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Clinical Experience with Glipizide in the Treatment of Mostly Complicated Diabetes

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Summary. Thirty-five diabetic patients (mean age 60) underwent regularly controlled treatment for an average of 7 months with 2½ to 20 mg of glipizide daily, the mean dose being almost 10 mg/daily. These patients had been diabetics for an average of 9 years, most had been previously treated with other sulphonamides, one third were obese and 90% had degenerative complications and/or an associated disease. Results showed a 23% mean decrease in mean blood sugar levels and a 21% decrease in maximal blood sugar levels during the day. There was an increase in the number of well or very well controlled patients and a decrease of non-satisfactory results. Renal, hepatic and haematologic monitoring reveared no abnormalities. Minor hypoglycaemic manifestations were not uncommon. Two severe hypoglycaemic attacks occurred in older patients with renal insufficiency associated with hepatic dysfunction. Glipizide is contra-indicated when kidney function is reduced by more than ¾ and additional caution seems to be necessary in the event of associated hepatic damage. The drug appears to enhance the antiprothrombin action of anticoagulants.

Key words: Anticoagulants, clinical use of sulfonylureas in diabetes, maturity onset diabetes, glipizide, hypoglycaemia, hypoglycaemic sulphonamides, oral antidiabetic substances, renal insufficiency, sulfonylureas, transaminases, triglycerides.

Among the numerous aminoethylphenylsulfonylureas synthesized in Italy by Ambrogi *et al.* [1, 2], N-(4-(B-(5-methylpyrazine-2-carboxamido)-ethyl)-benzenesulfonyl)-N'-cyclohexylurea (approved name, glipizide) has been shown to possess extremely potent hypoglycaemic properties. These properties have been the object of precise pharmacological research [3] in the Department of Pharmacology at the Carlo Erba Therapeutic Research Institute in Milan. These studies showed that glipizide exerts an antagonist action on hyperglycaemia following glucose loading, lowers the blood sugar level in healthy animals and increases insulinaemia by sensitizing pancreatic beta-cells to the physiological glucose stimulus. The dose necessary is more than one hundred times lower than that of other sulphonylureas studied comparatively (tolbutamide and glycyclamide).

The chemical structure of glipizide is close to that of glibenclamide. Its potent action, which makes it an antidiabetic sulphonamide of the "second generation", as well as the characteristics of its action [14] and its lack of toxicity have inspired its trial in clinical medicine. The first results of such trials were reported by Pedrazzi *et al.* [19], Parodi [18] and Greco *et al.* [8].

These trials, which involved a total of 134 patients, confirmed the potent therapeutic action of glipizide, which was equivalent and sometimes superior to that of glibenclamide in maturity onset diabetes in daily doses of 5 to 20 mg administered for periods up to a year and a half [18]. Good toleration of the drug was also confirmed. For the past year, we have been able to try this new antidiabetic in 35 patients, either in hospital or as out-patients, who were followed for an average of 7 months.

Patient Population

Clinical data concerning the 35 non-insulin dependent diabetic patients are summarized in Table 1.

Only seven patients had been diabetic for less than 5 years; 13 had had diabetes for more than 10 years.

Only four patients were free of any associated disorder or degenerative complications. The fact that these cases of diabetes were relatively longstanding accounts for the fairly high incidence of degenerative complications.

It should be pointed out that this population of mainly elderly and long standing diabetic patients was a high risk group for the use of a high potency oral hypoglycaemic agent; the use of such agents could conceivably be hazardous in severe cases of this type.

Thirty-three of the thirty-five patients had been previously treated; fo ronly two patients was glipizide the first antidiabetic treatment undertaken. In two cases only, previous treatment was with insulin, which was later discontinued; in the other cases it was one or two oral antidiabetics, a sulphonamide alone in 13 cases (glybutamide 1, chlorpropamide 2, glycodiazine 3, glibenclamide 1, glisoxepide 7), a combination of one of these sulphonamides with a biguanide in 15 cases (usually phenformin) and a biguanide alone in 2 cases.

Management and Supervision of Treatment

Treatment with glipizide was begun in 35 patients, of whom 28 were out-patients at the beginning

of therapy. These patients were periodically assessed at intervals of 1 to 2 months. Each time the following parameters of therapeutic efficacy were measured in addition to weight and any possible manifestations of hypoglycaemia or intolerance: blood sugar level after breakfast, before and 2 h after the midday meal, before and 1½ or 2 h after the evening meal and sometimes at midnight (titration by the Auto-Analyzer method with reduction of ferricyanide); twenty-four hour glycosuria; acetonuria; cholesterolaemia (Auto-Analyzer method, Pearson); lipidaemia (nephelometric method using dextran sulfate in the Auto-Analyzer); blood triglyceride levels (auto-analyzer fluorimetric method). In addition possible toxic effects were monitored by measuring proteinuria; urine cytology; blood urea (diacetylmonoxime method); blood uric acid levels (phosphotungstic reagent, Auto-Analyzer method); glutamic oxalacetic and glutamic pyruvic transaminases (U.V. absorption method); alkaline phosphatases (Bodanski's method); fibrinogen (ponderal method); red blood count, platelet and white cell counts including differential count.

Throughout the entire duration of treatment, the diet which had been adapted to the patient's usual requirements and to his weight and usually contained 180 g of carbohydrates daily, was not changed, but it should be noted that this diet was not always strictly followed by patients at home.

In all cases where the patient was on a biguanide before the beginning of treatment with glipizide, the former was maintained at the same dose during the trial so as to enable a valid comparison with the sulphonamide previously used. In only one case, a biguanide had to be added to glipizide during the 6th month of treatment because of insufficient control by the latter drug.

Dosage changes of glipizide were cautious and gradual, in view of the proven potency of its hypoglycaemic action. As a general rule, treatment was begun with one tablet containing 5 mg of glipizide as a replacement for 4 mg of glibenclamide, or 7½ mg of glisoxepide, or 750 mg of glycodiazine, or 500 mg of chlorpropamide, or 1000 mg of glybutamide.

This initial quantity, which was administered in one or two doses, depending on the case, was then adjusted, according to the results obtained, or maintained unchanged, or gradually increased. From the first to the eighth month of treatment, mean doses successively worked out at 5.90 mg, 6.16 mg, 7.05 mg, 8.6 mg, 8.75 mg, 9.15 mg, 9.40 mg and 9.60 mg daily. In some cases the daily dose was kept down to as little as 2½ mg while in others it had to be increased to 20 mg daily (in two cases and only after 3 months of treatment). Duration of treatment varied from 15 days to 10 months with a mean of 7 months; duration exceeded 6 months in 27 cases.

Table 1. *Clinical data of the treated patients*

Male 29 / Female 6	35 patients	
Age 34—82 years, mean age 60 years		
Family history of diabetes	30%	
Obesity (> due body weight +10%)	30%	
Diabetes known and/or treated since	9 years on average	
Associated pathological conditions:	gout	7
	chronic alcoholism	3
	liver cirrhosis	2
	active chronic hepatitis	each 1
	biliary lithiasis	each 1
	haemochromatosis	each 1
	asthma	each 1
	chronic pancreatitis	each 1
	rheumatoid arthritis	each 1
	chronic lymphoid leukemia	each 1
Degenerative complications of diabetes:	arteritis of the lower limbs.	16
	peripheral neuropathy	11
	coronary artery disease	11
	diabetic retinitis	11
	cataracts	3
	urinary infection	8
	renal insufficiency	8
	lung/skin infections	5

Results

1. Carbohydrate Metabolism

1a) Daily glycosuria cannot be considered representative of correct equilibrium of treated diabetes and of its course, especially in these relatively aged patients who have been diabetics for a considerable time.

1b) *No lasting acetonuria* and no drop in alkaline reserve occurred.

1c) Blood sugar levels were used to assess therapeutic activity. The mean blood sugar level on the day before glipizide therapy was begun, was 163 mg/100 ml and the maximum blood sugar level averaged 211 mg/100 ml (Fig. 1). If we consider the following as criteria for correctly balanced diabetes

very good	mean blood sugar level	≤120 mg/100 ml
	maximum blood sugar level	≤160 mg/100 ml
good	mean blood sugar level	≤140 mg/100 ml
	maximum blood sugar level	≤180 mg/100 ml
fairly good	mean blood sugar level	≤160 mg/100 ml
	maximum blood sugar level	≤200 mg/100 ml
poor	mean blood sugar level	>160 mg/100 ml
	maximum blood sugar level	>200 mg/100 ml

our patients could be divided up into the following categories prior to glipizide therapy

4 very good	= 11%	43%
11 good	= 32%	
6 fairly good	= 17%	
14 poor	= 40%	

On glipizide, the course of mean and maximal blood sugar levels showed gradual improvement during the first five months of treatment with an average drop in mean blood sugar level from 163 to 126 mg/100 ml (−23%) and in maximal blood sugar level from 211 to 167 mg/100 ml (−21%) (Fig. 1). The quality of the diabetic control thus obtained with glipizide was also improved (Table 2), with an increase of very good results from 11 to 46%, and an increase of very good and good results from 43 to 54%. The percentage of poor results dropped from 40 to 16% during the second trimester of treatment.

Between the 6th and the 8th months of treatment, results obtained with glipizide were not as good (mean blood sugar levels rose from 126 to 152 mg/100 ml and maximal blood sugar levels from 167 to 200 mg/100 ml on average, while the percentage of very good diabetic control dropped from 46 to 31% and that of poor results rose from 16 to 30%). However, this course was due to seven patients in whom dosage had to be increased to overcome this partial and transient "escape" from the action of the sulphonamide, which could possibly be due to less rigid dietary adherence as the trial progressed.

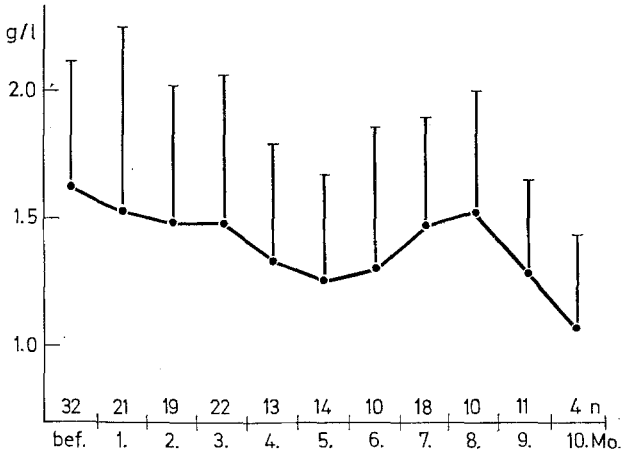

Fig. 1. Course of mean and maximal blood sugar levels during treatment of thirty-five diabetic patients with glipizide (n = number of patients controlled every month)

After the 8th month, following this dosage "readjustment", results were once again better, although admittedly in a smaller number of patients. Mean blood sugar levels dropped from 152 to 129 at the 9th month and to 107 mg/100 ml at the 10th month and maximal blood sugar levels dropped from 200 to 165 and to 144 mg/100 ml on average.

Comparison of glipizide with the sulphonamide previously used showed that patients on glipizide felt better in 11 cases, the same in 19 cases and only one patient felt worse.

In the course of treatment, patient's weights showed no appreciable sustained variation. There was a slight increase in half the cases, weight was stable in 25% of cases and decreased slightly in 25% of cases. Mean weight was 70.0 kg at the beginning of treatment, and 70.6 kg at the end of treatment with glipizide.

Comparison of glipizide's activity with that of the sulphonamides for which it was substituted showed that 5 mg of glipizide were approximately equivalent to 4 mg of glibenclamide or to 9 or 10 mg of glisoxepide. The number of patients previously treated with glycodiazine, chlorpropamide or glybutamide was too small to enable determination of precise weight-activity correlations.

Glipizide may thus be considered an antidiabetic sulphonamide of certain and sustained clinical efficacy, which is capable of markedly improving the therapeutic results previously obtained with other sulphonamides.

2. Lipid Metabolism

Glipizide did not exert any appreciable effect on lipid metabolism, which indirectly reflects diabetic equilibrium. It should be borne in mind, however, that in the immense majority of cases sulphonamide or mixed therapy had been previously administered and could have corrected any major disturbances of lipid metabolism.

2a) *Cholesterolaemia,* which was initially between 165 and 340 mg/100 ml (mean value 227 mg/100 ml), underwent non-homogeneous variations around the mean level calculated under treatment (129 observations) at 235 mg/100 ml.

2b) In the same way, *lipidaemia,* the mean value of which was initially 738 mg/100 ml, showed small and non-homogeneous variations around the mean value during treatment with glipizide, calculated at 714 mg/100 ml (128 observations).

Table 2. *Comparative therapeutic results obtained with other sulfonamides and with glipizide during the first three months and during the second and third trimesters of treatment in 35 controlled patients*

Results	Before glipizide	Months of treatment with glipizide									
		1st		2d		3d		4th–6th		7th–10th	
very good	11%	24%	33%	20%	55%	27%	46%	46%	55%	33%	53%
good	32%	9%		35%		19%		9%		20%	
fair	17%	18%		11%		16%		29%		17%	
poor	40%	49%		34%		38%		16%		30%	

Table 3. *Lipid levels during glipizide treatment*

Blood levels	Before glipizide			During glipizide treatment		
	extreme values	mean value	number of determinations	extreme values	mean value	number of determinations
Cholesterol mg/100 ml	165– 340	227	31	155– 330	235	129
Lipids mg/100 ml	500–1360	738	28	380–1200	714	128
Triglycerides mg/100 ml	60– 350	121	18	50– 285	89	107

2c) On the other hand, blood *triglycerides,* which were initially between 60 and 350 mg/100 ml (mean 121) exhibited a marked tendency to decrease and oscillated around the mean value of 89 mg/100 ml (107 observations) during treatment. This difference of 32 mg/100 ml is, however, not statistically significant ($p > 0.05$).

3. Incidents and Accidents of Treatment

3a) *Minor hypoglycaemic manifestations* were observed in 9 patients (26%) in spite of the care taken with the dose administered. It has to be noted, however, that these slight symptoms were most probably associated with the low caloric content of the usual French breakfast. This interpretation is supported by the fact that these manifestations were usually overcome by administering the drug in two doses or by increasing the carbohydrate content of the previous meal at the expense of the two others. In most cases they were observed during the first month of treatment and were expressed in the form of hunger and weakness with no other major symptoms of hypoglycaemia. These symptoms occurred around 11 o'clock in the morning after a dose of 2½ mg (2 cases) or 5 mg (5 cases) of glipizide at breakfast, or around 4 o'clock in the afternoon after absorption of 10 mg at midday (1 case). Proof of the hypoglycaemic nature of these symptoms was rarely obtained through the determinations performed. However, there is no doubt as to its authenticity. In only one case, these symptoms were of late onset, occurring during the 6th month of treatment after an increase in dosage. None of the patients who exhibited such manifestations had functional renal insufficiency. The same is not true for major attacks.

3b) *A major hypoglycaemic attack* made discontinuation of therapy obligatory after two and a half months of treatment with 10 mg daily in a 65 year old patient who had had diabetes for 23 years and whose renal insufficiency (blood urea 34 mg/100 ml, blood creatinine 1.4 mg/100 ml, urea clearance 24 ml/min, endogenous creatinine clearance 43 ml/min, P.A.H. clearance 112 ml/mn) and hepatic (increased transaminases) insufficiency should have contra-indicated the use of a sulphonylurea.

3c) Two patients died from a myocardial infarction during the observation period. Their ages were 71 and 72 years respectively.

The first occurred despite the correction of a hypoglycaemic coma after 20 days of treatment with only 5 mg glipizide daily in this patient whose renal insufficiency (endogenous creatinine clearance 25 ml/mn) and hepatic cirrhosis (SGOT 75 U., Alk. phosph. 10.5 Bod. U.) should have been a mandatory contra-indication.

The second case occurred during the 7th month of treatment with glipizide in a 72 year old patient

with arteritis, long-standing coronary artery disease and nephrosclerosis, with a blood urea of 60 mg/100 ml. With 7½ mg daily, satisfactory equilibrium had been obtained for 6 months. When this equilibrium was broken, dosage was increased to 10 mg daily in two doses and four days later the patient suffered an extensive myocardial infarction. There were no apparent manifestations of hypoglycaemia preceding the coronary accident and not once did the routine tests reveal hypoglycaemia.

4. Toleration and Toxicity

4a) *None of the thirty-five patients* treated had any functional symptoms, in particular gastrointestinal, nor any objective signs (skin allergy) suggesting intolerance to the drug. No antabuse-like effect was noted.

4b) *Renal function:*

A. There was no new onset of proteinuria nor were any abnormal urinary cytologic elements observed; when these abnormalities pre-existed, there was no aggravation.

A. The initial mean number of red blood cells (4354000/mm³) did not undergo any marked variations except for a frequent tendency to increase, with a mean "treatment" value of 4556000/mm³ (123 counts).

B. There was no depression of platelets by glipizide (103 counts), even in a case of thrombocytopenia due to splenic hyperactivity in a cirrhotic patient. In this case the initial count was 205000/mm³ and under treatment this value was maintained at 210000/mm³.

Platelets showed a tendency to increase during the first four months of treatment to around 230000/mm³ on average. This tendency later disappeared (200000/mm³ on average after the 5th month).

C. Examination of leukocytes and granulocytes did not demonstrate any toxic action of glipizide on white blood cells. The initial mean values of leukocytes and neutrophilic granulocytes before treatment were 6275 and 4170/mm³ respectively. White blood cell counts in 112 patients under treatment showed mean values of 6760 and 4300/mm³ for leukocytes and neutrophilic granulocytes respectively. There was a slight drop during the first four months of treatment, but after the 5th month mean values were higher than the initial values.

Table 4. *Biological toxicity-control determinations*

	Before glipizide			Under glipizide treatment		
	Extreme values	Mean value	Number of determinat.	Extreme values	Mean value	Number of determinat.
Blood urea mg/100 ml	18—70	40.6	32	15—75	41	138
Serum uric acid mg/100 ml	3.4—9.0	5.46	28	3.2—12.0	6.04	127
Erythrocytes/mm³	3300000—5400000	4354000	27	3150000—5800000	4566000	123
Platelets/mm³	120000—300000	205000	26	116000—350000	210000	103
Leucocytes/mm³	4100—10400	6275	27	3100—12000	6760	112
Granulocytes/mm³	2360—8100	4173	25	1700—10300	4290	111
S.G.O.T. (IU)	18—75	33.6	26	8—120	33.5	129
S.G.P.T. (IU)	5—54	23.3	26	5—113	34	128
Alk. phosphat. (BU)	1.5—10.5	3.80	22	1—10.7	3.80	128
Blood fibrinogen mg/100 ml	200—540	351	18	180—650	320	128

B. The mean value of blood urea was initially 40.6 mg/100 ml and under treatment it remained between 37 and 44 mg/100 ml, the mean being 41 mg/100 ml (138 estimations).

C. Blood creatinine levels, which were measured in a few cases, remained stable, even when they were high initially, in particular in the two cases mentioned above.

D. Blood uric acid levels, which were initially high in one quarter of the patients (mean value 5.46 mg/100 ml) underwent non-homogeneous variations around the mean level calculated at 6.04 mg/100 ml (127 estimations) during treatment.

4c) *Haematological toleration* of glipizide was also good.

4d) *Liver function tests.*

A. Serum glutamic oxalacetic transaminase levels, which were initially abnormal in six cases with a mean value of 33.6 U., oscillated during treatment around a mean value of 33.5 U. (129 estimations). Thus, pre- and post-treatment values were absolutely identical.

B. Glutamic pyruvic transaminase levels, which were initially abnormal in four patients, with a mean of 23.3 U., rose to a mean value of 34 U. during treatment (128 measurements). This difference is significant ($p < 0.05$). In fact, during the second

month of treatment, a rise in SGPT levels was recorded in 11 cases (exceeding 40 U. in only 2 cases and later remaining unchanged). One patient with active post-icteric chronic hepatitis for the past five years initially showed a rise of SGPT level from 40 to 113 U. and of SGOT level from 40 to 80 U. with 2½ mg of glipizide daily. But these levels later returned to normal during treatment, and liver biopsies performed during the 4th month showed lesions indicating that the antidiabetic sulphonamide was probably not responsible.

C. Alkaline phosphatase levels were perfectly stable under glipizide: the mean level was 3.80 Bod. U. before and during treatment (128 controls).

D. Blood fibrinogen levels remained unchanged under glipizide (128 titrations), the mean value before treatment being 351 mg/100 ml, and 320 mg/100 ml during treatment ($p > 0.05$).

E. As seen above, blood cholesterol levels remained stable.

F. No drop in blood prothrombin level was noted during treatment with glipizide. One of our patients, however, (prothrombin level 34 to 36%) who had been stabilized for the past 6 years following a myocardial infarction with 125 mg of phenylidanedione daily, suffered severe intestinal hemorrhage thirty-four days after beginning treatment with 5 mg of glipizide daily (substituted for 1000 mg of glybutamide). Investigations revealed a drop in prothrombin level to 10%. After discontinuation of the anticoagulant, later measurements showed a prothrombin level of 100% with continuation of glipizide.

Discussion and Conclusions

Treatment with glipizide for an average of seven months in our 35 patients with non insulin-dependent diabetes confirmed the hypoglycaemic properties of this new sulphonamide in small doses. These properties were demonstrated by experimental investigations and were later confirmed by the first clinical trial performed by Italian authors. In one third of the cases the patients reported subjective improvement and there was a regular decrease of both mean and maximal blood sugar levels in the majority of our patients (Fig. 1). These findings are all the more significant when one considers that most of the patients were aged, had degenerative complications or associated disorders in 86% of cases and were obese in one third of cases. Eighty per cent of the patients had had diabetes for more than 5 years and 38% for more than ten years, usually treated by other sulphonamides. During the second and third trimesters of treatment, after careful and gradual adjustment of dosage, the proportion of well stabilized diabetics increased appreciably (from 11% before glipizide to 39% with glipizide), while that of poorly controlled cases diminished markedly (from 40% to 23% respectively). In only one newly treated case was it necessary to add secondarily 200 mg of phenformin daily to the 15 mg of glipizide in order to obtain better control.

These results are comparable to those obtained by Parodi [18] with lower doses but in younger patients who had not been previously treated. They are also similar to those of Marigo *et al.* [4] in patients of comparable age but with a higher mean dosage (14½ mg/daily) substituted for glycyclamide or tolbutamide. None of our patients had become resistant to sulphonamides before the beginning of treatment with glipizide and we are therefore unable to confirm that the latter is capable of exerting action in patients who have become resistant to sulphonylureas, in particular to glibenclamide, as Parodi claims. Unlike this author, we do not have any experience with the possible benefit which may be expected from the association of glipizide and insulin, which would permit a reduction of dosage. On the other hand, with glipizide we obtained the same benefit that can be expected from associating a biguanide with a sulphonamide, i.e. economy of dosage of the latter, thus preventing hypoglycaemic incidents which are to be particularly feared with these "second generation" antidiabetic sulphonamides.

It is with this fear in mind that initial dose titration was and should be particularly careful and gradual and dosage should only be increased little by little in accordance with clinical and biological findings. This point should be emphasized.

In equivalent doses, glipizide appears as active as glibenclamide and more active than glisoxepide [9, 10]. With some "first generation" sulphonamides, the correlation appears to be one 5 mg tablet of glipizide for at least 2 tablets of glybutamide (= 1000 mg), chlorpropamide (= 500 mg) or glycodiazine (= 1000 mg); Marigo *et al.* [14] noted that 5 mg of glipizide were equivalent to 500 mg of tolbutamide or to 500 mg or more of glycyclamide.

Care in the management of treatment and in the adjustment of dosage is justified, particularly when dealing with the type of high risk patients we had in our study. The frequency of minor hypoglycaemic incidents, necessitating the division of daily dosage into two administrations (morning and midday) or its reduction in the case of biologically confirmed over-correction, was not negligible in our series of patients. Late morning hunger or weakness may be felt by the patient even after taking only 2½ mg of glipizide at breakfast, if the carbohydrate content of the latter is insufficient. Timely redistribution of carbohydrates over the three meals may prevent these phenomena.

A special characteristic of our group of patients is that quite a large proportion of them, i.e. eight, had some degree of renal insufficiency. The problem of sulphonylurea treatment in diabetic patients with damaged renal function has been considered by several investigators. Accumulation in the circulation of

these substances or their metabolites has been demonstrated in patients with severe, and even with a moderate, decrease in the glomerular filtration rate. These patients are prone to hypoglycaemic attacks for several reasons, such as decrease of insulin catabolism in the kidney, poor homeostatic mechanisms and last but not least, the accumulation of the sulphonylureas, either as unchanged drug or as active metabolites in patients receiving them. As far as glipizide is concerned, we know from the metabolic studies performed with this drug [7, 21] that it is metabolized in the liver into 4 metabolites of which only 2 are present in significant amounts. Both are almost devoid of hypoglycaemic activity and 80% of these metabolites are eliminated by the kidneys. Fabre, Balant and Zahnd [6] have recently shown the extent to which the excretion of these substances depends on kidney function. Using C^{14}-labelled glipizide (5 mg I.V.) these authors demonstrated that the half-life of total radioactivity (= unchanged drug + metabolites), as measured by the method used, rises from 3½ h in patients with normal kidneys to 6 h when the endogenous creatinine clearance falls to 30 ml/min and to 12 h when creatinine clearance is 10 ml/min; the renal excretion is reduced from 75% in 48 h to 30% when the kidney function is reduced by three-quarters. The same authors have, however, demonstrated that even in severe renal insufficiency the disappearance rate of glipizide itself, i.e. the unchanged drug, is not significantly reduced in comparison with normal subjects, but that the prolonged "half-life" is due to the accumulation in the plasma of the metabolites of the sulfonylurea. As the two major metabolites are virtually devoid of any hypoglycaemic activity, it is unlikely that hypoglycaemic attacks could occur through accumulation of unchanged drug or its metabolites except in severe renal insufficiency, where the glomerular filtration rate is lower than 30 ml/min (reduction of renal function by more than 75%). There is, however, one circumstance where such an incident is more likely i.e. when the impairment of renal function is associated with reduced hepatic function. When both kidney and liver are impaired, metabolism of the drug is slower and the unchanged active substance will accumulate. This was probably the sequence of events in our two patients who experienced severe hypoglycaemia during glipizide treatment. Both had renal insufficiency and abnormal hepatic function tests. In the light of our experience, we would like to recommend rules for glipizide, similar to those previously laid down for the other sulphonylureas. Its use should be avoided in the presence of severe renal insufficiency where the kidney function is reduced by 75% or more, while in moderate insufficiency (reduction by 50—75%) special attention should be given to hepatic function. This should prevent the occurrence of severe hypoglycaemia which has become more common over the past few years [3, 4, 10, 11, 12, 16, 17, 21, 22]. The absence of warning symptoms before the attack is common, and one of our patients illustrates this fact. If high potency sulphonylureas are to be used in such patients, precise rules concerning dosage in relation to the kidney's excretory capacity, should be specified and followed [5, 20].

We did not note other interference with the hypoglycaemic action of glipizide. However, our one and only observation of a diabetic on anticoagulants, prescribed before antidiabetic treatment, suggests that the usual rule of enhancement of anticoagulant action by hypoglycaemic sulphonamides [24] applies to glipizide.

On the basis of our 35 observations, we may conclude that glipizide is a potent hypoglycaemic drug capable of appreciably improving glycaemia previously obtained with other sulphonamides in type I diabetes. Its potency necessitates careful and gradual adaptation of dosage. No toxic effects were observed except for hypoglycaemia as the result of over-dosage or accumulation in the event of renal deficiency, combined with hepatic dysfunction, or in marked renal insufficiency.

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