ALPHA-GLUCOSIDASE INHIBITORS

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Alterations in the composition and caloric content of the diet have profound influences on the development of non-insulin-dependent diabetes mellitus (NIDDM) and the treatment of all individuals with diabetes mellitus.\(^{26,44}\) The peak rise in blood glucose following a meal is normally limited to approximately 30 to 50 mg/dL and is the result of the net balance between the rate of carbohydrate being absorbed from the gastrointestinal tract and the rate at which it is taken up by the liver and peripheral tissues. The factors controlling this balance are (1) the rate of nutrient propulsion through the gastrointestinal tract, (2) the quantity and kinetics of the digestive enzymes, (3) the rate and quantity of insulin secreted, and (4) the responsiveness of the liver and peripheral tissues to the secreted insulin. Although the insulin secretory response to ingested carbohydrate is determined by the rise in blood glucose, it is also amplified by the secretion of nutrient-stimulated gastrointestinal hormones such as gastric inhibitory polypeptide (GIP) and glucagonlike peptide 1 (GLP-1).\(^{17,28}\)

Dietary interventions to control hyperglycemia and diabetic dyslipidemia are the cornerstone of treatment for diabetic patients.\(^{38}\) In patients with insulin-dependent diabetes mellitus (IDDM), dietary management is integrated with insulin treatment to minimize early postprandial hyperglycemia and prevent late postprandial hypoglycemia. In patients with NIDDM, dietary management, although frequently focused on weight reduction, is also directed specifically at the management of hyperglycemia. Several studies have shown that short-term severe caloric restriction will lower fasting plasma glucose dramatically and increase insulin secretory function, and that this is not related to weight loss.\(^{16}\)

These types of observations led to the hypothesis that drugs which act on the gastrointestinal tract to interfere with carbohydrate digestion might be useful agents in the treatment of diabetes.\(^{40}\) Fifteen years of clinical investigation have provided evidence that such a therapeutic approach does indeed benefit diabetic individuals and has some unique characteristics.

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POSTPRANDIAL HYPERGLYCEMIA

Hyperglycemia in diabetic individuals is the result of an absolute or relative deficiency of insulin. Metabolic processes have different dose-response relationships for insulin. Insulin-mediated glucose uptake by adipose tissue and muscle occurs over an insulin concentration of 30 to 500 μU/mL. Suppression of hepatic glucose production is controlled by portal vein insulin concentrations of 10 to 50 μU/mL, and antilipolytic effects on adipose tissue are regulated at insulin concentrations of 1 to 20 μU/mL.

As insulin secretion becomes deficient, the earliest manifestation is a rise in the postprandial plasma glucose, because muscle is primarily responsible for the uptake of glucose after a meal, and this process requires the highest concentrations of insulin. At this stage in the evolution of diabetes, 2-hour postprandial plasma glucose will range from 140 to 199 mg/dL (impaired glucose tolerance) and then rise to greater than 200 mg/dL (diabetes). Fasting plasma glucose is less than 130 mg/dL in 58% of individuals with early NIDDM. Fasting plasma glucose above 125 mg/dL occurs as insulin deficiency becomes severe. Ketoacidosis occurs only when insulin secretion is virtually absent.

Postprandial hyperglycemia is usually present for 4 to 7 years before fasting hyperglycemia becomes evident. At any one time, approximately 30% of patients with NIDDM have predominately postprandial hyperglycemia.

Diabetic complications, both macrovascular and microvascular, begin to develop during the phase when postprandial hyperglycemia is the predominant abnormality. Death from myocardial infarction is 2 to 2.5 fold greater in individuals with impaired glucose tolerance in comparison with individuals with normal glucose tolerance. The Honolulu Heart Study revealed a significant correlation between the 1-hour postglucose challenge blood serum glucose level and the development of coronary heart disease. Several studies have shown that retinopathy is present in approximately 15% to 20% of newly diagnosed patients with NIDDM and coronary heart disease in 5% to 15%.

During pregnancy, fetal weight and size are highly correlated with the 1-hour postprandial blood glucose level of the mother. Complications which occur as a result of postprandial hyperglycemia may be the result of the high glucose levels themselves (e.g., retinopathy and microvascular disease), the associated absolute hyperinsulinemia (e.g., fetal macrosomia), or a combination of associated abnormalities (e.g., macrovascular disease).

Postprandial hyperglycemia is an important component of the elevated hemoglobin A1C levels seen in diabetic patients, and studies in pregnant women show that monitoring blood glucose with 1-hour postprandial glucose determinations results in significantly better overall glycemic control (hemoglobin A1C levels) and a reduction in obstetric complications in comparison with monitoring fasting plasma glucose. These and other data support the concept that treatment of fasting and postprandial hyperglycemia must be viewed as somewhat separate although partially related entities.

GASTROINTESTINAL REGULATION OF CARBOHYDRATE METABOLISM

The ingestion of a carbohydrate-rich meal causes a series of complex physiologic events which culminate in the utilization or storage of the carbohydrate. The initial entry of food into the mouth activates salivary gland amylase which has a small effect in cleaving starches. The food immediately enters the stomach where enzyme activity is stopped due to the acid pH. Gastric emptying can be influenced by many factors, including the level of blood glucose (hyperglycemia slows gastric emptying), GIP and GLP-1 serum levels, and the composition of the diet. 

Glycogen entry into the duodenum, complex carbohydrates are cleaved by pancreatic amylase into oligosaccharides. Oligosaccharides and disaccharides cannot be absorbed. They are bound to enzymes located in the brush border of the enterocytes of the jejunum called alpha-glucosidases. Following binding, the oligosaccharides and disaccharides are cleaved to monosaccharides which are immediately absorbed. Most carbohydrate is digested and absorbed in the upper jejunum. Little carbohydrate reaches the distal jejunum or ileum, and alpha-glucosidase levels in these enterocytes are low compared with the binding.

When glucose is transported across the enterocytes of the duodenum and jejunum, it stimulates the release of GIP into the plasma. The presence of carbohydrate in the lumen of the duodenum and jejunum originates a neurogenic stimulus which causes ileal mucosal cells to release GLP-1 into the plasma.

Both GIP and GLP-1 when elevated cause a delay in gastric emptying and amplify glucose-mediated insulin secretion to plasma levels greater than 120 mg/dL but not to fasting plasma levels less than 110 mg/dL. Gastrointestinal hormones thus help beta cells to increase insulin secretion appropriate to the magnitude of the carbohydrate load.

In NIDDM, several aspects of the pathophysiology disturb the normal gastrointestinal regulation of carbohydrate metabolism. As noted previously, hyperglycemia may cause gastric dilatation and delayed emptying. GIP secretion is inhibited, and GIP action is blunted. The beta cell becomes relatively insensitive to glucose, and there is a marked delay in the onset of insulin secretion following a meal. This delay leads to exaggerated postprandial hyperglycemia and, in the patient with relative hyperinsulinemia, can cause late postprandial hypoglycemia.

PHARMACOLOGY OF ALPHA-GLUCOSIDASE INHIBITORS

Currently available alpha-glucosidase inhibitors include acarbose, voglibose, and miglitol (Fig. 1). Acarbose is a nitrogen-containing pseudotetrasaccharide. Voglibose is a valiolamine derivative and miglitol a deoxynojirimycin derivative. Both acarbose and voglibose are of microbial origin, whereas miglitol is synthetically derived. Acarbose and voglibose act primarily in the gut because neither is significantly absorbed (acarbose < 2%; voglibose, approximately 3% to 5%).

Miglitol is rapidly absorbed through a transport mechanism in the jejunum which is, in part, identical to that for glucose. Miglitol is excreted quantitatively unchanged by the kidney. Although acarbose is poorly absorbed, cleavage products produced by bacterial enzymes in the colon result in 33% absorption of an administered radioactive acarbose. Acarbose digestion by bacterial enzymes results in metabolizable intermediates and 4-methylpyroglutal which is conjugated and excreted as sulfates or glucuronidates.

The mechanisms of action of the alpha-glucosidase inhibitors are similar although not identical. They all bind competitively to the carbohydrate-binding region of alpha-glucosidase enzymes. Therefore, they compete with the binding of oligosaccharides to the enzymes and interfere with their cleavage to monosaccharides.

Several aspects of the binding are noteworthy. Acarbose binds to intestinal sucrase with 106 to 107 greater binding affinity than sucrase. Acarbose inhibits intestinal brush border glucoseamyrase, maltase, sucrase, and dextrinase, as well...
hydrate spills into the large intestine where bacteria metabolize the carbohydrate to short-chain fatty acids, hydrogen, carbon dioxide, and methane. The magnitude and time course of the postprandial glycemic rise depend on the carbohydrate content of the diet, the extent of inhibition of alpha-glucosidase enzymes in the proximal jejunum, and the alpha-glucosidase enzyme activities in the distal jejunum and ileum.

Based on current understanding of the regulation of glucose metabolism, it is anticipated that alpha-glucosidase inhibitor administration would decrease plasma insulin and GLP levels and increase plasma GLP-1 in the late postprandial period. Initial treatment should lead to extensive leakage of carbohydrate into the large intestine unless very small doses are administered and the treatment algorithm provides time for enzyme induction in the distal small bowel before full therapeutic doses are used.

Because leakage of carbohydrate into the large intestine results in metabolism to short-chain fatty acids, no caloric loss occurs, and evidence of carbohydrate malabsorption is obscure. The most reliable method of assessing the leakage of carbohydrate into the colon is the measurement of hydrogen in exhaled air (breath hydrogen measurement). Plasma levels of acetate are elevated during alpha-glucosidase inhibitor treatment, but the magnitude of change is small, and the correlation with breath hydrogen is relatively poor.

CLINICAL EFFICACY OF ALPHA-GLUCOSIDASE INHIBITORS ON GLYCEMIC CONTROL

The primary benefits achieved by alpha-glucosidase inhibitor therapy in diabetic patients would be a reduction in postprandial glycemia and a decrease in the extremes between maximal and minimal postprandial glucose levels. A reduction in postprandial glycemia should be beneficial in patients with NIDDM and result in decreases in HbA1c. A decrease in the fluctuation between postprandial glucose levels should be of value in patients with IDDM and decrease hypoglycemic episodes, allowing better glucose regulation.

Results in Patients with NIDDM

Table 1 summarizes the results of published studies in which monotherapy with an alpha-glucosidase inhibitor has been compared with placebo in large prospective randomized trials. All of the studies used acarbose, and the dose in many was excessive. The most valid studies are those using 150 to 300 mg/day. The overall conclusions from these studies are as follows:

1. Maximum effects of acarbose are achieved at a dosage of 100 mg three times a day.
2. A mean decrease in postprandial plasma glucose of approximately 50 mg/dL is to be expected.
3. The mean fall in HbA1c is 0.86%, with a range of 0.6% to 1.4%.
4. The mean fall in fasting plasma glucose is 21.8 mg/dL.

Few studies have compared acarbose monotherapy with other oral antidiabetic agents. Published reports are presented in Table 2 and show relatively little...
Table 1. PROSPECTIVE RANDOMIZED PLACEBO-CONTROLLED TRIALS OF THE Efficacy of Alpha-Glucosidase Inhibitors on Glycemic Control in Diet-Treated Patients with NIDDM

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Dose (mg/day)</th>
<th>Duration (weeks)</th>
<th>Change in Plasma Glucose (mg/dL)</th>
<th>Fasti ng Post-prandial</th>
<th>Change in HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanefeld et al**</td>
<td>94</td>
<td>300</td>
<td>24</td>
<td>-15</td>
<td>-53</td>
<td>-0.6</td>
</tr>
<tr>
<td>Hotta et al**</td>
<td>37</td>
<td>300</td>
<td>24</td>
<td>-1</td>
<td>-65</td>
<td>-1.0</td>
</tr>
<tr>
<td>Santus et al**</td>
<td>62</td>
<td>150</td>
<td>16</td>
<td>-1</td>
<td>-90</td>
<td>-0.90</td>
</tr>
<tr>
<td>Hoffman and Spengler**</td>
<td>58</td>
<td>300</td>
<td>24</td>
<td>-25</td>
<td>-40</td>
<td>-1.1</td>
</tr>
<tr>
<td>Chiasson et al</td>
<td>67</td>
<td>150–600</td>
<td>52</td>
<td>-39</td>
<td>-81</td>
<td>-0.9</td>
</tr>
<tr>
<td>Coniff et al</td>
<td>180</td>
<td>150–900</td>
<td>24</td>
<td>-16</td>
<td>-50</td>
<td>-0.7</td>
</tr>
<tr>
<td>Coniff et al</td>
<td>120</td>
<td>600</td>
<td>24</td>
<td>-22</td>
<td>-49</td>
<td>-0.7</td>
</tr>
<tr>
<td>Coniff et al</td>
<td>122</td>
<td>300</td>
<td>16</td>
<td>-27</td>
<td>-76</td>
<td>-0.76</td>
</tr>
<tr>
<td>Braun et al</td>
<td>96</td>
<td>300</td>
<td>24</td>
<td>-23</td>
<td>-32</td>
<td>-1.4</td>
</tr>
<tr>
<td>Lindstrom et al</td>
<td>75</td>
<td>300</td>
<td>24</td>
<td>-25</td>
<td>-52</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

The addition of acarbose or miglitol to sulfonylurea-, metformin-, or insulin-treated patients with NIDDM results in improved glycemic control. Their addition to sulfonylureas reduces HbA1c approximately 1.1%; to metformin, 0.8%; and to insulin, 0.5%.

Results in Patients with IDDM

Relatively few studies have investigated the use of alpha-glucosidase inhibitors in patients with IDDM. Two types of benefits are reported. First, the addition of acarbose to an insulin treatment regimen improves glycemic control.

Table 2. PROSPECTIVE RANDOMIZED CONTROLLED TRIALS COMPARING EFFICACY OF ALPHA-GLUCOSIDASE INHIBITORS WITH OTHER ORAL ANTIDIABETIC AGENTS ON GLYCEMIC CONTROL IN PATIENTS WITH NIDDM

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (weeks)</th>
<th>Antidiabetic Drug</th>
<th>Dose (mg/day)</th>
<th>Number of Patients</th>
<th>Change in Blood Glucose (mg/dL)</th>
<th>Fasti ng Post-prandial</th>
<th>Change in HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman and Spengler**</td>
<td>24</td>
<td>Acarbose</td>
<td>300</td>
<td>32</td>
<td>-29</td>
<td>-60</td>
<td>-1.3</td>
</tr>
<tr>
<td>Coniff et al**</td>
<td>24</td>
<td>Metformin</td>
<td>1700</td>
<td>32</td>
<td>-25</td>
<td>-34</td>
<td>-1.1</td>
</tr>
<tr>
<td>Hoffman and Spengler**</td>
<td>24</td>
<td>Acarbose</td>
<td>600</td>
<td>67</td>
<td>-22</td>
<td>-49</td>
<td>-0.76</td>
</tr>
<tr>
<td>Hoffman and Spengler**</td>
<td>24</td>
<td>Acarbose</td>
<td>750–2000</td>
<td>66</td>
<td>-36</td>
<td>-59</td>
<td>-1.27</td>
</tr>
<tr>
<td>Hoffman and Spengler**</td>
<td>24</td>
<td>Acarbose</td>
<td>300</td>
<td>28</td>
<td>-25</td>
<td>-40</td>
<td>-1.1</td>
</tr>
<tr>
<td>Hoffman and Spengler**</td>
<td>24</td>
<td>Acarbose</td>
<td>3.5–10.5</td>
<td>27</td>
<td>-29</td>
<td>-34</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

Table 3. PROSPECTIVE RANDOMIZED PLACEBO-CONTROLLED TRIALS OF THE EFFICACY OF ADDITION OF ALPHA-GLUCOSIDASE INHIBITORS TO PATIENTS WITH NIDDM INADEQUATELY CONTROLLED ON OTHER ANTICYPERGLYCEMIC AGENTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (weeks)</th>
<th>Antidiabetic Drug</th>
<th>Number of Patients</th>
<th>Added Drug and Dose (mg/day)</th>
<th>Change in Blood Glucose (mg/dL)</th>
<th>Fasti ng Post-prandial</th>
<th>Change in HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiasson et al</td>
<td>52</td>
<td>Metformin</td>
<td>74</td>
<td>Acarbose, 150–600</td>
<td>-10</td>
<td>-63</td>
<td>-0.8</td>
</tr>
<tr>
<td>52</td>
<td>Sulfonylurea</td>
<td>90</td>
<td>Acarbose, 150–600</td>
<td>-25</td>
<td>-74</td>
<td>-0.9</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Insulin</td>
<td>79</td>
<td>Acarbose, 150–600</td>
<td>0</td>
<td>-49</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td>Coniff et al</td>
<td>24</td>
<td>Tolbutamide</td>
<td>122</td>
<td>Acarbose, 600</td>
<td>-8</td>
<td>-25</td>
<td>-0.51</td>
</tr>
<tr>
<td>Rayne et al</td>
<td>8</td>
<td>Sulfonylurea</td>
<td>18</td>
<td>Acarbose, 300</td>
<td>-50</td>
<td>-95</td>
<td>-2.2</td>
</tr>
<tr>
<td>8</td>
<td>Sulfonylurea</td>
<td>18</td>
<td>Metformin, 1500</td>
<td>-31</td>
<td>-52</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>May**</td>
<td>12</td>
<td>Glibenclamide</td>
<td>109</td>
<td>Acarbose, 300</td>
<td>-32</td>
<td>-52</td>
<td>-1.2</td>
</tr>
<tr>
<td>Coniff et al**</td>
<td>24</td>
<td>Insulin</td>
<td>207</td>
<td>Acarbose, 150–900</td>
<td>-16</td>
<td>-47</td>
<td>-0.53</td>
</tr>
<tr>
<td>Johnston et al**</td>
<td>14</td>
<td>Sulfonylurea</td>
<td>192</td>
<td>Miglitol, 150</td>
<td>-17</td>
<td>-57</td>
<td>-0.82</td>
</tr>
</tbody>
</table>

In a 6-month open-label study, Dimitriadis and coworkers found that acarbose, 100 mg three times daily, reduced postprandial blood glucose peaks by 20% to 30% and insulin requirements by 40% when assessed at 1 and 6 months in comparison with placebo at time 0 by 24 hours on the Biostat (Beckman, CA). In a recent double-blind randomized placebo-controlled study of 236 patients with type I diabetes, patients given acarbose, 50 to 300 mg three times daily, for 24 weeks showed a decrease in HbA1c of 0.5% in comparison with patients receiving a placebo without a significant change in either insulin dose or hypoglycemic events. McCulloch and coworkers used acarbose, 100 mg before the evening meal, to reduce nocturnal hypoglycemia in a few patients and showed positive benefits. Further studies are needed to demonstrate conclusively the value of alpha-glucosidase inhibitor treatment in patients with type I diabetes.

OTHER THERAPEUTIC EFFECTS OF ALPHA-GLUCOSIDASE INHIBITORS

Metabolic Parameters

Alpha-glucosidase inhibitors lower plasma insulin levels in patients with normal or high levels by virtue of decreasing the glycemic stimulus to insulin secretion. Alpha-glucosidase inhibitors have not caused improvements in insulin sensitivity as measured by euglycemic insulin clamp when given to patients with type II disease. However, when acarbose, 100 mg three times
daily, was administered for 4 months to subjects with impaired glucose tolerance and marked hyperinsulinemia for 4 months, a marked reduction in meal-mediated insulin secretion and a modest improvement in insulin action were found.\(^5\)

Alpha-glucosidase inhibitors reduce postprandial GLP secretion but increase GLP-1 secretion from 30 to 240 minutes postprandially.\(^5,15\) This effect may be mediated by the presence of carbohydrate in the ileum during alpha-glucose inhibitor treatment. The physiologic effect of the elevated GLP-1 plasma levels is not known but is being actively investigated.

Treatment with alpha-glucosidase inhibitors has been associated with small decreases in fasting or postprandial serum triglycerides in some studies.\(^36,40\) In general, however, these agents do not seem to have primary effects on either triglyceride or cholesterol metabolism. They do not cause significant changes in body weight.

A recent study by Ceriello and co-workers\(^3\) suggests that alpha-glucosidase treatment may have an additional metabolic benefit. Postprandial hyperglycemia activates coagulation as measured by rises in plasma concentrations of prothrombin fragments 1 and 2 and D-dimer (derived from fibrinogen). Reduction of postmeal hyperglycemia in patients with NIDDM with acarbose reduces this phenomenon. The ultimate benefit for preventing thromboembolic complications is speculative.

Treatment of Reactive Hypoglycemia

A logical therapeutic extension of the pharmacologic effects of alpha-glucosidase inhibitors is the treatment of nondiabetic postprandial hypoglycemia. Gerard and co-workers\(^4\) have shown that acarbose in doses of 100 mg significantly reduces the late postprandial hypoglycemia that occurs in patients with rapid gastric emptying, impaired glucose tolerance, and isolated reactive hypoglycemia. A small number of patients treated chronically with acarbose have had improvement of clinical symptoms. A large well-controlled study is needed to confirm these results.

Effects on the Colon

Treatment with an alpha-glucosidase inhibitor always results in minor spilage of oligosaccharides into the colon.\(^25,38,40\) Additionally, colonic bacteria metabolize agents such as acarbose.\(^39\) Concern arises as to the chronic effect, if any, that acarbose treatment has on the colon.

Chronic treatment (1 year) with acarbose increases fecal wet weight by approximately 50%.\(^30\) Short-chain fatty acid output in the stool increases by 212%.\(^30\) Fecal pH decreases by about 0.7 units. The short-chain fatty acids which increase are primarily acetate, propionate, and butyrate.\(^26,40,45\) Bacterial flora do not change.\(^36\) Rectal biopsy does not reveal any hyperplasia or change in rectal proliferation.\(^36\) Increases in breath hydrogen correlate well with the increased production of short-chain fatty acids.\(^26,40,45\) It can be concluded from all of the pertinent gastrointestinal tract studies that chronic acarbose treatment does not cause any detrimental effects on the colon and may, in fact, actually reduce the risk of colonic neoplasia because of the short-chain fatty acid production. The increased bulk of the stools will obviously lead to softer stools.

GUIDELINES FOR THE USE OF ALPHA-GLUCOSIDASE INHIBITORS IN THE TREATMENT OF DIABETIC PATIENTS

The practical use of alpha-glucosidase inhibitors in the treatment of diabetes is based on knowledge of their mechanism of action, their efficacy in improving glycemic control, and their side-effect profile.

The most dramatic effect of these agents is on postprandial plasma glucose levels, they should be considered a first-line treatment for diabetic individuals in whom postprandial hyperglycemia is significantly greater than fasting hyperglycemia. This group includes patients with impaired glucose tolerance, the estimated 8 million undiagnosed diabetic individuals, and older individuals in whom postprandial hyperglycemia is exaggerated by the known effect of aging. The 0.5% to 1.0% decrease in HbA\(_{1c}\) which is to be expected can be obtained without risk for hypoglycemia or, in predisposed patients, lactic acidosis. In a recent study of monotherapy in older patients with NIDDM (mean age, 68 years), glyburide therapy (median dose, 3.75 mg/day) was associated with self-monitored premeal blood glucose levels of less than 60 mg/dL 0.7% of the time in comparison with miglitol therapy, associated with such levels 0.1% of the time.\(^40\)

In individuals with more marked fasting hyperglycemia (greater than 200 mg/dL), alpha-glucosidase inhibitors are most effective in combination with sulfonylurea, metformin, or insulin in reducing HbA\(_{1c}\), to target goals.

Therapy with alpha-glucosidase inhibitors must be initiated with very small doses, and the incremental increase in dose must be dictated by the magnitude of gastrointestinal side effects. This permits the induction of alpha-glucosidase enzymes in the distal jejunum and ileum. Additionally, it is essential that the alpha-glucosidase inhibitor be given at the beginning of the meal, because it is a competitive inhibitor of oligosaccharide digestion. Recent studies have shown that in patients with NIDDM, maximal decreases in postprandial hyperglycemia occur when 100 mg of acarbose is given at the initiation or within 15 minutes of the initiation of a test meal.\(^48\)

SIDE EFFECTS OF ALPHA-GLUCOSIDASE INHIBITORS

The major side effects of acarbose and other alpha-glucosidase inhibitors are gastrointestinal and are a result of the pharmacologic action of the drugs.\(^27,28\) The amount of carbohydrate that escapes into the colon is dependent on dietary carbohydrate content, the dose of alpha-glucosidase inhibitor used, the rapidity with which drug dose is increased, and the duration of treatment. As noted previously, drug therapy should begin with a very low dose that is increased slowly. Gradual exposure to the agent permits the induction of alpha-glucosidase enzymes in those portions of the small intestine which normally have very low concentrations because of their lack of exposure to carbohydrates. Because the most gastrointestinal symptoms are flatulence, diarrhea, and abdominal discomfort,\(^27,28\) the initial severity and frequency will depend on the treatment regimen used. All symptoms regress with time, and, after several months of therapy, abdominal discomfort and diarrhea are minimal.

A treatment-emergent elevation in liver enzymes may occur but is uncommon with dosages of 300 mg per day or less. Postmarketing surveys have documented only 19 cases of transaminase elevation over 500 IU/L in 500,000 patients.\(^27\) The liver enzyme changes are reversible on withdrawal of the drug.
Table 4. ACARBOSE DOSING SCHEDULE

<table>
<thead>
<tr>
<th>Week</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Supper</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/2 of 50 mg</td>
<td>—</td>
<td>1/2 of 50 mg</td>
</tr>
<tr>
<td>2</td>
<td>1/2 of 50 mg</td>
<td>1/2 of 50 mg</td>
<td>1/2 of 50 mg</td>
</tr>
<tr>
<td>3-4</td>
<td>1/2 of 50 mg</td>
<td>1/2 of 50 mg</td>
<td>1/2 of 50 mg</td>
</tr>
<tr>
<td>5</td>
<td>1/2 of 50 mg</td>
<td>1/2 of 50 mg</td>
<td>50 mg†</td>
</tr>
<tr>
<td>6</td>
<td>50 mg†</td>
<td>1/2 of 50 mg</td>
<td>50 mg†</td>
</tr>
<tr>
<td>7-8</td>
<td>50 mg†</td>
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<td>50 mg†</td>
</tr>
<tr>
<td>9, if necessary</td>
<td>100 mg</td>
<td>50 mg†</td>
<td>100 mg</td>
</tr>
<tr>
<td>10, if necessary</td>
<td>100 mg</td>
<td>50 mg†</td>
<td>100 mg</td>
</tr>
<tr>
<td>12, if necessary</td>
<td>100 mg</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

*Drug should be taken with the first bite of food of each main meal.
†May substitute 1/2 of a 100-mg tablet (to reduce cost).

The carbohydrate content of the diet is an important factor in the use of alpha-glucosidase treatment. Diets that contain less than 50% carbohydrate will diminish the effectiveness of alpha-glucosidase inhibitors in the treatment of NIDDM. Patients following diets containing greater than 50% carbohydrates will have the best glycemic response to alpha-glucosidase inhibitors either alone or in combination with insulin or sulfonylureas.48,49

The primary elements necessary for effective glycemic responses to alpha-glucosidase inhibitors are as follows:
1. High-carbohydrate diet
2. Initiation with a very small dose
3. Slow titration of dose by patient side-effect profile
4. Chronic therapy with the lowest dose that gives maximal glycemic improvement as measured by hemoglobin A1c.

Acarbose does not interfere with the absorption of sulfonylureas, digitalis, angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, or warfarin.50 Early studies suggested that acarbose might inhibit the absorption of metformin, but this has not been confirmed. Cholestyramine, antacid agents, mucosal absorbents, and digestive enzyme preparations decrease the effects of acarbose.50

An example of a titration scheme for acarbose is given in Table 4.

References
42. May C: Efficacy and tolerability of stepwise increasing dosage of acarbose in patients with non-insulin-dependent diabetes (NIDDM), treated with sulphonylureas. Diabetes Stoffwechsel 43, 1995


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