Res. Exp. Med. (Berl.) 175, 81—86 (1979)

Research in
Experimental Medicine

The Effects of the α-Glucosidase Inhibitor BAY g 5421 (Acarbose) on Meal-Stimulated Elevations of Circulating Glucose, Insulin, and Triglyceride Levels in Man

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Summary. In blind studies the effects of a new α-glucosidase inhibitor (BAY g 5421) were tested in normal weight and overweight male volunteers after oral application of 75, 150, or 300 mg of BAY g 5421 or placebo per os before three standardized main meals of one day. Before and three hours after each meal blood glucose, serum insulin, and serum triglyceride levels were determined. In addition, safety studies were performed.

BAY g 5421 induced a statistically significant, in part dose-dependent inhibition of the postprandial increase of blood glucose- and serum insulin levels. The reduction of the postprandial increase of serum triglyceride levels was variable. Routine blood chemistry and hematology tests have revealed no adverse side effects; but the application of the drug was frequently associated with intestinal effects, such as flatulence and diarrhea, which were substrate (carbohydrate) and, in part, dose-dependent.

Key words: Glucosidase inhibitor – BAY g 5421 – Blood glucose – Serum insulin – Serum triglycerides – Acarbose

Cleave et al. (1969) have suggested that the consumption of refined carbohydrate, such as sucrose, may lead to the so-called saccharine disease; others, however, could not confirm these findings (Hillebrand, 1974). It is, nevertheless, tempting to use the inhibition or delay of carbohydrate (starch, sucrose) digestion or assimilation in order to treat metabolic diseases, such as diabetes, hypertriglyceridemia, and obesity (Roberts, 1974).

Such an attempt has been made by using an α-amylase inhibitor, BAY e 4609 (Puls and Keup, 1975), which did not prove to be of therapeutic value in diabetics or obese patients because most probably sucrose consumption, in addition to starch, abolished its effects on postprandial glycemia and insulinemia (Berchtold and Kiesselbach, 1976).

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0300-9130/79/0175/0081/$ 1.20

A new competitive α-glucosidase inhibitor, a complex oligosaccharide of microbial origin, BAY g 5421 (Schmidt et al., 1977), was developed and proved to be effective in animal experiments as well as in preliminary studies in man (Puls et al., 1977): The postcarbohydrate or postprandial increases of blood glucose- and serum insulin levels were inhibited or abolished.

This paper presents detailed clinicopharmacological studies on the effect of BAY g 5421 on the meal-stimulated glycemia, insulinemia and triglyceridemia in healthy volunteers. Preliminary results of this study have been reported (Berchtold et al., 1978).

Materials and Methods

Six normal weight male volunteers (mean age 27 ± 6 years; mean Broca index 0.98 ± 0.05) and six overweight male volunteers (mean age 34 ± 4 years; mean Broca index 1.25 ± 0.07) received orally 75, 150, or 300 mg of BAY g 5421 or placebo before the three main meals of one day in a blind incomplete block design. The meals were standardized and contained 40% carbohydrate, 40% fat, and 20% protein for breakfast and dinner. At lunch only 10% protein was given, and 10% of the total calories were replaced by beer. The total amount of calories were 2700 Cal./day (11,304 kJ) (standard carbohydrate diet).

Under the same trial conditions five normal weight male volunteers (mean age 29 ± 6 years; mean Broca index 0.96 ± 0.11) and six overweight male volunteers (mean age 32 ± 7 years; mean Broca index 1.27 ± 0.08) were studied under a carbohydrate-rich diet (2700 Cal./day; food composition: 60% carbohydrates, 30% fat, 10% protein). Following an overnight fast of >12 h, the volunteers came to the laboratory, and an indwelling catheter was positioned in an antebrachial vein and kept patent with saline 0.9%. Meals were given and blood samples drawn at times indicated in the figures, and blood glucose (Huggett and Nixon, 1957), serum insulin (Melani et al., 1965) and serum triglyceride values (Eggstein and Kreutz, 1966) were determined.

Before the study and on the day of the last test, routine clinical chemistry and hematology tests were performed: total bilirubin, cholesterol, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, γ-glutamyltransferase, alkaline phosphatase, leucine aminopeptidase, lactic acid dehydrogenase, iron, calcium, total protein, uric acid, blood urea, creatinin, Hb, RBC-, WBC-, platelet-, and reticulocyte count and a blood smear. All methods were conventional autoanalyzer or commercially available kit methods. The volunteers were asked to report side effects.

The statistical analysis of the effects of BAY g 5421 on blood glucose, serum insulin, and serum triglyceride profiles was performed after logarithmic transformation of the data. A five-factorial partially nested model for analysis of variance (volunteers = random periods, measurement times, treatment, and carry-over = fixed) was set up. The carry-over effect is confounded with a possible group heterogeneity. The error terms in this analysis are autocorrelated; the test variates are, therefore, too large. The program MAD of Brigham Young University (Utah), Statistics Department (Bryce and Carter, 1974) was used.

Results

BAY g 5421 led to an inhibition or abolition of the postprandial increases in the blood glucose, serum insulin, and, in part, in the serum triglyceride levels with standard carbohydrate diet:

Blood Glucose Levels

BAY g 5421 had significant effects in both groups of volunteers (Figs. 1 and 2) after lunch and after dinner ($P \leq 0.001$); the effect after breakfast was nearly significant ($P \leq 0.06$).

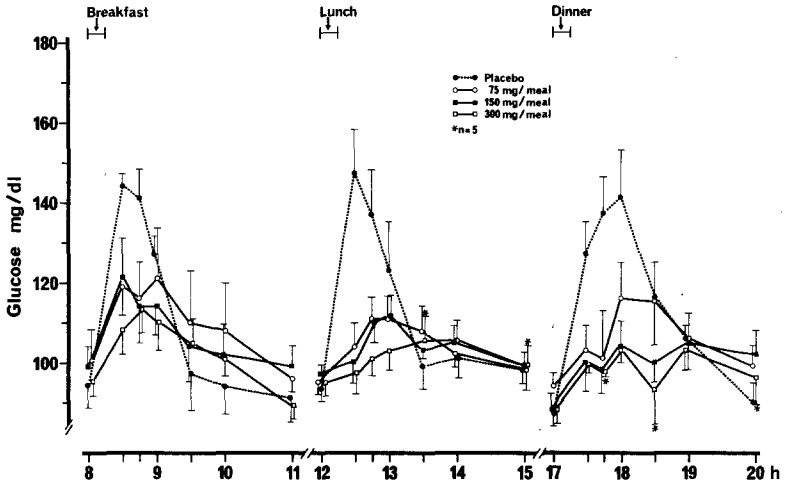

Fig. 1. Fasting and postprandial blood glucose levels in six normal weight volunteers (mean values ± SE). Meal composition: breakfast and dinner: carbohydrate 40%, fat 40%, protein 20%. Lunch: carbohydrate 40%, fat 40%, protein 10%, alcohol 10%. Each meal contained 900 Cal. (3766 kJ)

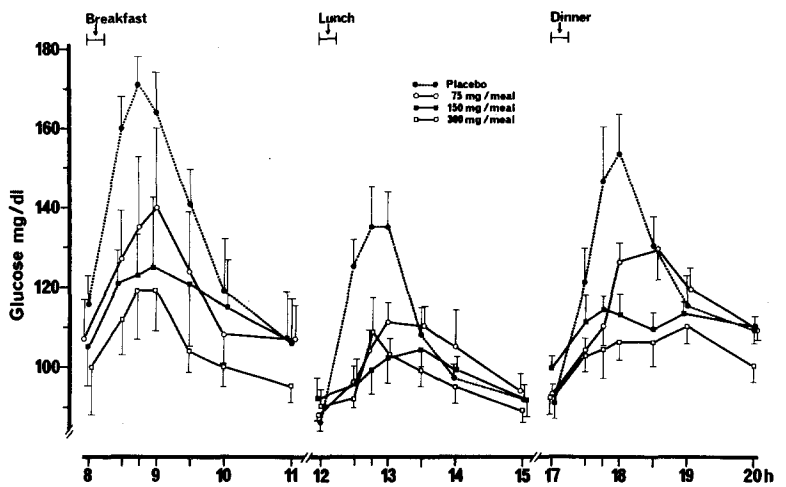

Fig. 2. Fasting and postprandial blood glucose levels in six overweight volunteers (mean values ± SE). Meal composition as in Figure 1

In normal weight volunteers (Fig. 1) higher dosages of BAY g 5421 were not more effective than the lower dosage, whereas in overweight volunteers a dose-dependence could be observed (breakfast $P \leq 0.12$; lunch $P \leq 0.05$; dinner $P \leq 0.003$) (Fig. 2): 75 mg of BAY g 5421 were less effective than a calculated mean dosage of 150 mg and 300 mg (geom. mean 212 mg).

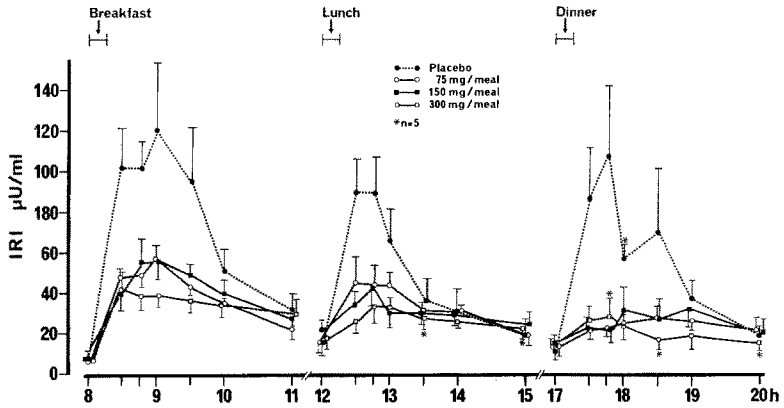

Fig. 3. Fasting and postprandial serum insulin levels in six normal weight volunteers (mean values ± SE). Meal composition as in Figure 1

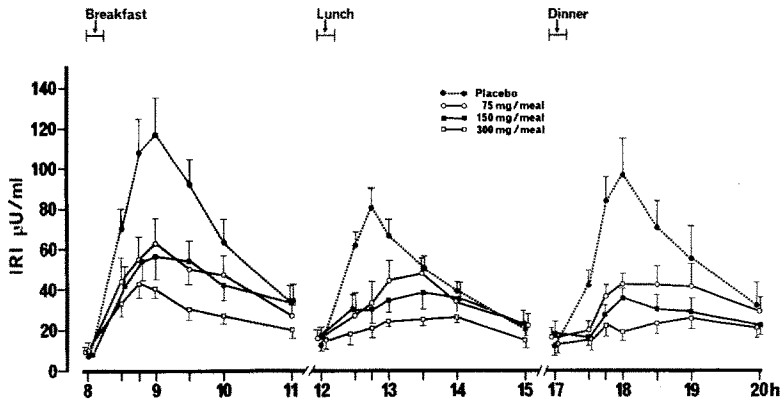

Fig. 4. Fasting and postprandial serum insulin levels in six overweight volunteers (mean values ± SE). Meal composition as in Figure 1

Serum Insulin Levels

The postprandial increase of the serum insulin levels was significantly reduced with BAY g 5421 in both groups of volunteers at all meals when compared with placebo ($P \leq 0.02$ to $P \leq 0.0007$), except in normal weight volunteers after breakfast ($P \leq 0.06$) (Figs. 3 and 4). In normal weight volunteers (Fig. 3) the effect was dose-dependent after lunch; in the obese volunteers after breakfast (Fig. 4).

Serum Triglyceride Levels

The effect of the drug on serum triglyceride levels was variable. In normal weight volunteers the postprandial increase of the serum triglyceride levels were significantly decreased after breakfast ($P \leq 0.006$), but no effect of the drug was found

after the other meals. In overweight volunteers no reduction of the serum triglyceride levels was achieved by BAY g 5421.

Because of intestinal effects of the drug, like diarrhea, the carbohydrate-rich diet study could not be completed in a controlled trial fashion. The results of the statistical analyses of the BAY g 5421 effects (abbreviated model without carry-over effect) were similar to those obtained in the studies with standard carbohydrate diet.

Tolerance

Clinical chemistry and hematology tests remained unaffected by BAY g 5421. Intestinal effects of the drug, like meteorism, flatulence or diarrhea, were dose-dependent. These effects, however, were much more markedly dependent on the amount of carbohydrate in the meal. Carbohydrate-rich meals increased the intestinal effects. The interindividual variability of the symptoms was considerable. All of the 23 volunteers reported intestinal effects.

Discussion

These clinicopharmacological studies in normal and overweight healthy volunteers demonstrate an inhibitory effect of BAY g 5421 on the postprandial increases of blood glucose, serum insulin and, in part, serum triglyceride levels. This is in accordance with the results of Puls et al. (1977) and Caspary (1978) who showed that the drug is effective on the blood sugar increase after an oral sucrose load. In addition, they showed that the BAY g 5421 induced delay of glucose uptake is due to sucrose malabsorption and sucrose fermentation by colonic bacteria.

The mechanism of action of this drug is the competitive inhibition of carbohydrate digesting enzymes, such as porcine small intestinal disaccharidase complex (Schmidt et al., 1977) and glucoamylase, sucrase, and maltase from human jejunal biopsy material (Caspary and Graf, 1978).

An effect of BAY g 5421 on the postprandial serum triglycerides increase was obtained after breakfast only, but not after lunch or dinner. Insulin stimulation of VLDL formation and secretion in the liver is only one of the assumed mechanisms in the pathogenesis of hypertriglyceridemia (Gries et al., 1978).

A substantial part of the triglyceride synthesis takes place in the intestinal tract (Den Besten et al., 1973), and its hormonal regulation has not yet been clarified. Therefore, the variable effect of BAY g 5421 on the postprandial triglyceridemia was not unexpected and only long-term studies will show whether a postprandial suppression of the stimulus insulin and the substrate glucose for VLDL formation will effectively lower elevated serum triglyceride levels.

This drug should prove to be valuable in the treatment of diabetic patients. Indeed, favorable blood glucose lowering and stabilizing effects by BAY g 5421 given orally with the meals have been described in diabetics (Walton et al., 1978; Sachse and Willms, 1978; Jaeger et al., 1978).

Additional studies and clinical trials are needed to assess the long-term efficacy and safety of this new drug which opens a new area of research on the treatment of metabolic diseases.

Acknowledgement. We thank Prof. H. Frerichs (Department of Medicine, University of Göttingen) for the determination of the serum insulin concentrations of this study. We are grateful to Ms. L. Nagel for superb technical assistance.

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Received October 9, 1978 / Accepted January 11, 1979