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Assessing the Antihyperglycemic Effect of Acarbose

Solid or liquid test meal?

The α-glucosidase inhibitor acarbose improves glycemic control by slowing carbohydrate absorption and reducing the rise of blood glucose levels after eating (1). Postprandial blood glucose has been measured in clinical trials to titrate the dose of acarbose (2), a procedure that may be useful in clinical practice. For this purpose, a standard test meal is required because the type and amount of carbohydrate influence glycemic responses (3). Meals containing glucose or lactose (milk) cannot be used because acarbose does not affect their absorption. Liquid formulas have been used for convenience (2), but they may not have the same effect as a normal diet.

To see whether the nature of the test meal influenced the antihyperglycemic effect of acarbose, six normal subjects (three men and three women: aged 34 ± 4 years; BMI 23.9 ± 1.4 kg/m^2) and six diabetic subjects (four men and two women: aged 62 ± 3 years; BMI 31.3 ± 2.0 kg/m^2; four treated by diet alone and two receiving glyburide) were studied on four separate mornings after overnight fasts. Each morning, subjects consumed either a liquid or a solid mixed meal with 50 mg acarbose or placebo, according to a randomized Latin square design. The liquid meal (336 ml Ensure, Abbott, Saint-Laurent, Quebec, Canada) contained 357 kcal, 54.5 g carbohydrate (50.0 g dextrins and sugars; 4.5 g dietary fiber), 9.6 g fat, and 13.4 g protein. The solid meal (Diabetes Screening Product [DSP], Ceapro, Edmonton, Alberta, Canada), containing 360 kcal, 53.8 g carbohydrate (41.1 g starch, 8.9 g sugars, and 3.8 g dietary fiber), 10.7 g fat, and 12.1 g protein, was taken with 1 cup of water. The DSP is a standardized test meal in the form of five wafers made from oats, honey, canola oil, and soy protein. Capillary blood glucose was measured before and at various intervals after the subjects started to eat, using a YSI analyzer (YSI, Yellow Springs, OH). Incremental areas under the curve (AUCs) were calculated geometrically (4). Blood glucose concentrations and AUCs after administration of acarbose and placebo were compared separately for each test meal and each subject group by the paired *t* test.

In normal subjects, acarbose had no significant effect on glycemic responses compared with placebo after the liquid meal, but blood glucose was significantly reduced at 15, 30, and 45 min after administration of the DSP (Fig. 1). The reduction of blood glucose AUCs by acarbose was not significant after the liquid meal (−35 ± 20%) but was significant after administration of the DSP (30 ± 11%; $P < 0.05$). In diabetic subjects, acarbose significantly reduced blood glucose after the liquid meal at 90 and 120 min and reduced AUC by 37 ± 5% ($P < 0.01$). After administration of the DSP, acarbose reduced blood glucose significantly at 30, 60, 90, and 120 min and reduced AUC by 38 ± 7% ($P < 0.01$). In diabetic subjects, the mean reduction in blood glucose induced by acarbose 60 min after administration of the DSP (2.7 ± 0.3 mmol/l) was

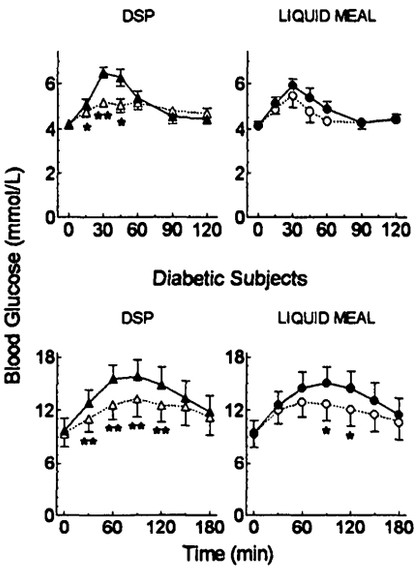

Figure 1—*Blood glucose responses in six normal and six diabetic subjects after a solid test meal (DSP) (▲) or liquid test meal with placebo (●) or 50 mg acarbose (△, ○). Values are means ± SE. *P < 0.05; **P < 0.01.*

1.7 times that after administration of the liquid meal (1.6 ± 0.6 mmol/l).

These results suggest that the antihyperglycemic effect of acarbose is more quickly and reliably demonstrated using a standardized starch-based test meal such as the DSP than after a liquid test meal. This difference is partly explained by the somewhat greater rise of blood glucose levels after the DSP than after the liquid meal. The delayed effect of acarbose after the liquid meal may also occur because the carbohydrate it contains, soluble dextrins and sucrose, empties more quickly from the stomach than does the starch in the solid meal, so that gastric emptying of the carbohydrate occurs before the acarbose tablet can dissolve and become active. One possible implication of these data is that the use of a liquid test meal to titrate acarbose dosage may result in the prescription of a higher dose than necessary to reduce blood glucose responses after normal solid meals. This higher dose, in turn, would tend to increase the chance of side effects and reduce patient compliance.

Measurement of blood glucose before and 60 min after, or even 30 min after, administration of the DSP alone, and after administration of DSP plus acarbose on another occasion, may be useful in clinical practice to guide acarbose dosage or to demonstrate to patients the magnitude of

the drug's effect, which in turn may enhance drug efficacy and patient compliance.

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T.M.S.W. holds stock in Ceapro, has received honoraria from Bayer, and has been a paid consultant of Bayer and Ceapro.

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Gestational Diabetes Mellitus Is Associated With an Increase in the Total Concentration of Amylin Molecules

Fasting concentrations of amylin, a 37 amino acid polypeptide secreted by the pancreatic β-cells, have been shown to be elevated in a number of conditions associated with insulin resistance (1), but have not been systematically studied in gestational diabetes mellitus (GDM). Previous studies in GDM have been small and may not have been appropriately matched for other factors that could have an influence on amylin concentrations (2,3). A recent paper showed an elevation in pregnancy but no significant difference between women with GDM and pregnant control subjects (4). To describe the association between GDM and fasting and post-glucose amylin concentrations, we therefore undertook a matched case-control study, using stored plasma samples from a previously conducted study of glucose tolerance in pregnancy (5).

Patients and control subjects were identified from a cohort study of all pregnant women in Cambridgeshire, U.K., who attended the antenatal clinic between August 1992 and July 1993. A total of 63 women were diagnosed as having GDM on the basis of a 3rd-trimester 75-g oral glucose tolerance test (OGTT). Of these, 52 women had complete biochemical data and were selected as patients for this study. Those 52 women who had a normal 3rd-trimester OGTT were selected as control subjects and were individually matched with patients by age and BMI. There was no significant difference in the gestational age at the time of the OGTT between patients (mean 31.8 ± 2.6 weeks) and control subjects (32.7 ± 1.8 weeks). Amylin was measured at all time points during the OGTT using two different assays (6). The first measures unmodified amylin, and the other measures the total of all amylin molecules. The difference between the total and unmodified amylin is mainly due to the presence of amylin molecules that have been modified by the attachment of O-linked oligosaccharide groups at threonine residues near the NH_2-terminus (7).

There was no significant difference in the concentration of unmodified amylin in women with GDM compared with control subjects at fasting or 30 or 90 min after the glucose load. At 120 min, there was a significant elevation in women with GDM (geometric mean 4.38 pmol/l, 95% CI 3.3–5.9) compared with control subjects (geometric mean 2.42 pmol/l, 95% CI 1.8–3.2, $P = 0.03$). In contrast, the concentration of total amylin was significantly higher in women with GDM compared with control subjects at each time point during the OGTT. The fasting concentration in women with GDM was 5.13 pmol/l (95% CI 3.7–7.1) compared with 2.58 pmol/l (95% CI 2.1–3.2) in control subjects ($P < 0.001$).

Patients and control subjects were allocated to quartiles on the basis of their fasting total amylin concentration. The relationship between the concentrations of total amylin and GDM was then determined using conditional logistic regression analysis. A strong linear association was demonstrated with an odds ratio for GDM per quartile of fasting total amylin of 2.31 (95% CI 1.5–3.5, $P < 0.001$). The odds ratio for the top quartile compared with the bottom quartile was 10.0, demonstrating the strength of this association. In contrast, when a similar analysis was undertaken using quartiles for fasting intact proinsulin, which we have previously demonstrated to be elevated in GDM, the odds per quartile was 1.48 (1.02–2.14), suggesting that the association of elevated fasting total amylin with GDM was much stronger. Because amylin has been shown to be co-secreted with insulin (8), we also examined the extent to which this association was independent of insulin by introducing this as a covariate in the logistic model. The overall association between quartile of fasting total amylin and GDM was unaffected (odds ratio 2.28, 95% CI 1.49–3.51), suggesting that this association cannot be explained by confounding by insulin concentrations.

We conclude from this study that concentrations of total amylin are increased in women with GDM compared with age- and BMI-matched pregnant control subjects of a similar gestational age. This association is stronger than that between intact proinsulin and GDM and cannot simply be explained by confounding by insulin. There was no elevation of fasting unmodified amylin in women with GDM. Although this could be explained by the fact that the concentrations of unmodified amylin are lower than that of total amylin and the power to detect a true difference was therefore greatest for total amylin, it is also possible that it is the glycosylated forms of amylin that are elevated in GDM. Further research should be directed toward the development of assays to measure these amylin species directly and to understand their pathophysiological role and usefulness as markers of diabetes risk.

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