drug.

+Time of maximum sulfonylurea level

a - Minimal plasma glucose level

b - Maximal plasma IRI level

and the 3-cis-hydroxylated derivatives of glipizide. The amount of unchanged glipizide was small and was measurable only in the first urine specimens. It represented about 3 to 15% of the extractable radioactivity from 0 to 6 hours after oral administration. After intravenous administration this proportion reached about 30%, but glipizide became undetectable in the later collections.

Almost no unmetabolized glibenclamide could be found in the urine. The proportion of unextractable metabolites increased with time from about 7% in the first urine samples, to 30% in the 24 to 48 hours sample. Chromatography of the extractable radioactivity in the first urine samples showed that a metabolite (probably the 4-trans-hydroxy-derivative of glibenclamide) was the main constituent. In later samples there was a larger proportion of the 3-cis-hydroxy-derivative, as well as an unidentified metabolite.

Table 5. Urinary and faecal excretion after oral administration of 5 mg glipizide or glibenclamide or intravenous injection of 1 mg glipizide (the results are given in % of the administered dose)

Subject and administered dose	Urine 24 h	Urine total	Faeces total	Urine and faeces
A.B. 1 mg glipizide i.v.	59.2	61.3	3.4	64.7
J.P.	74.3	74.5	6.8	81.3
J.H. 5 mg glipizide p.o.	59.7	61.6	9.5	71.1
Cl.B.	68.5	69.8	16.5	86.3
F.Z.	71.0	72.5	18.2	90.7
M.A.	64.0	71.7	-	-
L.A. 5 mg glibenclamide p.o.	31.1	35.8	42.6	78.4
C.B.	29.6	33.8	46.2	80.0

Faecal Elimination

The results of faecal analysis are shown in Table 5. After oral administration a higher proportion of radioactivity from glibenclamide was found in the faeces than after glipizide.

Discussion

Absorption of the Drugs

As discussed elsewhere (9), the similarity between the amount of glipizide excreted in urine after oral or intravenous administration, together with the close similarity of urinary metabolite patterns after the two routes of administration, strongly support the hypothesis that the absorption of glipizide is almost complete.

For glibenclamide no direct comparison was possible, since intravenous administration of the drug was not studied. However, by comparison with data on urinary excretion in the literature (Table 2), it may be concluded that the gastro-intestinal absorption of glibenclamide in the present experiments amounted from 60 to 80% of the administered dose. This could partly explain the significantly larger amount of radioactivity found in faeces after oral administration of this compound than glipizide.

Dosage Form of the Drugs

As was clearly shown for glibenclamide by Schmidt *et al.* (1) that the dosage form of the material administered orally is of considerable importance. Gastro-intestinal absorption of a preparation with a specific surface of 0.88 m^2/g (HB-A) was slower than the same material with a specific surface of 1.5 m^2/g (HB-B): see Table 1. The mean maximal blood level after oral administration of the same dose was 46.1 ng/ml at 4 to 8 hours for preparation HB-A, as compared to 95 ng/ml between 2 and 6 hours for preparation HB-B. The mean urinary excretion for HB-A was only 27.6% of the dose, whereas it amounted to 42.7% for HB-B; this too might be an indication of less complete absorption of preparation HB-A.

Rupp *et al.* (2) found that 43% of glibenclamide was absorbed from gelatine capsules. Later the same authors (4) found 90% absorption of the marketed dosage form (tablet).

Half-lives

One of the aims of pharmacokinetics is to predict the optimum dosage regimen for long term therapy. Theoretically, the rate constants of absorption,

distribution and elimination, which are needed for this type of prediction, can be determined after a single dose, and representative curves of amounts and concentrations in the various compartments can be calculated to predict the effect of repeated doses at any given interval (14).

In this respect, the fact that the "apparent half-life" of total radioactivity increased with time for both drugs (Table 3) was of great importance. As shown by Garrett (15), prolongation of the apparent half-life with time after administration of a drug may indicate the presence of a slowly equilibrating "deep" compartment. If the same dose were administered repeatedly, the possibility of accumulation of large amounts of drug in the "deep" compartment and its slow release from this compartment would be manifested as an increase in the apparent half-life of the drug after each dose until equilibrium had been reached. This phenomenon has been observed by Doluisio (16) and by Fabre *et al.*(17) for tetracyclines.

In the case of drugs that show this type of elimination process, it can be demonstrated that it is the longest half-life which is the most important for cumulative behaviour. With increasing numbers of doses, the longest half-life moves steadily towards higher blood concentrations.

In the case of glipizide and glibenclamide the determination of half-lives appears even more complicated since it is necessary to distinguish between at least two possible causes of the increase with time of the apparent half-life after administration of a single dose. First, in the hours following oral administration, the "nose effect" indicates that distribution in the superficial compartment was slower than absorption, and secondly, the more slowly increasing "apparent half-life" after the first phase could be an indication of equilibration with a "deep" compartment. However, the data do not reveal whether or not the latter phenomenon was the consequence of a change with time in the rate of metabolism of the drugs, or of altered clearance of their metabolites.

The half-life of glipizide has been calculated by one group of workers according to a one compartment model from plasma levels measured up to 12 hours after oral administration; the value was about 2 hours (6). Values as low as one hour may be obtained if the "apparent half-life" is calculated in the region of the steepest slope, immediately after the maximum level. Half-lives may be significantly underestimated if kinetics are interpreted in terms of a model system containing fewer compartments than are actually present (18). "Short-early" and "long-late" half-lives of the total plasma radioactivity have been estimated by others after oral administration of glibenclamide. The "short-early" half-life was reported to be 2.1 hours (4). These authors suggested that only the "short-early" half-life was of pharmacokinetic significance since 24 hours after administration of a single dose the amount of radioactivity remaining in the blood amounted only to 2% of the maximal plasma levels. We consider this a misconception, because underestimation of the half-life due to calculations based only on values obtained immediately after the peak plasma concentration of a drug may result in wrong predictions about drug accumulation after multiple doses (18).

Urinary Excretion

The distribution of glipizide, glibenclamide and their metabolites in the plasma and the urine indicated that the metabolites were rapidly excreted through the kidneys as well as in bile.

A tentative determination was made of the renal clearance of glipizide and its metabolites. The calculation was based on the distribution patterns of the radioactivity in plasma and urine after oral administration of the drug, but no correction was made for protein binding. For the extractable metabolites the results were in good agreement for all the subjects and indicated a renal clearance of about 200 ml/min. The calculation was hazardous for the unextractable metabolites owing to their very low concentration in plasma. It is only possible to give a very approximate value being higher than 300 ml/min. The apparent renal clearance of unchanged glipizide was low, which was in agreement with the relatively small amount of unchanged drug found in the urine.

As the metabolites of glibenclamide and the unchanged drug in plasma were not separated completely, their renal clearances could not be calculated. However, the results did show good agreement with the data of Rupp *et al.*(2) who showed that at 8 hours unchanged glibenclamide amounted to 73% of total radioactivity in plasma. Thus, the renal clearance of the principal hydroxylated metabolite (4-trans) was about 100 ml/min (2). The relatively high clearance of this compound was confirmed recently by Schmidt *et al.* (19).

These findings, as well as the fact that the disappearance rate from plasma of unchanged glipizide and glibenclamide was only slightly increased in patients with renal insufficiency (9, 20) tend to confirm the hypothesis that both these sulfonylureas are metabolized by the liver, and that the kidneys play only a minor role in their biotransformation and elimination from plasma.

Pharmacological Responses

The insulinogenic and hypoglycaemic responses to glipizide and glibenclamide were similar, even though the plasma levels of glipizide were almost twice as high for the same dose. The nadir of the blood sugar level occurred before the maximal plasma levels of the sulfonylureas. Then, by an effect of counter-regulation, the blood sugars returned towards their initial values, even though the sulfonylurea levels were still rising. The same effect were found for IRI, which returned to pretreatment values after its peak, despite maximal or continued high plasma levels of the sulfonylureas. These observations show clearly that the effects of sulfonylureas may differ markedly according to the metabolic status of the subject.

Conclusion

The present data provides evidence that the close chemical similarity of glibenclamide and glipizide is reflected in their closely related pharmacokinetic behaviour. It is apparent that only critical examination of pharmacokinetic data can ensure that the clinician will receive appropriate information about a new drug. This is true, however, only if the dosage form of the drug used for the commercial preparation remains as close as possible to that employed in the pharmacokinetic studies.

In complicated situations it may be difficult to give a precise prediction of the consequences of multiple dosage regimens from data obtained by a single oral dose. It would be very useful, therefore, to undertake prolonged experimentation with the commercially available dosage form of the drug.

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