New Directions in Type 2 Diabetes Mellitus: An Update of Current Oral Antidiabetic Therapy

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This article reviewed the relevant literature including published clinical trials and reviews on currently available oral hypoglycemic agents. Results showed that the benefits of glycemic control have been established through multiple clinical trials. Long-term control of blood glucose levels in type 1 and type 2 diabetic patients will decrease the incidence and prolong the time until progression of diabetic retinopathy, nephropathy, and neuropathy. Our increased understanding of the pathophysiology behind type 2 diabetes has led to the development of many new agents that are aimed at treating the underlying insulin resistance and relative insulinopenia. The sulfonylureas as a group have been used for many years and act by stimulating insulin secretion. They are useful alone or as combination therapy with insulin or another oral hypoglycemic agent. The biguanides act by decreasing hepatic glucose production and by increasing peripheral insulin sensitivity. The alpha-glucosidase inhibitors act nonsystemically by blocking the metabolism of digested polysaccharides and therefore lowering the amount of carbohydrate absorbed in a meal. Benzoic acid derivatives act in a manner similar to that of sulfonylureas by enhancing pancreatic insulin production. They offer a shorter duration of action, lowering the risk of hypoglycemia. The thiazolidinediones increase peripheral insulin sensitivity and are effective as both monotherapy and combination therapy. Oral hypoglycemic agents, when properly administered, are very effective in controlling type 2 diabetes and preventing long-term complications. (*J Natl Med Assoc.* 1999;91:389-395.)

Key words: diabetes mellitus ◆ hypoglycemic agents

Diabetes mellitus is a disorder of abnormal glucose homeostasis, often resulting in acute and chronic complications of hyperglycemia. Obesity, physical inactivity, and a genetic predisposition are risk factors for the development of glucose intolerance and type 2 diabetes in all ethnic groups. It is unclear why these risk factors are more prevalent in the black community and how these factors lead to a disproportionately higher prevalence of the disease and a higher incidence of its complications in African Americans. It is estimated that 5% of Americans have diabetes and that 95% of these people have type 2 diabetes. At least three million African Americans have diabetes mellitus, with the disease affecting 8.5% of black men and 12% of black women.[1-3] This can be compared with the 2.5%-8% of whites who suffer from the disease. In addition, African Americans historically have had a disproportionately higher prevalence of diabetic complications such as nephropathy and retinopathy.[2] Today

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Table 1. Type 2 Diabetes: A Summary of Oral Therapy

Class of Drug	Chemical Structure	Effects	Toxicity/Side Effects	Combination Therapy
Sulfonylurea	Sulfonic acid-urea nucleus	Increases insulin secretion; reduces $HgbA_1C$ 1%-2% as monotherapy; glimepiride may have peripheral insulin-sensitizing effects	Hypoglycemia Glyburide must be used with caution in the elderly or renally impaired patient; glipizide is safer in the elderly patient	Biguanide or thiazolidinediones
Biguanide	Structurally distinct from sulfonylureas; dimethylimidodicarbonic compound	Decreases hepatic glucose output; can cause mild weight loss & reduce triglycerides; reduces $HgbA_1C$ 1.5%-2% as monotherapy	Risk of lactic acidosis; contraindicated in patients with renal, hepatic or cardiorespiratory compromise; gastrointestinal irritation	Thiazolidinediones, sulfonylurea, benzoic acid derivative
Thiazolidinediones	Thiazolidinedione-α tocopherol compound	Increases peripheral insulin sensitivity; reduces $HgbA_1C$ .9% alone and 1.5% on average in combination with insulin; may need 3-4 weeks prior to seeing effects	Hepatotoxicity LFTs must be monitored during therapy; peripheral edema, weight gain	Originally approved for combination therapy with insulin biguanide, sulfonylurea, nylurea, or benzoic acid derivative
Benzoic acid derivatives	Benzoic acid compound; some sequence homology to the nonsulfonylurea moiety of glyburide	Increases insulin secretion with meals	Hypoglycemia if tablet is not taken with meals	Biguanide or thiazolidinediones
Alpha-glucosidase inhibitors	Oligosaccharide inhibitor of intestinal hydrolases	Blocks intestinal carbohydrate absorption	Gastrointestinal irritation and flatus	Biguanide or thiazolidinediones

the country is in the midst of a nationwide initiative to improve the care of individuals with diabetes and to reduce the severity of complications among all Americans, especially African Americans.

The pathophysiology of type 2 diabetes is multifactorial in nature. Insulin resistance and impaired insulin secretion both lead to the development of the disease. This is in contrast to type 1 diabetes in which the disease is caused by an autoimmune-mediated destruction of pancreatic islets and resultant absolute insulin deficiency. Normally, in the fasting state, insulin is essential in regulating hepatic glucose output. In the fed state, insulin secretion in response to an ingested meal increases cellular glucose uptake and maintains normal circulating glucose concentrations. When insulin sensitivity is impaired, hyperinsulinemia and glucose intolerance develop. This leads to increased basal and postprandial glucose concentrations. Over time, the beta cell gradually loses its ability to secrete adequate

amounts of insulin and increased glucose concentrations further retard insulin secretion. Patients with type 2 diabetes have defects in both insulin sensitivity and insulin secretion. However, the relative contributions of these factors may vary in different patients. Identifying the major factors that have led to diabetes can guide the physician in developing a treatment plan.

Therapies are now available to enhance insulin secretion, decrease hepatic glucose output, and increase peripheral insulin sensitivity. Once the underlying factors have been identified that led to the development of diabetes in an individual, the physician can choose the most appropriate medication(s) for the patient. Several studies have unequivocally demonstrated that intensive therapy of type 1 and type 2 diabetes results in a decreased incidence of complications and improved overall morbidity.[4-6] This article summarizes the indications, efficacy, and potential dangers of the oral agents currently available for treatment of type 2 diabetes. With effective use of these medications, the control of type 2 diabetes in African Americans will improve and the incidence of its complications will decrease.

SULFONYLUREAS

These agents are derivatives of sulfonic acid and urea, and produce their effects by binding to receptors on the surface of pancreatic beta cells. The binding of sulfonylureas results in depolarization of the cell membrane, the influx of calcium ions, and subsequent release of insulin. The sulfonylureas were developed in 1954 and continue to be the most widely prescribed oral agents for the treatment of type 2 diabetes. Early evidence of associated increased cardiovascular morbidity has not been reproduced, and today sulfonylureas are considered relatively safe agents that have proven effective over long-term use.[4,7]

First-Generation

Sulfonylureas consists of two groups or generations of agents. The first-generation agents are now less commonly used because second-generation agents are as effective and have fewer side effects. Two first-generation agents, chlorpropamide and tolbutamide are still popular with some physicians. This group also contains tolazamide and acetohexamide; both are rarely used today.

Chlorpropamide. Chlorpropamide is administered once daily in a 100 mg or 250 mg tablet. Its half-life is extremely long, with effects lasting up to >48 hours. The principal disadvantage of this agent is that it is excreted almost entirely renally. Therefore, the risk of hypoglycemia makes this drug relatively contraindicated in the elderly and absolutely contraindicated in those with renal insufficiency. Chlorpropamide also enhances the effects of vasopressin, at times resulting in the syndrome of inappropriate antidiuretic hormone (SIADH). With the introduction of more potent agents that have a much shorter half-life and fewer side effects, today there is little reason to use chlorpropamide.

Tolbutamide. Tolbutamide has a much shorter duration of action (6-10 hours) and is metabolized primarily by the liver. It is a safer agent than chlorpropamide; however, it is relatively weak in its antidiabetic activity.

Second-Generation

Second-generation sulfonylureas are the most commonly prescribed agents for treating type 2 diabetes. As a group, they are at least 100 times more potent than tolbutamide. They include glyburide, glipizide, and the newest agent, glimepiride. Glyburide and glipizide, when used as monotherapy, have proven effective in lowering $HgbA_1C$ 1% to 2% in most studies.

Glyburide. Glyburide is metabolized in the liver to metabolites with reduced hypoglycemic activity. These metabolites are then excreted renally. Therefore, in the elderly and patients with compromised renal function, glyburide is relatively contraindicated because of the risk of hypoglycemia. Even in normal subjects it is not unusual to see persistence of glyburide's effects for up to 24 hours. In the United Kingdom Prospective Diabetes Study (UKPDS), a multicenter trial of >5000 patients with type 2 diabetes mellitus, the incidence of hypoglycemia with glyburide was similar to that seen with chlorpropamide.[4] Patients usually are started on a 2.5-mg or 5-mg tablet in the morning before the first meal of the day. The dose can be escalated gradually to a maximum of 20 mg/day. However, it is rare to see further improvement in efficacy with doses >10 mg/day. Again, this agent should be used with caution in the elderly population and in those with renal insufficiency.

There also is a micronized form of glyburide. However, it has been difficult to find exactly equivalent dosages between the two forms, which can lead to confusion for the patient and physician. The micronized agents have not been shown to have a

higher bioavailability or greater efficacy than regular glyburide.

Glipizide. Glipizide is completely metabolized in the liver and excreted primarily by the kidneys. However, it is not as potent as glyburide at raising basal insulin levels and therefore is the preferred sulfonylurea in elderly patients or those with renal insufficiency. It usually is started with 5 mg orally 30 minutes prior to breakfast. If the dose exceeds 15 mg/day, then it is best to divide the doses by giving it before breakfast and before dinner. The maximum recommended dose is 40 mg/day, although it is rare to see additional efficacy with doses >20 mg/day. There is also an extended release form of glipizide, which allows for once a day dosing.

Glimepiride. In 1996, a new sulfonylurea, glimepiride, was approved for use in the treatment of type 2 diabetes. It is the most potent of the sulfonylureas to date, requiring a 1-, 2-, or 4-mg dose once daily. It is completely metabolized in the liver, making it safe in the elderly and in those with renal insufficiency. The maximal recommended dose is 6 mg/day, and this agent is of equal efficacy whether given once or twice daily.[8] Like the other sulfonylureas, glimepiride acts as an insulin secretagogue,[9] but in comparative trials, it caused fewer episodes of hypoglycemia.[10] Other data from comparative trials show that glimepiride provides greater postprandial insulin secretion, but fasting glucose control and $HgbA_1C$ lowering is similar to that of glyburide.[11] Glimepiride has been shown to have extrapancreatic in vitro effects on glucose uptake, but the clinical significance of these effects is still to be determined.[10]

BIGUANIDES

Metformin

Metformin is the only biguanide currently approved for the treatment of type 2 diabetes mellitus. It was originally developed in the 1950s in Europe and has been used there for many years. This agent was approved for use in the United States in 1995. While the mechanism of action is not completely clear at the present time, we do know that metformin is not an insulin secretagogue. It is effective in reducing hepatic and renal gluconeogenesis, thereby lowering fasting blood glucose values.[12] Metformin also is effective in reducing postprandial blood glucose by a mechanism that is thought to involve retardation of gastrointestinal absorption.[13] There also are some data that metformin improves peripheral insulin sensitivity by increasing the expression of glucose transporters and by increasing non-oxidative glucose metabolism.[13]

Metformin usually is given initially as one 500-mg tablet once daily with a meal. One week later, the dose should be increased to 500 mg twice daily and can eventually reach a maximum of 2500 mg/day. Most studies show maximum effect with 2000 mg/day, with no additional efficacy at 2500 mg/day.[13] There also are 850-mg tablets, allowing for convenient twice-daily dosing. Most studies analyzing the effects of metformin show that patients will on average lower $HgbA_1C$ by 1.5%-1.9% when it is used as monotherapy.[13]

This agent can be added to a sulfonylurea or insulin therapy (Table 1), in which case a further decrease in $HgbA_1C$ of 1.5% can be expected.[14] Metformin alone is not associated with hypoglycemia, but this can occur when combined with insulin or sulfonylurea therapy. Metformin has the added benefit of reducing triglycerides and inducing mild weight loss in some overweight patients.[15] The use of metformin to achieve glycemic control was studied in a subset of 342 obese diabetic patients in the UKPDS.[5] Although reduction in myocardial infarction endpoints did not quite reach statistical significance ($P<.052$) in the insulin- and sulfonylurea-intensively treated groups, the obese diabetic patients treated with metformin had significant reductions in myocardial infarction, nonfatal stroke, and all cause mortality.[5] The increased effect of metformin on prevention of macrovascular disease may be related to its known effects on decreasing low-density lipoprotein and triglyceride levels. More information should be available with the release of the UKPDS results concerning lipid profiles.

The main potential complication of metformin use is the risk of lactic acidosis. Unlike its predecessor phenformin, metformin does not strongly inhibit oxidative metabolism of glucose. Due to the absence of this effect, the risk of lactic acidosis is present, but much lower. The incidence of lactic acidosis is quite rare; however, it is recommended to avoid using metformin in patients who are predisposed to lactic acidosis or cannot metabolize lactate. Therefore, patients with a history of hepatic insufficiency, renal insufficiency, severe cardiac or respiratory disease, chronic metabolic acidosis, or alcohol abuse should not take metformin. It also is recommended that metformin should be stopped at the time of any interventional procedures, particularly

surgical procedures or those requiring contrast dye. This will prevent a rise in metformin levels should acute renal failure occur. Metformin also should be used with caution in elderly patients secondary to their diminished renal function.

There are no known drug interactions and the most commonly seen side effect from metformin use is gastrointestinal irritation. Administering the tablet with food and beginning with the 500-mg dose usually prevents or ameliorates this side effect. Less than 5% of individuals will actually require cessation of metformin due to gastrointestinal side effects.

ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors also were popular in Europe prior to their introduction into the American market. At this time, they remain one of the most frequently prescribed antidiabetic agents in Europe. Acarbose was the first agent in this class widely available in the United States. Alpha-glucosidase inhibitors act by blocking the absorption of carbohydrate from the gastrointestinal tract and are most effective in decreasing postprandial glucose elevation. The main advantage of these agents is that they act locally in the gut and are not systemic in their activity. Due to their nonsystemic activity, hypoglycemia is not associated with alpha-glucosidase inhibitors. The disadvantages, however, are greater in number.

Acarbose

Acarbose and the other agents of this class have relatively weak antidiabetic activity, only reducing $HgbA_1C$ by .5%-1% in most patients.[14,16] Diarrhea and flatulence are the most common side effects, occurring in up to 40% of patients in most trials. Secondary to the high incidence of gastrointestinal distress, acarbose should be initiated slowly. It comes in 50-mg and 100-mg tablets, and it is currently recommended that patients begin with 25 mg daily taken with a meal. Afterward, it can be advanced to 25 mg with two meals and slowly increased to a maximum of 300 mg/day. Acarbose should be taken with the first bite of the meal and the most benefit is achieved with doses >150 mg/day. It is at these higher dosages that a recent study has shown reduction of $HgbA_1C$ of 1%-2%.[17] Unfortunately, the incidence of gastrointestinal side effects often precludes reaching these doses.

Miglitol

Recently, miglitol, a new alpha-glucosidase inhibitor, was approved by the Food and Drug Administration. It reportedly has many of the gastrointestinal side effects that limit acarbose use. However, in preliminary studies, miglitol effectively lowered postprandial blood glucose and glycosylated hemoglobin levels.[18]

THIAZOLIDINEDIONES

Thiazolidinediones were developed in Japan and have been available in the United States since March 1997. Today, more than 600,000 people in the United States are being treated with troglitazone. Until recently, troglitazone was the only available member of this group.

Troglitazone

Troglitazone has been shown to improve peripheral insulin sensitivity (ie, increase peripheral glucose disposal) by an as yet undetermined mechanism. We do know that the drug binds to an intranuclear receptor (PPARgamma), and this complex has been found to function as a transcriptional activator.[19] How PPARgamma activation by troglitazone results in improved insulin sensitivity is not clear.

Troglitazone comes in 200-mg and 400-mg tablets, and patients are started at 200 mg in the morning with food to aid in rapid absorption. Thereafter, the dose can be increased to 400 mg/day and eventually to the maximum of 600 mg/day. The tablets should be given once in the morning, as there is no advantage to dividing the dose.

Troglitazone was initially proven effective in type 2 diabetic patients who already were being treated with insulin. In 1998, troglitazone was approved by the FDA for use as monotherapy in the treatment of type 2 diabetes. Studies in patients already receiving insulin therapy have shown a significant improvement in $HgbA_1C$ and a reduction in insulin requirements. A 1.5% reduction in $HgbA_1C$ has been reported when troglitazone is added to conventional insulin therapy.[14] Monotherapy has been less effective, with an average decrease in $HgbA_1C$ of .9%. Whether used as single or combination therapy, there is a lag time of several weeks for troglitazone to have a glucose-lowering effect and a delay of several months for maximum glucose lowering effect. The drug is not effective in those patients with relative insulinopenia. It is important to use clinical judgment in determining which patients with type 2 diabetes have significant insulin resistance with hyperinsulinemia and therefore are better candidates for troglitazone thera-

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