CHAPTER 17

NEW ORAL AGENTS FOR THE TREATMENT OF DIABETES

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Diabetes is a commonly encountered disease in the practice of podiatric medicine. Non-insulin-dependent diabetes mellitus (NIDDM) accounts for 85% to 90% of all diagnosed cases of diabetes in the United States. NIDDM has been highly associated with macrovascular complications (coronary artery disease, myocardial infarction, heart failure, stroke) and microvascular complications (blindness, renal failure, and amputations). Even today, there continues to be a high incidence of complications in patients with NIDDM which indicates that the current approach to therapy is inadequate for maintaining good health. Preventing marked hyperglycemia while accepting moderately increased levels of blood glucose seems inefficient, considering a higher incidence of cardiovascular disease has even been associated with blood glucose levels at the high end of the normal range. Microvascular complications are seen at blood glucose levels of 140 mg/dl and higher. These findings suggest that a more intensive approach to the treatment of NIDDM is needed.

The current approach to a newly-diagnosed patient with NIDDM is initially a diet low in fats and high in carbohydrates and fiber, with energy restriction in obese patients, and increased physical activity. Only five percent of patients maintain near-normal fasting plasma glucose concentrations of less than 108 mg/dl, and most patients are unable to maintain increased levels of physical activity. Eventually, an oral hypoglycemic agent is needed to maintain normoglycemia.

Sulfonylureas have been the mainstay in oral therapy. These agents decrease blood glucose levels by increasing beta-cell insulin secretion from islets of Langerhans, increase the uptake of glucose in insulin target tissues by increasing the binding of insulin to cellular receptors, and increase the number of binding sites. These mechanisms may lose effect with chronic administration due to a progressive decrease in beta-cell function. Approximately thirty percent of patients initially treated with sulfonylureas have a poor response, and in the remaining seventy percent, the subsequent failure rate is approximately four to five percent per year.

Prior to 1995, the only other choice following failure of sulfonylureas was insulin. The unwanted side effects of intensive therapy with insulin or sulfonylurea - increased risk of hypoglycemic episodes, increased body weight, and increased fasting insulin levels, which might contribute to atherogenesis with chronic administration - have led to the FDA approval of two new oral agents in the past year. Glucophage and Precose both lower blood glucose concentration by different mechanisms than sulfonylureas and insulin without the adverse side effects. Therefore, these two agents will be encountered more often in the future, and must be understood in order to avoid complications in the podiatric practice.

GLUCOPHAGE AND PRECOSE

Glucophage (metformin) is a member of the biguanide class. Historically, Galega officinalis (goat's rue or French lilac) was used to treat diabetes in Medieval Europe. Guanide is the active component of Galega. In the late 1950s, two members of the biguanide class, phenformin and metformin, were introduced in the United States. These were widely used until the late 1970s when they were pulled off of the market due to a high association of fatal lactic acidosis with phenformin. Metformin differs from phenformin in that it is not metabolized. Patients who have suffered from phenformin-induced lactic acidosis possessed a genetic inability to metabolize the drug, which led to an excessive amount in the circulation. The incidence of metformin-induced lactic acidosis is 1 per 30,000, while the incidence with phenformin is twenty-fold more. Because of continued success in Europe and the establishment of a strict exclusion criteria, metformin was reintroduced to the United States market last year.

Precose (acarbose) is a complex oligosaccharide produced by the microbe, Actinoplanes utahensis, which works at the intestinal brush border by decreasing the amount of glucose absorbed into the blood stream after a meal. Precose has been shown to work well in NIDDM as well as IDDM. This reduction in post-prandial blood glucose levels has been proven to lower the concentration of glycosylated hemoglobin (HbA1c). HbA1c is a more significant predictor of onset or progression of retinopathy in NIDDM patients than blood glucose concentration, for even small increases in HbA1c levels are associated with increased risk of microvascular disease.

Clinical Pharmacology

Glucophage is absorbed mainly in the small intestine. It has a bio-availability of fifty to sixty percent, and peak blood levels are reached within two hours after oral dose. The levels of Glucophage in the liver and kidneys are two times that of plasma levels, and the drug accumulates in the walls of the gastrointestinal tract at levels between ten to one hundred times plasma levels. Glucophage does not bind to plasma proteins, and is excreted unchanged primarily by secretion in the proximal convoluted tubules of the kidney.

Precose acts locally at the cellular level of the small intestine, as it goes through the GI tract practically unabsorbed (less than two percent is absorbed). Precose binds to various alpha-glucosidase enzymes found in the brush border of the intestinal cells. It has a higher affinity for these enzymes than other oligosaccharides, thereby competitively and reversibly inhibiting their binding with the enzymes. These oligosaccharides, instead of being digested in the upper jejunum, escape into the lower jejunum and ileum where they are ultimately digested by bacteria. The inhibition by Precose is greatest for glucoamylase and sucrase and is minimal for lactase. Therefore, if a patient on combination therapy with Precose suffers from hypoglycemia, oral glucose (dextrose) should be given instead of sucrose. Peak plasma levels are attained within one hour after oral dose. Precose is metabolized exclusively within the GI tract, by bacteria and digestive enzymes. The two percent that is absorbed systemically is excreted along with an insignificant amount of metabolite in the urine.

Mechanism of Action

Glucophage decreases hepatic glucose production by enhancing suppression of gluconeogenesis by insulin and reducing glucagon-stimulated gluconeogenesis, while glycogenolysis is unchanged. Insulin-targeted peripheral tissue uptake of glucose is increased with Glucophage, however, this effect is rendered useless without the presence of insulin. This enhanced glucose uptake is seen primarily in muscle, while hepatic uptake of glucose is unaffected by Glucophage. Intestinal glucose absorption rate is decreased, and intestinal glucose metabolism is increased. Glucophage also increases the uptake and oxidation of glucose by adipose tissue as well as decreases fatty acid oxidation by ten to twenty percent, which in turn reduces plasma glucose concentrations by means of the glucose-fatty acid cycle. These mechanisms result in improved glucose tolerance with normal or decreased insulin levels.

Other positive effects associated with Glucophage include no weight gain and some weight loss, decreased levels of VLDL triglycerides, decreased total cholesterol levels, increased HDL cholesterol levels, and no incidence of hypoglycemia. Decreased platelet sensitivity and aggregating agents have been seen during Glucophge therapy. Increases in fibrinolytic activity and mild decreases in fibrinolytic inhibitor plasminogen-activator inhibitor type 1 have also been reported. These findings suggest that Glucophage might have a combative effect on atherogenesis.

Precose, like glucophage, does not enhance insulin secretion. Precose is a competitive, reversible inhibitor of pancreatic alpha-amylase in the intestinal lumen and alpha-glucosidases on the brush border of intestinal cells. This leads to a delay in the absorption of glucose, thereby decreasing postprandial hyperglycemia, HbA1c levels, and post-prandial insulin rises with little effect on serum C-peptide and lipid concentrations. Clinical studies have shown decreases of .5 to 1.0% in HbA1c levels with continued use of Precose as monotherapy for NIDDM.

Precose decreases postprandial secretion of gastric inhibitory polypeptide (GIP), a GI hormone released from cells in the duodenum and upper jejunum when glucose is absorbed. This hormone slows gastric emptying, and potentiates glucose-mediated insulin secretion at plasma glucose levels

in the postprandial, not fasting, range. Glucagon-like peptide 1 (GLP 1) is released from L-cells in the ileum, and has similar effects to GIP. GLP 1 release is stimulated normally by a neurogenic or hormonal response to carbohydrate in the duodenum or upper jejunum. Precose delays the digestion of carbohydrates until they reach the ileum which thereby renders the effect of this hormone useless. Thus, Precose not only interferes with digestion of carbohydrates but also interferes with the GI hormone axis.

CLINICAL USES IN MONOTHERAPY AND COMBINATION THERAPY

After failure of diet and increased physical activity to reduce hyperglycemia, both Precose and Glucophage make acceptable choices for initial monotherapy for NIDDM. Both agents cause weight loss, which is important with the obese NIDDM patient. Neither agent causes hyperinsulinemia, which reduces the risk of hypoglycemia and atherogenesis. Glucophage and sulfonylureas have been shown to have equivalent effects on blood glucose when used as monotherapy. Both Precose and Glucophage have similar results on HbA1c levels when used as monotherapy and combination therapy with a sulfonylurea.

How does one go about selecting the proper agent to begin monotherapy in a NIDDM patient? Metformin is an excellent choice in morbidly obese, insulin-resistant patients who have clinical hypoglycemia or other side effects of sulfonylureas, and in cases of hyperlipidemia associated with NIDDM. As soon as the cost of therapy decreases, Glucophage will likely be used in many NIDDM patients except the thin, insulin-deficient patients due to the fact that Glucophage requires insulin in order to be effective. Precose can be initiated as monotherapy in any patient with NIDDM, especially elderly patients, patients with mild to moderate elevation of HbA1c values, or those in whom metformin and sulfonylureas are contraindicated.

Despite the availability of these new agents, sulfonylureas are still the first choice of monotherapy for NIDDM patients. In the past, when sulfonylureas failed to maintain acceptable blood glucose levels at maximum dose, the next step was insulin therapy. Because of the undesirable side effects of insulin, Precose or Glucophage is now combined with a sulfonylurea for a trial period before placing a patient on insulin. Precose and Glucophage when combined with a sulfonylurea decrease blood glucose and HbA1c levels while decreasing the dosage of the sulfonylurea. Because Precose and Glucophage have two distinctly different mechanisms from sulfonylureas, the result is an additive effect when used in combination therapy. There will still be some patients who inevitably will need insulin, but combination therapy may delay the time frame before that switch is needed.

Combination therapy with Glucophage and Precose has been shown to decrease HbA1c levels an additional 1%. Studies on the effects of combination of Precose with insulin show that Precose can decrease the amount of insulin needed to maintain normoglycemia. A combination of Glucophage and insulin is not recommended due to insufficient studies, but clinical reports show that it may be successful, especially in the morbidly obese, insulin-resistant patients.

Contraindications

Glucophage is contraindicated in patients with:

1. Renal disease or dysfunction (as suggested by a serum creatinine level of >1.5 mg/dL for men and >1.4 mg/dL for women) which can also result from cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
2. Patients undergoing radiologic studies involving intravenous administration of iodinated contrast materials because of their association with acute alteration of renal function.
3. Known hypersensitivity to the drug.
4. Acute or chronic metabolic acidosis. This includes diabetic ketoacidosis, with or without coma.
5. Impaired hepatic function or excessive alcohol intake due to impairment of their ability to clear lactate.

Precose is contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis.
3. Cirrhosis.
4. Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or patients predisposed to intestinal obstruction.

5. Chronic intestinal diseases associated with marked disorders of digestion or absorption.
6. Conditions that may deteriorate as a result of increased gas formation in the intestine.

Side Effects

Side effects of Glucophage include:

1. Lactic acidosis in 1 per 30,000 patients, however, fifty percent of the cases are fatal. Strict exclusion of patients with renal and hepatic dysfunction, as well as alcoholism, significantly decreases the potential for lactic acidosis.
2. Gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal bloating, flatulence, usually disappear spontaneously with continued use. These symptoms seem to be dose-related, so a gradual dose escalation and dosage with meals may decrease their incidence.
3. Unpleasant, metallic taste which usually resolves spontaneously.
4. Rash/dermatitis.
5. Asymptomatic decrease in serum vitamin B12 levels. Only five cases of megaloblastic anemia have been reported. There has been no increase in incidence of neuropathy.

Side effects of Precose include:

1. Gastrointestinal symptoms such as flatulence, cramps, abdominal distension, borborygmus, and diarrhea. These effects diminish over time and are caused by the presence of undigested carbohydrate in the lower GI tract.
2. Asymptomatic, reversible elevation of serum transaminase levels that are not associated with other evidence of liver dysfunction. This is not seen with lower dosages of Precose.
3. Small reductions in hematocrit without reductions in hemoglobin. This is thought to be due to decreased absorption of iron.

Drug Interactions

Nifedipine enhances the absorption of Glucophage. Cationic drugs (such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triampterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion compete with Glucophage for common renal tubular transport systems, thereby causing an increase in plasma metformin levels. Certain drugs that tend to produce hyperglycemia include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. Strict monitoring of blood glucose levels are of utmost importance when these drugs are administered with Glucophage and Precose. These patients should be closely monitored for hypoglycemia when such medications are withdrawn. Intestinal adsorbents (charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (amylase, pancreatin) may reduce the effect of Precose, so concomitant use should be avoided.

Dosage and Administration

Glucophage is available in 500 mg and 850 mg tablets. The starting dose is 850 mg at breakfast or 500 mg at breakfast and dinner. The dose is increased gradually to avoid GI side effects. Manufacturer's recommendation is to increase 500 mg/day dose by one tablet per day per week, or the 850 mg/day dose by one tablet per day every two weeks until target blood glucose is reached, or to a maximum of 2250 - 2550 mg/day.

Precose is available in 50 mg and 100 mg tablets. The starting dose is 25 mg three times a day with the first bite of each meal. Dosage of Precose should be adjusted at four to eight week intervals. Dosage can be increased from a starting dose to 50 mg tid and, if necessary, 100 mg tid. Maximum dosage is 50 mg tid in patients < 60 kg and 100 mg tid in patients > 60 kg. The dosage of Glucophage and Precose should be adjusted accordingly in those patients receiving combination therapy with a sulfonylurea.

ON THE HORIZON

A second generation alpha-glucosidase inhibitor, Miglitol, will soon be approved by the FDA. Troglitazone improves hyperglycemia, improves insulin resistance, and decreases hepatic glucose production in diabetic animals. Glimeperide, a newly developed sulfonylurea, has a lower dosage, more rapid onset, longer duration of action, lower insulin and C-peptide levels possibly due to less stimulation of insulin secretion, and more pronounced extra-pancreatic effects. Other agents

with different mechanisms than sulfonylureas, Glucophage and Precose include insulin secretagogues, incretins, gluconeogenesis inhibitors, inhibitors of fatty acid oxidation, agents which mimic or enhance insulin action without effects on beta cell insulin secretion, and glucagon analogues.

CONCLUSION

Glucophage and Precose are both acceptable alternatives to sulfonylureas and insulin when diet and exercise fail to lower blood glucose levels in NIDDM patients. They also provide additive effects when used in combination therapy with one another, a sulfonylurea, or insulin. The use of Glucophage and Precose is gaining more acceptance because of the few associated side effects. Therefore, the podiatric physician must be aware of their mechanisms, contraindications, and adverse reactions in order to properly treat the NIDDM patient.

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