A New Era in Diabetic Agents: Hope for Diabetics

By

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In 1997, there were an estimated 15.7 million Diabetics in the United States alone, with an additional 798,000 new cases diagnosed each year. Diabetes Mellitus is characterized by abnormal glucose homeostasis, resulting in chronic hyperglycemia. Prolonged hyperglycemia has been associated with retinopathy, peripheral neuropathy, autonomic neuropathy, coronary artery disease, peripheral vascular disease, and nephropathy. As Primary care providers, we need to seek out better and more effective treatments for this devastating disease. This paper will discuss: pharmacodynamics, pharmacokinetics, current research, adverse effects, and possible treatment options of diabetic agents lispro, troglitazone, glimepiride, metformin, and acarbose.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>2</td>
</tr>
<tr>
<td>Manuscript</td>
<td>4</td>
</tr>
<tr>
<td>Table 1</td>
<td>14</td>
</tr>
<tr>
<td>Figure 1</td>
<td>15</td>
</tr>
<tr>
<td>Reference List</td>
<td>16</td>
</tr>
</tbody>
</table>
Introduction

In the United States alone, there were an estimated 15.7 million cases of diabetes in 1997, with an additional 798,000 new cases diagnosed each year (National Institute of Health, 1998). Diabetes Mellitus, one of the most common and devastating diseases known to man, is characterized by abnormal glucose homeostasis, resulting in chronic hyperglycemia. Prolonged hyperglycemia has been associated with retinopathy, peripheral neuropathy, autonomic neuropathy, coronary artery disease, peripheral vascular disease, and nephropathy (McPhee, Lingappa, Ganong, and Lange, 1995). These ailments can lead to further complications of renal failure, infection, blindness, stroke, myocardial infarction and amputation. A consistent reduction in blood glucose levels has been shown to directly reduce the incidence of these devastating complications (Riddle and Karl, 1995). The American Diabetes Association has estimated that for every one dollar spent on preventing hyperglycemia, seven dollars are saved in the long term treatment of the complications of diabetes (Manley, 1997).

In addition to the problem of chronic hyperglycemia, there is also the problem of secondary failure. It is estimated that once diagnosis has taken place in type II diabetes, all mono treatments tend to succeed at first, and then tend to lose efficacy over time. This process is known as secondary failure (Riddle et al., 1995). The advent of new drug options have given far more choices for combinations to help combat secondary failure, and increase our ability to keep tighter blood glucose control for diabetics, and therefor, reduce complications. This article will discuss: pharmacodynamics, pharmacokinetics, current research, adverse effects, and the possible treatment options of lispro, troglitazone, glimepiride, metformin, and acarbose.
Lispro

**Pharmacodynamics**

Insulin lispro (Humalog) is an insulin analog of recombinant DNA origin. Lispro stimulates insulin receptors, which leads to phosphorylation of multiple intracellular signaling molecules. Intracellular signals cause translocation of glucose transporters from the endosomal compartment to the plasma membrane where they increase glucose uptake (Page, Curtis, Sutter, Walker and Hoffman, 1997). Lispro differs from human insulin in having lysine at the B28 position and proline at the B29 position.

**Pharmacokinetics**

Lispro is more rapidly absorbed, produces higher peak concentrations and lowered postprandial glucose levels. Lispro peaks in 30 to 90 minutes (Grimley, 1997). Lispro’s half-life is one hour (as shown in table 1). Compared with regular insulin, the peak serum insulin concentration of insulin lispro is three times higher, time to peak is 4.2 times faster, the absorption rate constant is double, and the duration of action is half as long (Campbell, R. Campbell, L., and White, 1996).

**Current research**

Pflutzner et al., (1996) evaluated overall long-term glucose reduction by measuring HbA1c and found no significant difference between regular human insulin and lispro. The same study noted that there were significant decreases in 1 and 2 hour postprandial glucose excursions in patients treated with lispro. However, Zinman, Tildesley, Chiasson, Tsui, and Strack (1997) found a significant decrease in HbA1c after their subjects changed from regular human insulin to lispro for three months. Researchers found consistently that HbA1c was equal or reduced with use of lispro.
Jehle et al., (1996) found lispro increases the number and affinity of insulin receptors on circulating monocytes to a level similar to that observed in healthy subjects. Jehle et al., (1996) concluded that the above phenomenon is related to lispro's more physiological pharmacokinetic profile. Additionally it was determined that lispro decreased overall insulin dosage (Pflutzner, et al., 1996). Pampanelli, et al., (1995) determined that IDDM subjects with some residual pancreatic beta cell function are ideal candidates for prandial use of lispro because they can maintain near normoglycemia longer after the subcutaneous analog injection related to their residual endogenous insulin secretion. Until the release of lispro, no preparations were available to provide the high concentrations needed to stimulate postprandial glucose disposal (White, 1996). Schernthaner, et al. (1998), concluded that using insulin lispro immediately postprandial is as effective as regular insulin 40 minutes before meals, which gives diabetics another treatment option.

Campbell et al., (1996) concluded that indeed lispro does reduce the incidence of hypoglycemic events, particularly nighttime episodes because of it's increased elimination time. Garg et al., (1996) determined type I diabetics had a lower number of hypoglycemic events and better postprandial controls.

Lispro also has a diminished tendency to self-associate (Fineburg et al.,1996). In a year long randomized trial the immunogenicity of insulin lispro and regular human insulin were compared. Lispro was shown to be less likely to create antibodies than regular human insulin (Fineburg et al.,1996). Lispro was determined to be an excellent alternative to regular human insulin in diabetics with substantially increased human insulin antibodies. Apparently, the structural difference between lispro and human insulin molecules prevented lispro from binding to the human insulin antibodies (Lahtela, Knip, Paul, Antonen, and Salmi, 1997). Kumar et.al, (1996) also found that lispro would be useful in managing patients with an allergy to human insulin.
Lispro’s onset of action is not changed by injection sites which allows more potential sites for subcutaneous injection with assured rapid response (Braak et al., 1996). Patient satisfaction seems to be improved in patients receiving lispro because injections can be given immediately before mealtime, with no need to wait before eating thereby increasing flexibility for patients (P’flutzner et al., 1996). In quality of life studies conducted on subjects using lispro, the subjects (N=942) listed: the ability to eat immediately after injection, better control, more freedom, and feeling better were all advantages when using lispro (Grimley, 1997). Some treatment options of lispro are noted in figure 1.

**Adverse effects**

Campbell et al. (1996), noted that lispro is very similar to human insulin with reference to dose, toxicity, adverse effects, and drug interactions. The major side effect of both human insulin and lispro is hypoglycemia (as shown in table 1), which appears to be reduced with lispro use. Weight gain is a possible side effect of regular human insulin; it is unclear at this time if lispro has the same effect.

**Troglitazone**

**Pharmacodynamics**

Troglitazone (Rezulin) is a thiazolidinedione derivative that lowers insulin resistance by improving the action of endogenous insulin in the liver, skeletal muscle, adipose tissue and peripheral tissue. It increases the activity of hepatic enzymes, which catalyze glycogenosis and suppress gluconeogenesis, and increases the activity of enzymes that catalyze muscle glycogenosis (Parke-Davis, 1997). Troglitazone’s unique mechanism is dependent on insulin for activity.

**Pharmacokinetics**

Troglitazone’s peak plasma levels are reached within 2-3 hours following oral administration. Troglitazone’s plasma half-life ranges from 16-34 hours (as shown in table
1. Troglitazone is absorbed rapidly by oral route and food enhances absorption by 30-85%, thus it is imperative that this drug be administered with food. Troglitazone is extensively metabolized into inactive metabolites (Parke-Davis, 1997).

**Current research**

The patient population to most benefit from this drug are type II diabetics who are using > 30 units of insulin a day with a HbA1c > 8.5. These figures represent insulin resistance which is this drug’s primary target (Parke-Davis, 1997). Unlike sulfonylureas, troglitazone does not increase insulin secretion, and is not active in insulin deficient patients (Parke-Davis, 1997). Therefore this drug is not appropriate for type 1 diabetics. This same quality also makes hypoglycemic episodes with this drug in mono therapy very unlikely.

Graf, Xi, Hsueh, & Law (1997) demonstrated that troglitazone decreased the development of neointimal hyperplasia and atherosclerosis. Troglitazone partially restored the basal heart rate and cardiac work in diabetic subjects to nearly control values. Troglitazone treatment had cardioprotective effects on basal post ischemic cardiac function (Shimabukuro et al. 1996). Troglitazone exerts multiple effects on cardiomyocytes. It was suggested that an increased glucose supply may be beneficial for the diabetic heart and that troglitazone improves insulin action on cardiac tissue (Bahr et al., 1996). Ghazzi et al. (1997), demonstrated that patients (N=154) treated with troglitazone did not show an increase in cardiac mass or an increase in cardiac function impairment.

Troglitazone also seems to have positive effects on lipid profiles of patients receiving the drug. Reductions in total cholesterol and total triglycerides were noted. Additionally, there was an increase in high-density lipids (Dunaif et al. 1997). Kumar et al. (1996), also found reductions in cholesterol and total triglycerides in clinically significant numbers. Dose
adjustment for patients with renal dysfunction is not necessary (Parke-Davis, 1997). Elderly patients tolerate this drug well, provided they have good liver function (Parke-Davis, 1997).

Troglitazone was found to have positive benefits for women with polycystic ovary disease (Dunaif, Scott, Finegood, Quintana, and Whitcomb, 1996). Polycystic ovary disease is believed to be linked to insulin resistance (Dunaif et al., 1996). Troglitazone resulted in the resumption of ovulation in some premenopausal anovulatory women with insulin resistance (Parke-Davis, 1997).

Adverse effects

Troglitazone metabolite concentrations with chronic liver disease were increased from 30% to 400%, compared to healthy subjects without hepatic dysfunction. Therefore, it is recommended that this drug be used cautiously in patients with hepatic diseases (Parke-Davis, 1997) (see table 1). Additionally, elevated liver function tests have been observed in 2.2% of patients on troglitazone (Parke-Davis, 1997).

This drug is not recommended in breast feeding women, as it is excreted in breast milk in animal studies (Parke-Davis, 1997). There is a tendency for neutrophil counts to drop at very high dosing of the drug (over 800 mg) (Grimley, 1997). A slight decrease in white blood cells, hemoglobin, and hematocrit were observed in clinical trials, yet these changes were not associated with clinical effects (Parke-Davis, 1997).

Glimepiride

Pharmacodynamics

Glimepiride (Amaryl) is a second-generation sulfonylurea similar to glibenclamide (Glyburide). Glimepiride blocks adenosine triphosphate and potassium channels in the pancreatic beta cells. This causes depolarization and subsequent activation of voltage sensitive calcium channels and increased insulin release (Page et al., 1997). Glimepiride may also increase insulin sensitivity in peripheral tissues (Grimley, 1997).
Pharmacokinetics

Glimepiride’s bioavailability approaches 100%. It is highly protein bound at 99.5%. Peak time is 2-3 hours. The serum half-life is about 5-9.2 hours (Table 1). Glimepiride is metabolized into two major metabolites, M1 and M2. These metabolites are excreted in the urine and feces (Grimley, 1997).

Current Research

Many of the studies done on glimepiride compare and contrast it with its popular predecessor glibenclamide. Glimepiride has some significant advantages in cardiovascular effects over glibenclamide according to Pogatsa (1996). Patients taking glimepiride are reported to have a decreased incidence of fatal myocardial infarct and the development of ventricular fibrillation than glibenclamide (Pogatsa, 1995).

Glimepiride produced fewer hypertensive events, better coronary blood flow, lower coronary resistance, increased mechanical activity, and more stable potassium levels than glibenclamide the same glucose lowering levels (Geisen, Vlegh, Krause, & Papp, 1996).

Glimepiride also has a more potent hypoglycemic action than glibenclamide (Wolffenbuttel & Graal, 1996). This has been speculated to be related to an extrapancreatic effect in the form of hepatic glucose uptake. Dills & Schneider, (1996) found that although there were similar decreases in fasting plasma glucose with both drugs, there was a lower incidence of hypoglycemia with glimepiride than glibenclamide. Cheta, Lim, Chan, Kunakorn, and Charles (1995), determined that glimepiride has preventive effects against the onset of diabetes in animal studies, even in treatment periods of as short as forty days, and decreases the severity of islet inflammation. Some treatment options for glimepiride are shown in figure 1.
**Adverse effects**

Rosenkranz (1996) demonstrated that patients with significant renal impairment (N=31) were more likely to experience hypoglycemic effects from glimepiride as the elimination of the metabolites was impaired. These metabolites have similar pharmacological activity as the parent drug. Pharmacokinetic data on sulfonylureas are generally inconsistent in cirrhotic patients (Rosenkranz, 1996). These studies imply that the pharmacokinetics of glimepiride are altered in renal disease, but not seriously affected in patients with liver diseases (Rosenkranz, 1996). Qi, et al.(1995), suggests that glimepiride has a direct inhibitory effect on platelet aggregation.

Glimepiride is not without its adverse effects (Table 1). These include: hypoglycemia, dizziness, asthenia, headache, and nausea, although these occur in less than 2% of recipients (Grimley, 1997).

**Metformin**

**Pharmacodynamics**

Metformin is an oral antihyperglycemic agent and not a hypoglycemic agent. Metformin enhances the effects of insulin on liver, muscle, and adipose tissue (Riddle et al., 1995). Metformin lowers blood glucose by enhancing insulin stimulated glucose transport in skeletal muscle. It also reduces hepatic glucose production in type II diabetics that may be secondary to a reduction in gluconeogenesis (Riddle et al., 1995).

**Pharmacokinetics**

The peak time of metformin is 2-3 hours, and the half-life is 17.6 hours (Table 1). Bioavailability is 50 to 60%. Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion (Drug facts and comparisons, 1996)
Current Research

Metformin (Glucophage) is a drug related to phenformin, a drug introduced in 1957 which can cause fatal lactic acidosis and was removed from the market (White, 1996). The mechanism of action differs from sulfonylureas because it does not increase insulin secretion, does not cause hypoglycemia, and does not induce weight gain (White, 1996). Metformin reduced fasting glucose levels an average of 58 mg/dl and HbA1c an average of 1.8% compared to diet plus placebo (Defranzo and Goodman, 1995). Metformin is associated with a reduction in triglyceride levels, low-density lipids and cholesterol. Metformin is associated with increased high-density lipids, and modest weight loss (Riddle et al., 1995). Some treatment options for metformin are shown in figure 1.

Adverse effects

Metformin does have adverse effects, which are relatively common. Patients treated with metformin had 30% more reports of abdominal bloating, nausea, cramping, a feeling of fullness and diarrhea (Table 1) than did patients receiving a placebo (Bristol-Meyers Squibb, 1996). These side effects are usually self-limiting, transient and can be mitigated by starting with a low dose and titrating up slowly, as well as taking the medication with food (White, 1996).

Metformin is contraindicated in patients with renal dysfunction (serum creatinine >1.5 mg/dl in males or >1.4 mg/dl in females). Hepatic dysfunction is also a contraindication relating to the association of hepatic dysfunction with acidosis. Metformin is also contraindicated for patients with alcoholism or binge drinking (White, 1996). Metformin should be withheld from patients that are at risk for renal failure or acute acidosis. Conditions such as acute myocardial infarction, exacerbation of congestive heart failure, or major
surgery can predispose a patient to renal failure or acute acidosis. (Bristol-Meyers Squibb, 1996).

Naivaiz, Cleveland, Gaines, and Chan (1998) suggested that metformin also be withheld for at least 48 hours prior to the test if the patient is undergoing procedures using iodinated contrast and has renal impairment as indicated by an abnormally high creatinine. The same study group suggested that metformin need not be withheld if renal function is normal. However, Rasuli and Hammond (1998) found that it is commonly the contrast media that causes renal failure, and if metformin is continued in the presence of renal failure, lactic acidosis will occur. It is their recommendation that metformin be withheld for 48 hours post procedure, and renal function studies done to rule out renal failure before the metformin is resumed. It would seem reasonable in light of these studies to do renal function tests both pre and post procedure to ensure renal function is not impaired.

Acarbose

Pharmacodynamics

Acarbose (Precose) is a competitive reversible inhibitor of pancreatic alpha amylase, which hydrolyses complex starches to oligosaccharides. In the small intestine, alpha glucosidases and the brush border membrane are responsible for the digestion of complex polysaccharides to glucose or monosaccharides. By inhibiting these enzymes, acarbose is capable of delaying digestion of complex carbohydrates and subsequent absorption of glucose, which results in a smaller rise in postprandial blood glucose concentrations. Acarbose inhibits the metabolism of sucrose to glucose and fructose. Acarbose is a competitive inhibitor of the alpha glucosidases (Bayer Corporation, 1995). Ranganath, Norris, Morgan, Wright & Marks, (1998) noted that there is a significant delay in gastric emptying which also contributes to the therapeutic affect of acarbose.
Pharmacokinetics

The peak time of acarbose is 2-3 hours, and half-life is 8-9 hours (Table 1). The primary route for elimination of unchanged acarbose (51%) is in the feces. Systemic bioavailability is 1-2%. The remainder of acarbose appears to be degraded by digestive enzymes or microorganisms in the gastrointestinal tract (Ahr, 1989).

Current Research

Further effects of acarbose are a decreased beta pancreatic response to meals, and influences on gut hormone secretion and plasma lipid levels (Salvatore & Giugliano, 1996). A reduction in very-low-density lipids, triglycerides and low-density lipids have also been noted (Bayer Corporation, 1995). However, Chiasson et al., (1994) found no changes in lipid levels, so it is unclear if decreasing lipid levels is a consistent effect of this drug. An efficacy study by Spengler & Cagatay, (1995) cited therapeutic benefit and good tolerability. HbA1c and capillary glucose were found to be consistently lower than the control group (Colomer, Cotaia, & Baena, 1995).

Acarbose would appear to be helpful for type I and type II diabetics. Fasting, postprandial glucose and HbA1c levels were all decreased for both type I and type II diabetics (Spengler & Cagatay, 1995). Reduction in fluctuations of glucose levels throughout the day, may help control type I diabetics with "brittle diabetes" (Salvatore & Giugliano, 1996). Acarbose was found useful as a first line drug in type II diabetics who did not get good glucose control with diet alone (Hanefeld, 1991). Additionally, 50% of subjects (N=316) were shown to respond to acarbose regardless of their concurrent antidiabetic medication (Chiasson et al., 1994). Acarbose is not associated with weight gain or hypoglycemic effects (Yee & Fong, 1996). Acarbose does not appear to be contraindicated for patients with decreased renal function. Hepatic deficiency has not been documented as a contraindication.
Acarbose may prevent dumping syndrome. Dumping is a result of gastric resection when the physiological regulatory system has been physically altered. This change results in a hyperosmolar chyme entering the intestine, drawing vascular fluids into the gastric lumen causing hypotension. Acarbose decreases the osmolarity by decreasing the breakdown of carbohydrates, leading to improvement of symptoms (Mimura, Tsukakubo, Tsujiguchi, & Hoshikawa, 1996). Some treatment options for acarbose are shown in figure 1.

Adverse effects

Adverse effects of acarbose include flatulence, borborygmus, abdominal distention, abdominal pain, and loose stools (Table 1). Most of these side effects decrease with time or may be alleviated by a reduction in dose (Bayer Corporation, 1995). Rachman & Turner, (1995) published one case study where acarbose was thought to have reduced digoxin levels, but more information on that possible side effect has not been noted. An elevation in serum transaminase levels has been reported in 15% of patients being treated with acarbose. This appears to be dose related, more common in females, and were generally asymptomatic and reversible (Bayer Corporation, 1995). Patients with GI disturbances such as Crohn's disease, or with a history of abdominal obstruction should avoid acarbose usage (Bayer Corporation, 1995).

Conclusion

Until recently, the treatment of diabetes had changed little in almost 45 years (White, 1996). We are now entering a new frontier in the history of diabetic treatment, which provides us with many options and dilemmas. Primary care providers can look forward to more information regarding the new diabetic agents, and look with hope to the future for even better and more effective treatments for this devastating disease.
Treatment Strategies
With so many new agents available, where shall treatment begin? White (1996) suggested a proposed treatment plan for type II diabetics. If inadequate response after 2-3 months have passed; move on to the next step

Figure 1

Step 1: Evaluation and nonpharmacological approaches: diet, exercise and education. This step should be continued throughout the other phases.

Step 2: Oral monotherapy

**Obese patients**
Consider Metformin

**Non-Obese patients**
Consider Glimepiride or Acarbose

**Step 3: Obese patients**
combination oral therapy Metformin and glimepiride or other sulfonylurea. For those patients that are within 20 mg/dl of fasting plasma glucose goal with Metformin monotherapy, Acarbose rather than a sulfonylurea should be considered.

**Step 3: Non-Obese patients**
who have failed Acarbose therapy: Glimepiride or other sulfonurea should be considered. For patients who have failed sulfonylurea monotherapy: consider adding Metformin or Acarbose

Step 4: Two options; 1 a single or evening bedtime injection of NPH or lente, while continuing oral therapy, sulfonylureas have been most widely studied. 2 initiate three times a day dosing of Lispro with a single oral agent. This form of therapy should offer good postprandial glycemic control without the insulin meal-timing issues.

**Obese patients** with inadequate response to Metformin/Acarbose therapy, the Acarbose should be dropped and insulin added.

**Non-Obese patients** with inadequate response to Acarbose/sulfonylurea combination, the Acarbose should be stopped and insulin started. Non-Obese patients on Metformin/Sulfonylurea combinations, the Metformin should be removed and insulin started.

Step 5: Insulin therapy
Lispro should be considered in place of regular insulin.
<table>
<thead>
<tr>
<th>Agent / Total daily dose (Mg)</th>
<th>Half life/ Peak time</th>
<th>Mechanism of action</th>
<th>Adverse effects/ Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro (Humalog) Variable</td>
<td>Half life 1 hour Peak time 30-90 min</td>
<td>An insulin analog used as a replacement for endogenous insulin, increasing glucose transport across fat and muscle cell membranes</td>
<td>Adverse effects Hypoglycemia Possible Weight gain Contraindications None reported</td>
<td>Use for type I and II diabetics Rapid absorption Lower post prandial glucose Reduction in insulin dosage Reduced hypoglycemic events Less immunogenicity More injection sites</td>
</tr>
<tr>
<td>Troglitazone (Rezulin) 200-600 mg/Day</td>
<td>Half life 16-34 hours Peak time 2-3 hours</td>
<td>Improves the action of endogenous insulin in the liver, skeletal muscle, and adipose tissue. Increases hepatic enzymes that catalyze glycogenosis and suppresses gluconeogenesis, and increases muscle glycogenosis</td>
<td>Adverse effects Neutrophil counts drop with high dosing (800 mg) Elevated liver function tests Contraindications Hepatic dysfunction Breast feeding</td>
<td>Use for type II diabetics only 99% bound to plasma Administer with food Useful for insulin resistance May decrease insulin use Cardioprotective effects Decreased lipid profiles Useful in patients with renal impairment May result in resumption of ovulation</td>
</tr>
<tr>
<td>Glimepiride (Amaryl) Single therapy 1-4 mg/ Day Adjunct to insulin 8 mg/ Day</td>
<td>Half life 5-9 1/2 hours Peak time 2-3 hours</td>
<td>Stimulates secretion of insulin from functional beta cells in the pancreas, may also increase insulin sensitivity in the peripheral tissues</td>
<td>Adverse effects Hypoglycemia Dizziness Asthenia Less cardiovascular activity</td>
<td>Use for type II diabetics only 99% protein bound Less cardiovascular activity Less hypoglycemia May have preventive effects Decreases inflammation of islet cells</td>
</tr>
<tr>
<td>Metformin (Glucophage) 1000-2500 (mg)/Day</td>
<td>Half life 17.6 Hours Peak time 2-3 hours</td>
<td>Enhances the effects of insulin on the liver, muscles and adipose tissue, and reduces hepatic glucose production</td>
<td>Adverse effects Abdominal bloating, nausea, cramping, diarrhea Contraindications Renal dysfunction, Hepatic dysfunction Alcoholism Major surgery Cardiac dysfunction Hold for iodinated contrast procedures</td>
<td>Use for type II diabetics only Does not cause hypoglycemia Does not cause weight gain Decreased Lipid profiles</td>
</tr>
<tr>
<td>Acarbose (Precose) 150-300 (mg)/ Day</td>
<td>Half life 8-9 hours Peak time 2-3 hours</td>
<td>Acarbose is a competitive reversible inhibitor of pancreatic alpha amylase which hydrolyses complex starches to oligosaccharides. Acarbose delays digestion of complex carbohydrates and subsequent absorption of glucose.</td>
<td>Adverse effects Flatulence Borborygmus Abdominal distention, abdominal pain, loose stools Elevations in serum transaminase Contraindications Crohn’s disease GI disturbances, or prone to obstruction</td>
<td>Use for type I and type II diabetics Lowers lipid profiles May improve dumping syndrome Does not cause weight gain or hypoglycemic events</td>
</tr>
</tbody>
</table>
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