Experience of 12-month therapy with acarbose, glibenclamide, and metformin in uncontrolled Saudi Type 2 diabetic patients

D H Akbar, T Zawawi, S Mira, K Marzoki and I Hashim

Abstract

We conducted this study to evaluate the effect of adding acarbose to a regimen of maximum glibenclamide and metformin combination on the glycaemic control of Saudi Type 2 diabetic patients. A total of 176 patients were included with mean age of 56 years and mean duration of diabetes of 8.7 years. There was a significant drop in the median fasting and postprandial blood glucose level and HbA1c from 11.6 mmol/L to 17.8 mmol/L (9.9%), to 6.9 mmol/L (7.1%), respectively (p < 0.001 for all). There was a significant change in the median body mass index or serum lipids during the study period. Gastrointestinal side-effects developed in 34% of patients but none of the patients developed any hypoglycaemic attacks. Acarbose can be combined successfully with glibenclamide and metformin for better glycaemic control in Type 2 diabetic patients.

Introduction

Acarbose is an α-glucosidase inhibitor that binds competitively to the carbohydrate-binding region of α-glucosidase enzyme. Administration of α-glucosidase inhibitors with carbohydrates will slow absorption. Instead of complete digestion of carbohydrates and absorption of monosaccharides in the proximal jejunum, the digestion in the jejunum is incomplete and the rise in postprandial glucose is diminished and delayed. Clinical trials on α-glucosidase inhibitors used as monotherapy compared to placebo showed their efficacy in reducing postprandial and fasting plasma glucose levels and a mean fall in HbA1c of 0.86%. Few studies have compared acarbose monotherapy with other oral hypoglycaemic agents. Some have showed relatively little difference between sulfonylureas, metformin, and acarbose, each associated with an approximately 1% decline in HbA1c. As α-glucosidase inhibitors lower blood sugar by a totally different mechanism compared to other oral hypoglycaemic agents, adding it to the treatment regimens of the other oral hypoglycaemic drugs is expected to lead to improvement in glycaemic control. Good glycaemic control is essential if the risk factors of diabetic complications are to be minimised. The aim of this study is to test the effect of adding acarbose to a regimen of maximum glibenclamide and metformin combination for the glycaemic control of Saudi Type 2 diabetic patients being followed at King Abdulaziz University Hospital (KAUH) and to report on side-effects of treatment.

Method

This was a prospective study, in which Saudi Type 2 diabetic patients being followed at the KAUH outpatient clinics who were poorly controlled on maximun doses of combined oral hypoglycaemic agents (glibenclamide, 10 mg twice daily, and metformin, 500 mg three times daily) used for a period of 12 weeks, with good dietary and drug compliance, were selected. Patients were referred to a dietician for dietary control and they were maintained on the same diet during the study period. Uncontrolled blood glucose was defined as an HbA1c level >7%. The diagnosis of diabetes was based on World Health Organisation criteria. All patients with documented gastrointestinal disease and those taking medications likely to alter gut motility or absorption were excluded. Patients’ age, sex, body mass index (BMI), duration of diabetes, history of hypertension (defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg) and hyper-liipidaemia (defined as total cholesterol >5.2 mmol/L, triglyceride >2.3 mmol/L, HDL-cholesterol <0.9 mmol/L, or LDL-cholesterol >3.4 mmol/L) were recorded, as well as a history of any concurrent illnesses, and use of medications. Complete physical examination and the following investigations were done at the beginning of the study – fasting and 2-hour postprandial blood glucose, HbA1c, complete blood count (CBC), urea and electrolytes, liver enzymes, bilirubin, albumin, serum cholesterol, triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)-cholesterol. Patients were given acarbose tablets in addition to their oral hypoglycaemic agents (for dosage recommendations see Table 1). Patients were seen at 4-weekly intervals. On each visit, compliance was checked by tablet count and the development of any adverse events was reported. Physical examination, body weight, and repeat biochemistry were done each time, while HbA1c was measured every 3 months during the study.

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Table 1 Dosage recommendations for acarbose treatment

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<th>Breakfast</th>
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period, which was 12 months. The dose of acarbose was increased according to blood glucose control, according to the patient’s tolerance and absence of side-effects. Desirable blood glucose control was defined as an HbA1c <7%, fasting blood glucose <8 mmol/L, and a 2-hour postprandial blood sugar <11 mmol/L.

Blood samples were collected in plain and EDTA tubes. Analyses were performed on the 911 Hitachi autoanalyzer. LDL-cholesterol values were calculated using the Friedwald formula. Data analyses were performed using SPSS 7.5 statistics computer software.

Results
A total of 212 patients participated in the study. Thirty-six patients (18% - 16 females and 20 males) were withdrawn from the study as they could not tolerate the gastrointestinal side-effects of acarbose. The remaining 176 patients finished the whole study period of 12 months. The median age of the patients was 56 years (57-74) with a male: female ratio of 1.2:1. The mean duration of diabetes was 8.7 years (8 months - 20 years). Seventy-six patients (43%) were hypertensive and 18 (10%) were hyperlipidaemic. The median serum lipid levels at baseline for all patients were 1.9 mmol/L for TG, 5.1 mmol/L for cholesterol, 3.3 mmol/L for LDL, and 1.1 for HDL, which did not change significantly during the study period. Also, no significant change in the median BMI was observed before and after acarbose treatment (28 and 28.5 respectively). A significant drop in the median fasting plasma glucose was noticed (11.6 mmol/L to 6.9 mmol/L, p < 0.001), and the same was true for postprandial plasma glucose (17.8 mmol/L to 10 mmol/L, p < 0.001). Median HbA1c at baseline was 9.9%, and 7.1% at the end of the study period (p < 0.001). Sixty patients (34%) developed mild gastrointestinal side-effects, mainly in the form of epigastric discomfort and flatulence, but they continued their treatment. No patients developed any hypoglycaemic attacks.

Discussion
Persistent hyperglycaemia has been linked to the development of diabetic complications, and to the exaggeration of insulin resistance and impaired insulin secretion characterising the pathophysiology of Type 2 diabetes. Secondary failure of oral hypoglycaemic agents is common, and more than 25% of patients with Type 2 diabetes require insulin to achieve acceptable glycaemic control. Acarbose reduces postprandial plasma glucose and insulin responses. We found a significant reduction in the postprandial plasma glucose (from 17.8 mmol/L to 10 mmol/L, p < 0.001). The clinical relevance of the effect of acarbose on postprandial hyperglycaemia is highlighted by the significant decrease in HbA1c from 9.9% to 7.1% (p < 0.001). The decrease in HbA1c levelled off at slightly more than 7%, a result similar to that obtained in the diabetes complication clinical trial (DCCT) for an experimental group of patients with Type 1 diabetes, who were receiving intensive insulin therapy, and also Type 2 diabetic patients in the United Kingdom Prospective Diabetes Study (UKPDS). Although most studies in patients with Type 2 diabetes have not shown any effect of acarbose on fasting plasma glucose levels, a few studies have shown some beneficial effects of the drug on these levels, finding similar to our results. The lowering effect of acarbose on fasting plasma glucose levels might be explained by decreased glucose toxicity with improvement in insulin sensitivity and β-cell response to glucose.

The effect of acarbose on serum triglyceride levels is variable; some studies showed a small decrease in fasting and postprandial serum triglyceride, while others have not shown any effect – finding similar to ours. No change in BMI has been noticed in patients receiving acarbose. The major side-effects of acarbose are gastrointestinal and are a result of the pharmacological action of the drug. The most frequent gastrointestinal symptoms are flatulence, diarrhoea, and abdominal discomfort – developing in 34% of our patients. These effects may be mitigated by beginning therapy at a low dose and slowly increasing to the maximally effective dose. Elevation of liver enzymes may rarely occur with acarbose treatment, but none of our patients developed any disturbance in liver enzymes. Also, none developed hypoglycaemic attacks. Acarbose, with its novel mechanism of action, is of potential benefit. Its antihyperglycaemic effect targets mainly postprandial hyperglycaemia, which means that it can be combined successfully with other agents such as sulphonylureas and metformin, as shown by our results and reported by Lam et al. The lack of serious side-effects, absent hypoglycaemic risk, and absence of body weight changes make it a safe and well tolerated drug that can be used in patients with Type 2 diabetes for better plasma glucose control.

References

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