Diabetologia 17, 287–290 (1979)

Diabetologia

Effect of the α-Glucosidase-Inhibitor BAY-g-5421 on Blood Glucose Control of Sulphonylurea-treated Diabetics and Insulin-treated Diabetics

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Summary. BAY-g-5421 is an α-glucosidase-inhibitor which inhibits intestinal absorption of carbohydrates. In a double-blind cross over study 12 diabetics taking sulphonylureas and 12 insulin-treated diabetics were treated additionally with BAY-g-5421 or a placebo for two seven day periods. In the pretreatment period and on the 7th and 14th day of the treatment periods serial blood glucose profiles were measured. In comparison to placebo BAY-g-5421 significantly lowered the mean (140 versus 157 mg/dl) and the maximal (192 versus 230 mg/dl) blood glucose values and the integrated blood glucose response (3112 versus 3421 mg/dl · 24 h) in the sulphonylurea-treated group as well as in the insulin-treated group (mean blood glucose 161 versus 192 mg/dl, maximal blood glucose 238 versus 283 mg/dl, integrated blood glucose response 3109 versus 3857 mg/dl · 24 h). The amplitude of glycaemic excursions was significantly decreased only in the sulphonylurea-treated group (96 versus 129 mg/dl), but not in the insulin-treated diabetics. No influence on routine liver function, renal function or haematological tests was observed. Side effects included hypoglycaemia in 3 patients of the insulin-treated group and meteorism in both groups. BAY-g-5421 could be a useful additional treatment for diabetic patients.

Key words: α-glucosidase-inhibitor, sulphonylurea-treated diabetics, insulin-treated diabetics, blood glucose control.

One of the most difficult components of blood glucose control in diabetics is the ability to keep postprandial rises down to normal levels. This is particularly difficult in insulin-treated diabetics when subcutaneous insulin absorption is much slower than food absorption. One possible approach is to slow the absorption of glucose either with substances like guar or by inhibiting the breakdown of starch and sucrose.

A lowering effect of α-amylase-inhibitors (BAY-d-7791, BAY-e-4609) on postprandial blood glucose originating from starch digestion has been described in earlier studies [1, 2, 3]. In sucrose loading tests similar results could be demonstrated with a sucrase inhibitor [4].

It has been demonstrated, that the new α-glucosidase-inhibitor BAY-g-5421 delays starch digestion as well as inhibits sucrase and maltase activities of intestinal disaccharidases [5, 6].

The aim of the present investigation was to evaluate some of the biochemical effects of BAY-g-5421 in sulphonylurea- and insulin-treated diabetics.

Materials and Methods

a) Subjects

The studies were carried out in twelve diabetics taking sulphonylureas (eight taking glibenclamide, two taking tolbutamide, one taking glisoxepide, one taking glibornuride) and twelve insulin-dependent diabetics on two daily insulin injections of an intermediate acting insulin.

Throughout the whole study period the patients were admitted to hospital.

Twelve diabetics on sulphonylureas were selected, whose one hour postprandial serum glucose values in the morning were between 100 and 250 mg/dl on the third to the fifth day after admission. The mean age of these patients was 59 years (range 41–72), the mean Broca index $\left(\frac{\text{height (cm)} - 100}{\text{weight (kg)}}\right)$ was 1.4 (range 1.2–1.7) in men and 1.5 (range 1.3–1.9) in women.

The mean age of the twelve insulin-dependent diabetics was 41 years (range 24–60), the mean Broca index was 0.9 (range 0.7–1.1) for men and 0.9 (range 0.6–1.2) for women. Urine glucose had to be more than 15 g/24 h.

0012-186X/79/0017/0287/$01.00

In both study groups criteria for exclusion were: febrile infections, myocardial infarction less than three months before, and any intercurrent disease known to affect carbohydrate metabolism.

The patients were kept under metabolic ward conditions. There was no clinical or laboratory evidence of abnormal liver and kidney function in any subject.

Six of the sulphonylurea-treated patients were taking digitalis and two TMP/SMX (trimethoprim-sulphamethoxazole). The insulin-treated diabetics were on no medications other than insulin.

A diet comprising 40% carbohydrate, 40% fat, and 20% protein was given to all subjects. The same diet was given in the pretreatment period, in the placebo period, and in the drug period.

Meals were given at 07.45, 10.15, 12.30, 15.00, 19.00, and 21.00 h. The distribution of carbohydrate over the six meals in the sulphonylurea-treated group was (mean and range) 24 (12–36) g, 12 g, 30 (24–36) g, 12 g, 30 (24–36) g, 12 g; in the insulin-treated group 36 (24–48) g, 40 (24–54) g, 36 (24–48) g, 18 (12–36) g, 40 (24–54) g, 24 (12–36) g.

No change was made in diet, insulin or sulphonylurea therapy during the course of the study. Informed consent was obtained from all subjects.

b) Protocols

After a one week pretreatment period a double blind cross over study was started.

Six subjects in the sulphonylurea-treated group and six insulin-treated subjects received placebo in the first week and BAY-g-5421 in the second week in addition to their usual therapy. The remaining twelve subjects – six sulphonylurea-treated and six insulin-treated – were given BAY-g-5421 in the first week and placebo in the second week.

The distribution of treatment periods was random.

All subjects received six × 50 mg BAY-g-5421 per day, i. e. 50 mg at the beginning of each meal. On the last day of the pretreatment period and on the 7th and 14th day of the study periods measurements were made of serial blood glucoses, serum triglycerides and cholesterol, creatinine, blood urea nitrogen, bilirubin, glutamate-oxaloacetate-transaminase, glutamate-pyruvate-transaminase, alkaline phosphatase, y-glutamyl-transpeptidase, plasma electrolytes, leucocyte, erythrocyte and thrombocyte counts, and in the twelve sulphonylurea-treated diabetics serum insulin before and 30, 60, and 90 min after breakfast (07.45 h).

The timing of the serial blood glucose determinations were: 07.00, 07.30, 08.30, 08.45, 09.00, 09.15, 09.45, 10.15, 11.00, 11.45, 12.30, 13.30, 14.45, 15.45, 17.00, 18.15, 19.45, 21.00, 22.00, 24.00, and 04.00.

c) Laboratory and Statistical Analysis

Capillary blood glucose was measured in duplicate on each sample by the hexokinase method (Boehringer Test-Combination Glucoquant) with an Eppendorf substrat automat 5031.

Serum insulin was determined by radioimmunassay in triplicate with Boehringer Test-Combination Insulin. The interassay coefficient of variation was 6.9%.

Serum triglycerides and cholesterol, haemotological tests, serum enzymes, creatinine, BUN, and serum electrolytes were measured with routine laboratory methods using Boehringer Test-Combinations (Boehringer, Mannheim, W. Germany).

The mean blood glucose values were calculated from the 21 blood glucose values/24 h in each patient.

The integrated blood glucose response was calculated using the trapezoid rule without subtraction of the fasting blood glucose value and given in mg/dl · 24 h.

The amplitude of glycaemic excursions was calculated as the difference between the minimal preprandial and the maximal postprandial blood glucose values in our serial determinations.

All values are presented as mean ± SEM. Results were analyzed using the Student paired t-test.

d) Materials

BAY-g-5421 was supplied by BAYER AG, Wuppertal, W. Germany.

Results

Blood Glucose Values

In the twelve diabetics on sulphonylurea therapy and in the twelve insulin-dependent diabetics there was no significant change in fasting blood glucose levels after BAY-g-5421 or placebo (Table 1).

However, in both groups of patients there was a statistically significant lowering effect of BAY-g-5421 on the maximal blood glucose values compared with placebo (Table 1, Fig. 1, and Fig. 2).

There was a significant difference in mean blood glucose values between the placebo period and the BAY-g-5421 period in both groups (Table 1, Fig. 1, and Fig. 2), though the fall in blood glucose was less than 20% and the values were still elevated even after treatment with the drug.

BAY-g-5421 lowered significantly the integrated blood glucose response compared with the placebo period in both groups of patients (Table 1).

A significant effect of BAY-g-5421 in reducing the amplitude of glycaemic excursions in patients on sulphonylureas was demonstrated. In the insulin-treated group there was no effect (Table 1).

Serum Insulin

The serum insulin concentrations in the sulphonylurea-treated group before and 30, 60, and 90 min after breakfast were not significantly different in the three periods. The fasting and 60 minute value on placebo were 33 and 62 μU/ml, on BAY-g-5421 43 and 56 μU/ml respectively.

Other Laboratory Analyses

There was no effect of BAY-g-5421 on serum triglycerides and cholesterol, liver and kidney function, serum electrolytes, and haematological tests.

Side Effects

Three insulin dependent diabetics experienced hypoglycaemic symptoms during the BAY-g-5421 period.

Table 1. Fasting, mean, and maximal blood glucose levels, integrated blood glucose response and amplitude of glycaemic excursions in sulphonylurea-treated and insulin-treated diabetics. (n. s. = not significant. Values are mean ± SEM. P-value for comparison of the test group to the placebo group)

		Pretreatment	Placebo	Test	P
a. *Sulphonylurea-treated*					
Fasting blood glucose levels	mg/dl	163 ± 18.8	141 ± 16.7	130 ± 18.2	n. s.
Maximal blood glucose values	mg/dl	231 ± 15.3	230 ± 12.1	192 ± 10.4	<0.001
Mean blood glucose levels	mg/dl	162 ± 12.1	157 ± 12.4	140 ± 10.7	<0.005
Integrated blood glucose response	mg/dl · 24 h	3564 ± 235.3	3421 ± 201.0	3112 ± 190.5	<0.005
Amplitude of glycaemic excursions	mg/dl	123 ± 9.5	129 ± 6.1	96 ± 6.4	<0.005
b. *Insulin-treated*					
Fasting blood glucose levels	mg/dl	179 ± 19.9	184 ± 21.1	173 ± 18.8	n. s.
Maximal blood glucose values	mg/dl	271 ± 23.1	283 ± 17.9	238 ± 19.3	<0.005
Mean blood glucose levels	mg/dl	180 ± 20.8	192 ± 23.9	161 ± 20.2	<0.005
Integrated blood glucose response	mg/dl · 24 h	3612 ± 289.8	3857 ± 383.4	3109 ± 358.0	<0.005
Amplitude of glycaemic excursions	mg/dl	171 ± 21.4	168 ± 19.1	147 ± 16.5	n. s.

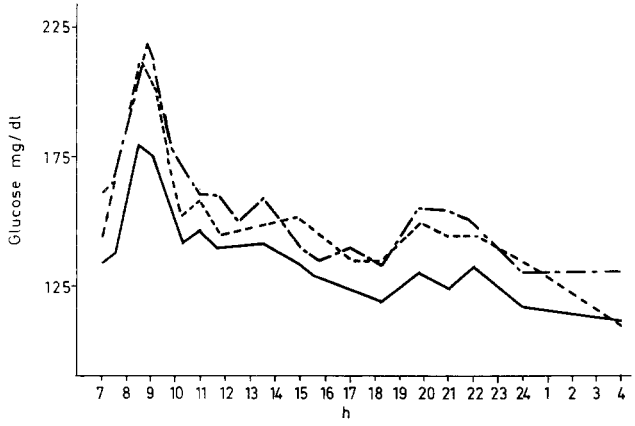

Fig. 1. Mean diurnal blood glucose values of twelve sulphonylurea-treated diabetics before treatment and after seven days therapy with either BAY-g-5421 or placebo. ———— Bay-g-5421; – – – – – Placebo; — · — · — Pretreatment values

Fig. 2. Mean diurnal blood glucose values of twelve insulin-treated diabetics before treatment and after seven days therapy with either BAY-g-5421 or placebo. — · — · — Pretreatment values; – – – – – Placebo; ———— Bay-g-5421

Ten orally treated diabetics and eight diabetics in the insulin-dependent group complained of meteorism and flatulence, but this diminished after four to five days.

Discussion

BAY-g-5421 lowers the integrated blood glucose response in patients taking sulphonylureas as well as in insulin-treated subjects. Similar effects of BAY-g-5421 in insulin-treated patients have recently been published by Walton et al. [7]. They observed in addition a blunting by BAY-g-5421 of the postprandial blood glucose increase after breakfast which may be explained by the bad control of their patients (fasting blood glucose about 15 mmol/l) and the higher dose of BAY-g-5421 (100 mg) employed.

The maximal blood glucose values in both groups were decreased by BAY-g-5421. The maximal blood glucose concentration was with one exception the postprandial peak after breakfast (07.45). To decrease these peaks in diabetics receiving sulphonylureas it is often necessary to prescribe a very restricted diet, which is not well tolerated. The lowering effect of BAY-g-5421 on blood glucose is presumably the consequence of delayed absorption caused by the delay of starch digestion although inhibition of sucrose digestion may also be important [8]. From our short term study we cannot say if malabsorption plays a part in the reduction of blood glucose levels by BAY-g-5421. In view of the small

dose used we consider this unlikely. Long-term treatment with the drug does not produce substantial weight loss [9] suggesting that delayed absorption of carbohydrates and not a reduction of the total amount absorbed may be the "therapeutic" mechanism.

Some of the insulin-dependent diabetics experienced hypoglycaemic symptoms during the BAY-g-5421 period. In the sulphonylurea-treated group counterregulation may be more effective and possibly prevents hypoglycaemia. This may result in a decreased amplitude of glycaemic excursions. A similar "smoothing" effect has been observed with biguanides. Because of the occasional severe side effects of the biguanides, the α-glucosidase-inhibitor BAY-g-5421 may be an alternative treatment.

The most disturbing side effect of BAY-g-5421 was flatulence and meteorism. It is an open question as to whether patients will tolerate this. In the present study BAY-g-5421 was given for one week only, and there was a slight diminution of meteorism and flatulence after four to five days. Thus, it is possible that symptoms will diminish in the long term.

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Received: October 10, 1978,
and in revised form: May 25, 1979

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