The effect of miglitol and acarbose after an oral glucose load: A novel hypoglycaemic mechanism?

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1 Alpha-glucosidase inhibitors such as miglitol and acarbose lower blood glucose after a starch load in healthy volunteers and diabetic patients by interfering with the conversion of disaccharide to monosaccharide in the gastrointestinal tract.

2 The effect of placebo, 100 mg miglitol and 100 mg acarbose given 30 min prior to a 75 g oral glucose load was investigated in nine healthy Caucasian volunteers.

3 Miglitol produced a statistically significant fall in post-peak blood glucose levels when compared with placebo and acarbose. Serum insulin did not change significantly.

4 As miglitol is well absorbed and acarbose is not, it is suggested that miglitol has a systemic hypoglycaemic effect, probably related to its close structural similarity to glucose, which warrants further investigation.

Keywords alpha-glucosidase inhibitors miglitol acarbose
oral hypoglycaemic agents

Introduction

The alpha-glucosidase inhibitors are drugs that interfere with the conversion of disaccharide to monosaccharide in the gastrointestinal tract. They have been developed as adjuncts to the diet in the management of diabetes mellitus and are used to decrease the rate of entry of glucose into the systemic circulation after carbohydrate ingestion. After a starch load, these agents decrease post-prandial blood glucose levels in healthy volunteers (Hillebrandt *et al.*, 1986; Joubert *et al.*, 1985) as well as in patients with diabetes mellitus (Schnack *et al.*, 1986; Walton *et al.*, 1979).

The two drugs of this type that have been studied the most extensively are acarbose and miglitol. The former is a pseudotetrasaccharide which is poorly absorbed from the gastrointestinal tract, the mean systemic bioavailability being between 0.5 and 1.6% (Putter, 1980). Miglitol, on the other hand, is a small molecule, closely related to glucose in the pyranose form and is

well absorbed with a 100% systemic bioavailability (Ramsch *et al.*, 1986). In view of its systemic absorption and structural resemblance to glucose, we recently investigated the effect of 50 mg of miglitol given 30 min before a 75 g oral glucose load to assess whether there are any systemic effects on glucose homeostasis or effects on glucose transport in the gastro-intestinal tract. In this study it was found that miglitol produced a significant post-peak reduction in plasma glucose levels in healthy volunteers (Joubert *et al.*, 1987). Serum insulin levels appeared to be unaffected.

As the blood glucose-lowering effect of alpha-glucosidase inhibitors has, up to now, in clinical settings, been considered purely as an effect on carbohydrate digestion in the gastrointestinal tract and a systemic blood glucose lowering effect had not been described previously, a further similar study appeared to be necessary. Firstly we felt it necessary to confirm or refute our previous findings and secondly to compare the effect of

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miglitol with that of acarbose. As the latter drug has the same mechanism of action in the gut, but is poorly absorbed, one would expect a systemic effect to be absent or much less than with miglitol. For this study a 100 mg of each of the drugs were used.

Methods

Nine healthy Caucasian male volunteers between the ages of 21 and 40 years, who were non-smokers and within 10% of ideal body mass (Metropolitan Life Insurance tables) participated in the study. They were free of significant laboratory and clinical abnormalities as evidenced by physical examination, an electrocardiogram and appropriate laboratory blood and urine tests. The study was conducted according to the guidelines of the declaration of Helsinki. Approval was obtained from the South African Medicines Control Council and the Research and Ethics Committee of the Medical University of Southern Africa. All volunteers gave informed written consent.

On each of the 3 test days, separated by a wash-out period of at least 7 days, volunteers reported to our clinical laboratory at 7.30 h after an overnight fast. On each occasion they received identical tablets of either placebo, 100 mg miglitol or 100 mg acarbose in a double-blind randomized fashion. Thirty minutes later they received orally 75 g glucose dissolved in 250 ml water. Blood samples were obtained through an indwelling size 21 butterfly needle in a suitable arm vein at -35, -30, 0, 15, 30, 45, 60, 90, 120 and 180 min, where 0 min was the time of glucose administration.

Blood glucose determinations were done using a fluorescence polarization immunoassay (Abbot) and plasma insulin by radioimmunoassay (CIS Bioindustries). Serum levels of miglitol and acarbose were determined by the laboratories of the department of Pharmacology of the University of the Orange Free State using *p*-nitrophenyl- α -D-glucopyranose as a substrate and using u.v. spectrophotometry to detect the formation of *p*-nitrophenol (Müller & Hillebrandt, 1986).

Data points for the three regimens were compared statistically using the Wilcoxon test.

Results

Miglitol produced a significant depression of post-peak blood glucose levels when compared with placebo and with acarbose. Although acarbose values appeared to be between that for

Figure 1 Mean blood glucose levels after a 75 g oral glucose load (0 h) on placebo (●), miglitol (○) and acarbose (▲).

Figure 2 Mean serum insulin levels after a 75 g oral glucose load (0 h) on placebo (●), miglitol (○) and acarbose (▲).

placebo and miglitol they did not differ significantly from placebo. The glucose curves are depicted in Figure 1 whereas Table 1 depicts the *P* values for the statistical analysis.

In terms of areas under the curve (AUCs) for glucose the values (mean $\pm$ s.d.) were 301 ± 248 , 240 ± 65 and 189 ± 72 mmol min⁻¹ for placebo, acarbose and miglitol respectively. The *P* values (Wilcoxon test) were 0.594 (acarbose vs placebo), 0.112 (miglitol vs placebo) and 0.0155 (miglitol vs acarbose).

Insulin values showed the same pattern as the glucose values (Figure 2, Table 2), but there were no significant differences between the treatment groups (Table 1).

The serum levels of the drugs in relation to the placebo glucose curve are shown in Figure 3. It shows that the glucose peak is reached well before that of miglitol and also the poor absorption of acarbose.

Table 1 Statistical analysis of blood glucose and insulin levels (*P* values [Wilcoxon test])

	-35 min	-30 min	0 min	+15 min	+30 min	+45 min	+60 min	90 min	120 min	180 min
Miglitol vs placebo (glucose)	0.615	0.615	0.674	0.615	0.638	0.313	0.015**	0.258	0.024**	0.085
Acarbose vs placebo (glucose)	0.342	0.327	0.857	0.215	0.615	0.258	0.516	0.615	0.057	0.53
Miglitol vs acarbose (glucose)	0.764	0.258	0.615	0.110	0.764	0.615	0.033**	0.044**	0.764	0.313
Miglitol vs placebo (insulin)	0.162	0.139	0.087	0.764	0.857	0.313	0.066	0.258	0.258	0.516
Acarbose vs placebo (insulin)	0.615	0.258	0.075	0.066	0.215	0.258	0.441	0.857	0.441	0.313
Miglitol vs acarbose (insulin)	0.516	0.952	0.952	0.56	0.651	0.772	0.313	0.215	0.441	0.087

Table 2 Spread of blood glucose and serum insulin values at 0, 60, 120 and 180 min for the three treatment regimens

	Blood glucose (mmol l^{-1})				Serum insulin ($\mu\text{u ml}^{-1}$)			
	Median	Percentiles 25th 75th	Minimum	Maximum	Median	Percentiles 25th 75th	Minimum	Maximum
0 min								
Placebo	4.5	4.2 4.8	3.6	5.3	22	17 25	12	35
Miglitol	4.6	4.4 4.7	4.1	5.3	15	13 18	10	28
Acarbose	4.5	4.3 4.9	4.0	5.5	14	13 16	12	26
60 min								
Placebo	7.2	6.1 7.7	5.4	11.9	75	59 79	44	129
Miglitol	6.0	5.1 6.3	4.9	7.3	38	29 44	23	75
Acarbose	7.2	5.4 7.4	4.4	8.6	59	37 62	21	179
120 min								
Placebo	5.8	4.9 5.9	4.6	9.6	23	21 56	17	241
Miglitol	5.1	4.3 5.6	3.9	6.3	29	18 31	13	79
Acarbose	5.2	4.8 5.5	4.1	6.1	34	31 45	16	68
180 min								
Placebo	4.9	4.5 5.0	3.5	7.0	17	13 27	11	46
Miglitol	4.4	4.0 4.4	3.8	5.1	18	14 19	9	36
Acarbose	4.6	4.3 4.7	4.0	6.9	26	20 26	16	63

Figure 3 Mean $\pm$ s.d. serum levels of miglitol (●) and acarbose (□) related to the glucose curve (---) on placebo.

Discussion

The post-prandial lowering of blood glucose by alpha-glucosidase inhibitors such as miglitol and acarbose after a starch load, is well established. The mechanism of action is the inhibition of the last step in carbohydrate digestion, namely the conversion of disaccharide to monosaccharide (glucose) and a consequent decrease in the rate of entry of glucose into the systemic circulation.

The current study confirms our previous findings that miglitol also lowers post-prandial blood glucose after a glucose load. The nature of the blood glucose curves is however different after a glucose load when compared with a starch load. After a starch load, the time to peak and the peak height of the plasma glucose curve are reduced. These two parameters are however unchanged after a glucose load and plasma glucose suppression occurs post-peak. Acarbose, which is poorly absorbed, appeared to have no effect at all or perhaps an effect between that of placebo and miglitol. The insulin curves appeared to show the same trends as the glucose curves, but none of the differences between the drugs were statistically significant.

One could speculate on several mechanisms that could explain the effects observed when one considers the structural similarity between miglitol and glucose. As studies done in guinea-pig jejunum (Steinke, 1986) indicated that miglitol utilizes the same active transport system as glucose, one could expect miglitol to compete with glucose for active transport across various membranes. If competition for transport across the gut wall occurred, one would expect a decrease in pre-peak blood glucose values. As this was not the case, such an effect is unlikely. On the other hand for 100 mg of drug to interfere visibly with the absorption of 75 g of glucose would need an extremely high relative affinity

Figure 4 Box and whisker plots of insulin to glucose ratio and blood glucose found in this study (100 mg miglitol) and a previous study using 50 mg miglitol.

for the carrier. Interference with absorption could still be an explanation if one takes cognizance of the fact (Figure 3) that the glucose peak occurred well before the miglitol peak. It could be possible that at this stage where the amount of glucose still being absorbed is relatively small, interference with absorption can now become manifest.

If miglitol interfered with systemic glucose transport mechanisms one would expect an increase in blood glucose levels. If one wants to postulate an effect to explain our findings, a facilitation and not inhibition of transport needs to be presumed.

A further possible explanation could be enhanced insulin release, but there is no evidence from our data for this. The literature in fact reports a depression of insulin release from the rat isolated pancreas (Goke *et al.*, 1984). If one compares box and whisker plots of the data of this study (100 mg miglitol) with that of our previous study with 50 mg (Joubert *et al.*, 1987) it seems as if the two doses have similar blood glucose lowering effects, but the higher dose

showed a tendency for insulin to decrease (Figure 4). In view, however, of the complex homeostatic relationship between glucose and insulin, these observations should be treated with reservation.

The appearance of the miglitol blood glucose curve could also be consistent with enhanced glucose disposition, e.g. uptake into the cell or conversion to glycogen. On appearances this seems the most likely explanation, but further investigation is indicated.

If this effect of miglitol could be elucidated more clearly, it could lead to more rational ideas about dosage and timing of the dose. Furthermore one could look for similar chemical structures with a more pronounced effect.

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