Miglitol (Bay m 1099) has no extraintestinal effects on glucose control in healthy volunteers

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In this double-blind, cross-over, placebo-controlled, randomized study, possible extraintestinal effects of miglitol, an absorbable α -glucosidase inhibitor, were investigated. Sixteen healthy male volunteers underwent two 75 g oral glucose tolerance tests with concomitant administration of miglitol or placebo. Peak and post-peak areas under the curve values for blood glucose, serum insulin and serum C-peptide after miglitol were not different from those found after placebo. The post-peak AUC-ratio (AUC (peak, 180 min) on miglitol/AUC (peak, 180 min) on placebo) was for glucose 1.15 (CI 0.94–1.40, $P=0.16$), for insulin 1.12 (CI 0.95–1.33, $P=0.17$) and for C-peptide 0.98 (CI 0.81–1.18, $P=0.82$). It is concluded that miglitol exerts no clinically relevant extraintestinal effects on glucose control.

Keywords α -glucosidase inhibitors miglitol systemic effects

Introduction

In the treatment of subjects with non-insulin-dependent diabetes mellitus (NIDDM) complex carbohydrates, dietary fibre and α -glucosidase inhibitors are recommended to delay carbohydrate absorption, thereby aiming to reduce post-prandial blood glucose fluctuations [1]. The α -glucosidase inhibitors act in this process through a competitive inhibition of brush border enzymes that cleave oligo- and disaccharides into monosaccharides [1, 2]. These compounds comprise acarbose, a nitrogen-containing tetrasaccharide, and miglitol, which is derived from 1-deoxynojirimycin and is structurally similar to glucose. In contrast to the non-absorbable acarbose, miglitol is almost completely absorbed from the small intestine, raising the possibility that it could exert extraintestinal effects. Joubert *et al.* [3, 4] demonstrated in healthy control and NIDDM subjects a decrease of post-peak blood glucose values after an oral load of glucose in combination with miglitol but not with acarbose. Subsequent findings by other groups were interpreted in accordance with the results of that study. Our group [5] showed in an acute study in NIDDM subjects that ingestion of a testmeal together with miglitol reduced the post-prandial blood glucose rise but not serum insulin and C-peptide rises. Schnack *et al.* [6, 7] also reported glucose-lowering but not insulin-lowering effects in NIDDM subjects. However, repetition of Joubert's study in a larger

number of patients failed to confirm these findings (unpublished observations) [8]. To settle the contradictory findings prior to further studies we felt it necessary to once more repeat the studies of Joubert *et al.* to establish reproducibility of their findings and to find out whether this approach is suitable for further exploration of possible systemic effects of miglitol.

Methods

The study was performed in 16 healthy volunteers. The mean $\pm$ s.d. age of these subjects was 28 ± 9 years and the body mass index was 42.2 ± 2.3 kg m⁻². The subjects did not have renal or hepatic disease, had no family history of diabetes and were not taking other investigational drugs or medications altering the gastrointestinal motility and/or absorption. Written consent to participate was obtained from all subjects after oral and written information regarding the study.

The design of the protocol was a double-blind, cross-over, randomized, placebo-controlled study and was approved by the Ethics review committee of the University Hospital Maastricht. Two oral glucose tolerance tests were performed with an interval of at least 1 week. On each occasion, the participants were cannulated after an overnight fast in a forearm vein 30 min prior to the start of the test. In each procedure 100 mg

of miglitol or placebo was chewed and swallowed with 50 ml water at $t = -30$ min. At $t = 0$ min 75 g glucose in 100 ml water was ingested. Blood samples for determination of blood glucose, serum insulin and serum C-peptide were taken at -30 , -15 , 0 , 15 , 30 , 45 , 60 , 90 , 120 , 150 and 180 min and for miglitol at -30 (prior to medication), 0 , 30 , 60 , 90 , 120 , 150 and 180 min. Samples for determination of serum insulin and serum C-peptide were allowed to clot and then centrifuged at 4°C and stored at -20°C until assay. Samples for miglitol levels were collected in heparin tubes, separated in a refrigerated centrifuge and stored in polypropylene tubes at -20°C until assay. Blood glucose was determined in venous whole blood with an automated hexokinase method on Cobas MIRA (Roche, Basel, Switzerland). Serum insulin (Pharmacia, Upssala, Sweden) and C-peptide (Byk-Sangtec, Dietzenbach, Germany) were measured with radioimmunoassay after previous polyethylene glycol precipitation in order to eliminate proinsulin and other cross-reacting substances. These assays have an interassay coefficient of variation of 7.5% and 9.0% respectively. Miglitol levels were determined using a specific enzymatic assay (Dr Brendel, Bayer, Wuppertal).

Statistical analysis

To estimate the number of subjects to be included for valid interpretation of the results, available data on healthy volunteers were used [9]. Using a power of 95%, giving a two-sided significance level of 0.05, and the formula described by Fleiss [10], the required number of healthy volunteers to demonstrate relative to placebo a decrease of the area under the curve of the post-peak blood values of 10% after miglitol, as found by Joubert *et al.* [3, 4], was calculated to be 12. Hence, a sample size of 16 was considered sufficient.

Data are given as mean $\pm$ s.d., or median and range when not normally distributed. Blood glucose levels were used as primary efficacy measures. Serum insulin and C-peptide levels were used as secondary efficacy measures. For all these variables time-to-peak values, peak values and intra-individual post-peak area under the curve ratios (AUC (peak, 180 min) on miglitol/AUC (peak, 180 min) on placebo) were calculated. In the case of a systemic effect of miglitol post-peak AUCs on

miglitol must be smaller than post-peak AUCs on placebo.

Analysis of variance for sequence, subject, treatment and period was used to evaluate the results. All null hypotheses were to be tested two-sided at the $\alpha = 0.05$ significance level.

Results

Blood glucose, serum insulin and serum C-peptide levels and the course of blood glucose after oral ingestion of 75 g glucose are shown in Table 1 and Figure 1. No carry-over effect was found for the various parameters, and hence all data were pooled. For blood glucose, serum insulin and serum C-peptide the time-to-peak and the incremental peak after miglitol administration were similar to those found after placebo. The post-peak AUC-ratio (AUC (peak, 180 min) on miglitol/AUC (peak, 180 min) on placebo) was for glucose 1.15 (CI 0.94–1.40, $P = 0.16$), for insulin 1.12 (CI 0.95–1.33, $P = 0.17$) and for C-peptide 0.98 (CI 0.81–1.18, $P = 0.82$).

Figure 1 Blood glucose values after ingestion of miglitol (■) or placebo (●).

Table 1 Blood glucose, serum insulin and serum C-peptide values after an oral load of glucose (75 g in 100 ml water) and miglitol (M) or placebo (P)

		Time to peak (min)	Peak	AUC (peak, 180 min) (mmol l ⁻¹ min)
Glucose (mmol l ⁻¹)	M	30(30–60)	7.6 $\pm$ 0.9	709 $\pm$ 87
	P	37.5(15–150)	7.3 $\pm$ 1.2	646 $\pm$ 181
Insulin ($\mu\text{u ml}^{-1}$)	M	37.5(15–120)	56.8(26.7–198.1)	2620(1228–12765)
	P	52.5(30–120)	58.6(23.4–111)	2775(1168–6508)
C-peptide ($\mu\text{u l}^{-1}$)	M	60(15–120)	3.45 $\pm$ 1.07	229 $\pm$ 122
	P	60(30–120)	3.01 $\pm$ 0.78	231 $\pm$ 102

Results are given as mean $\pm$ s.d. or median and range.

Mild or moderate adverse events were noticed in seven subjects. In only two cases a remote relation to the use of miglitol was suspected. In both of these the adverse event was headache which resolved within 1 day.

Discussion

In their short-term studies with miglitol Schnack *et al.* [6, 7] found a reduction of post-prandial blood glucose observed after each meal, but serum insulin and C-peptide levels were reduced after breakfast and dinner only. At lunch-time these values were almost identical to those found after placebo. Together with the observations of Joubert *et al.* [3, 4] these observations were compatible with indications that miglitol, in addition to a delay of intestinal carbohydrate absorption, may indeed exert extrapancreatic effects particularly on disposal of glucose or insulin counterregulatory factors. In contrast to the original finding of Joubert *et al.* [3, 4] but in line with the larger (unpublished) subsequent study, we found no effect of miglitol on blood glucose excursions after an oral load of glucose. Peak glucose as well as post-peak areas under the curve (AUC) for glucose were not different from those found after placebo. As shown in Figure 1 the post-peak curves are not parallel. If any significant difference would be present between 30 and 180 min post glucose ingestion, it will be reflected in the post-peak AUC value. Also, the post-miglitol values of serum insulin and serum C-peptide were similar to the post-placebo values. We have no clear explanation for the discrepancies between our findings and those of Joubert *et al.* The test procedures were similar. The same quantity of glucose (75 g in 100 ml) was ingested and the times of administration of miglitol and placebo were also similar as well. The plasma levels of miglitol which we measured after intake of this compound were not different from those measured by Joubert *et al.*, which excludes differences in absorption. A possible explanation could be the statistical analysis. Joubert *et al.* used a paired *t*-test to compare values at different time points, which is not an adequate way to analyse this kind of data. Another explanation may, however, be differences in the number of subjects studied. We calculated that at least 12 subjects should be studied to obtain interpretable results. We included therefore 16 subjects in our studies. In contrast, Joubert *et al.* [3, 4] studied originally nine or less subjects per series of tests, which may imply that the statistical outcome of their results was caused by chance. This possibility is supported by the fact that in one of the studies of Joubert *et al.* [4] the post-peak glucose AUC after miglitol was different from that found after acarbose, but not different from that found after placebo. It is further supported by the later findings of Venter *et al.*, who showed no difference between miglitol and placebo, where the number of subjects was increased. This possibility does, however, not explain the glucose-lowering but not insulin and C-peptide lowering effects of miglitol after (test)meals observed by Kingma *et al.* [5] and Schnack *et al.* [6]. It may be

that in these situations interactions between meal constituents, its effects on hormone release from the intestinal tract and miglitol are involved. On the other hand, a variety of other studies with testmeals has shown insulin-lowering effects of miglitol parallel to its glucose-lowering effects [11–14].

Our negative findings do not completely exclude extraintestinal effects of miglitol. Salehi & Lundquist [15] demonstrated that miglitol strongly inhibits glucose-induced insulin release *in vitro* concomitant with a suppression of pancreatic islet α -glucosidase activities. In these studies, direct addition of miglitol to islet homogenates suppressed acid amyloglucosidase and acid α -glucosidase. These observations are, however, likely not clinically relevant as in that case one would expect an increase rather than a decrease of blood glucose values during treatment of NIDDM subjects with miglitol. In addition, Reuser & Wisselaar [16] reported on the potential risk of inducing a deficiency of one or more of the α -glucosidases involved in cellular glycogen metabolism and biosynthesis of glycoproteins. As for these effects a tissue concentration of miglitol is required 200- to 1000-fold higher than that reached when miglitol is applied in an oral dose of 1 mg kg^{-1} , they consider this risk for daily practice irrelevant in subjects with normal kidney function.

For these reasons we feel it justified to conclude that miglitol in itself exerts no clinical relevant extraintestinal effects. Our intended studies for more precise exploration of possible systemic effects of miglitol were therefore cancelled.

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