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NEW ORAL THERAPIES FOR TYPE 2 DIABETES MELLITUS: The Glitazones or Insulin Sensitizers*

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■ **Abstract** Type 2 diabetes mellitus is a growing problem not only in the United States but also across the world. There is now strong evidence that intensive control of blood glucose can significantly reduce and retard the microvascular complications of retinopathy, nephropathy, and neuropathy. Ultimately however, up to 80% of type 2 diabetics die from macrovascular cardiovascular disease. This increased incidence of atherosclerotic disease is intricately associated with insulin resistance, which is a major pathophysiologic abnormality in type 2 diabetes. There is strong evidence that insulin resistance is involved in the development of not only hyperglycemia, but also dyslipidemia, hypertension, hypercoagulation, vasculopathy, and ultimately atherosclerotic cardiovascular disease. This cluster of metabolic abnormalities has been termed the insulin resistance or cardiovascular dysmetabolic syndrome. The thiazolidinediones (rosiglitazone and pioglitazone), a new class of oral antidiabetic agents, are "insulin sensitizers" and exert direct effects on the mechanisms of insulin resistance. These effects not only improve insulin sensitivity and glycemic control with reduced insulin requirements, but also have potentially favorable effects on other components of the cardiovascular dysmetabolic syndrome. Long-term studies are needed to determine whether the insulin-sensitizing effects of the glitazones can prevent or delay premature atherosclerotic cardiovascular disease, morbidity, and death.

INTRODUCTION

Type 2 diabetes mellitus is a chronic disease characterized by hyperglycemia and numerous other metabolic abnormalities. This chronic and disabling disease affects more than 16 million people in the United States (1) and some 200 million people worldwide (2). Its chronic complications include retinopathy, nephropathy,

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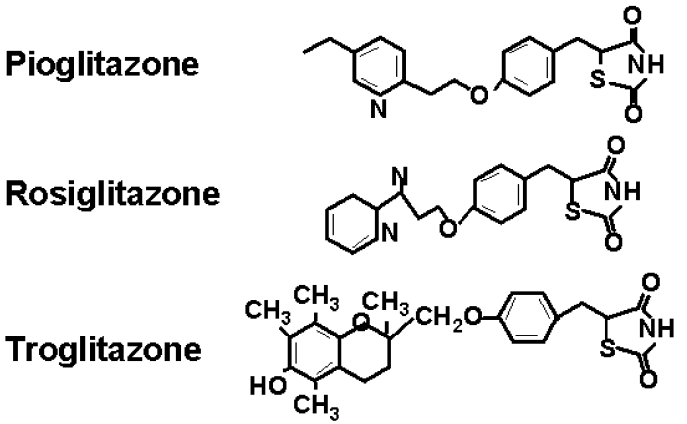

Figure 1 The structure of thiazolidinedione agents.

neuropathy, and accelerated atherosclerosis, which result in blindness, end-stage renal disease, amputations, and premature cardiovascular mortality.

There are three major pathophysiologic abnormalities associated with type 2 diabetes: impaired insulin secretion, excessive hepatic glucose output, and insulin resistance in skeletal muscle, liver, and adipose tissue (3). The oral pharmacologic agents available for the treatment of type 2 diabetes act primarily by increasing insulin availability (sulfonylureas and meglitinides); delaying gastrointestinal glucose absorption (α-glucosidase inhibitors); suppressing excessive hepatic glucose output (metformin); and reducing insulin resistance at target tissues, mainly skeletal muscle, adipose tissue, and liver (thiazolidinediones or glitazones). There is strong evidence that insulin resistance is intricately involved in the development of not only hyperglycemia but also dyslipidemia, hypertension, hypercoagulation, vasculopathy, and ultimately atherosclerotic cardiovascular disease (4).

The thiazolidinediones appear to be ideally suited for treatment of this cluster of metabolic abnormalities, which has been termed the insulin resistance or cardiovascular dysmetabolic syndrome (4). These agents are chemically and functionally unrelated to the other classes of oral antidiabetic agents. All agents of this class have a thiazolidine-2-4 dione structure (Figure 1), but they differ in their side chains, which alter their pharmacologic and side-effect profiles. Two compounds in this class have been approved for use in the United States. Rosiglitazone (Avandia®) was approved by the US Food and Drug Administration (FDA) in May 1999 and Pioglitazone (Actos®) in July 1999. The first agent in this class, troglitazone (Rezulin®) was marketed in the United States from March 1997 until it was withdrawn in March 2000, when the FDA determined that the risk of idiosyncratic hepatotoxicity associated with troglitazone therapy outweighed its potential benefits. In clinical use so far, rosiglitazone and pioglitazone appear to be devoid of idiosyncratic, fulminant hepatotoxicity. Monotherapy with the

glitazones results in significant improvements in fasting plasma glucose (FPG) by 60–80 mg/dl and in glycosylated hemoglobin (HbA1c) by 1.4%–2.6% compared with placebo. Rosiglitazone is currently approved for use as monotherapy and in combination with metformin and sulfonylurea. Pioglitazone is approved for use as monotherapy and also in combination with insulin, metformin, or sulfonylurea. Here, we review the mode of action, pharmacology, and clinical applications of the newest antidiabetic agents, the thiazolidinediones—rosiglitazone and pioglitazone.

MECHANISM OF ACTION

The thiazolidinediones are highly selective and potent agonists for the peroxisome proliferator activated receptor–γ (PPAR-γ) (5, 6; Figure 2). The PPARs are a family of nuclear receptors comprised of three subtypes designated PPAR-α, PPAR-γ, and PPAR-δ (7). PPAR-γ receptors are found in key target tissues for insulin action, such as adipose tissue, skeletal muscle, and liver, and evidence indicates that these receptors are important regulators of adipocyte differentiation, lipid homeostasis, and insulin action (6, 7). There is a close relationship between the potency of various thiazolidinediones to stimulate PPAR-γ and their antidiabetic action (8).

In freshly isolated human adipocytes, rosiglitazone increased p85-α phosphatidylinositol 3-kinase (p85-α PI3K) and uncoupling protein (UCP)-2 mRNA levels, and it decreased leptin expression. p85α PI3K is a major component of insulin action and the induction of its expression might explain, at least in part, the insulin-sensitizing effect of the thiazolidinediones (9). In animal studies, glitazones

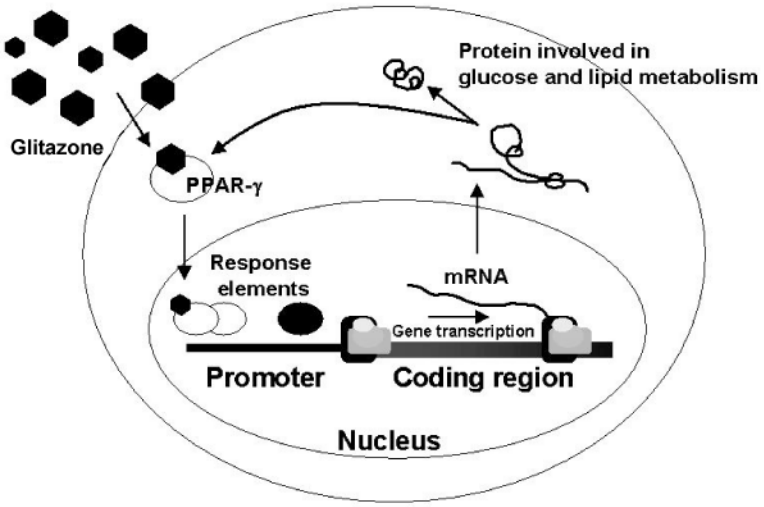

Figure 2 Glitazone activation of the nuclear receptor PPAR-γ.

have been shown to stimulate *GLUT1* and *GLUT4* (glucose transporters) gene expression (10) and to reduce *ob* gene, tumor necrosis factor–α (TNF-α), and hepatic glucokinase expression through activation of PPAR-γ (11). In obese Zucker rats, treatment with a thiazolidinedione (specifically troglitazone) reduces leptin levels and lowers ob gene and TNF-α expression. Associated with this is apoptosis of large adipocytes and an increase in the number of small adipocytes (with no net change in adipose tissue weight) (12). Both TNF-α and leptin (an *ob* gene product) have been associated with insulin resistance, and it is possible that the reduction in large adipocytes and the lower TNF-α and leptin levels ameliorate insulin resistance. The increase in the number of small adipocytes may also contribute to the reduction of insulin resistance. Small adipocytes take up more glucose than large adipocytes at submaximal insulin levels and are also more sensitive to the antilipolytic action of insulin (13, 14). This could result in lower free fatty acid (FFA) and triglyceride levels and improved insulin sensitivity. The glitazones also appear to exert beneficial effects on glucose and lipid metabolism in the absence of adipose tissue. Burant et al (15) demonstrated beneficial metabolic changes after troglitazone treatment in muscle and liver of aP2/DTA mice, whose white and brown fat were virtually eliminated by fat-specific expression of diphtheria toxin. In isolated liver cells, pioglitazone has been shown to reverse insulin resistance induced by TNF-α (16).

Some studies even suggest that the glitazones have primary effects in skeletal muscle. In human skeletal muscle culture systems, troglitazone treatment markedly increases PPAR-γ protein expression along with other genes involved in glucose and lipid metabolism (17). In the same skeletal muscle culture system, troglitazone has been demonstrated to have acute effects on glucose uptake and chronic effects on glucose uptake and glycogen synthase activity (18). Concomitantly, there were increases in GLUT1 mRNA and protein and no change in GLUT4 or glycogen synthase mRNA or protein.

Even the vascular effects of the glitazones appear to be mediated through PPAR-γ agonism (19–21). Human and rat vascular smooth muscle cells (VSMCs) express mRNA and nuclear receptors for PPAR-γ 1 (19, 21). These receptors are upregulated during vascular injury and are present in early human atheroma and precursor lesions. Pharmacological activation of PPAR-γ with troglitazone and rosiglitazone inhibits VSMC proliferation and migration and thus can limit restenosis and atherosclerosis. Also, both troglitazone and pioglitazone inhibit vasopressin and platelet-derived growth factor (PDGF)-induced Ca^{2+} entry and proliferation in rat VSMCs (19).

The important role played by PPAR-γ in glucose and lipid metabolism and vascular endothelial function has stimulated intensive research into PPAR-γ gene mutations. Recently, O'Rahilly and colleagues reported two different heterozygous, loss-of-function mutations in three subjects who had severe insulin resistance, early-onset diabetes, and hypertension. These findings provide genetic evidence that the PPAR-γ receptor is important in the control of insulin sensitivity, glucose homeostasis, and blood pressure in humans (19a). However, in an earlier

publication, Kahn and associates reported a heterozygous mutation in PPAR-γ in three unrelated obese subjects who paradoxically had normal insulin sensitivity (19b).

Thus, the thiazolidinediones act, at least in part, by binding with PPAR-γ in various tissues to enhance the expression of genes encoding proteins involved in glucose and lipid metabolism, endothelial function, and atherogenesis (5, 19–21). In the near future, it is likely that numerous other genes will be identified that are affected by thiazolidinediones and contribute to the insulin-sensitizing, lipid-lowering actions and vascular effects of these compounds.

PHARMACOKINETICS

After oral administration, both rosiglitazone and pioglitazone are rapidly absorbed, and peak serum concentrations occur within 1 h for rosiglitazone and within 2 h for pioglitazone. The pharmacokinetics of rosiglitazone are not altered by food intake, but the time to peak serum concentration of pioglitazone is delayed to 3–4 h, although total absorption is unchanged. Steady-state serum concentrations of both drugs are achieved within 7 days; protein binding is high (>99%) and is primarily to serum albumin.

Rosiglitazone is extensively metabolized with no unchanged drug detected in urine. The major routes of metabolism include N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. In vitro data show that rosiglitazone is predominantly metabolized by cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 serving as a minor pathway. Metabolites are active but have significantly less activity than the parent compound.

On the other hand, pioglitazone is extensively metabolized by hydroxylation and oxidation. The major hepatic cytochrome P450 enzymes involved are CYP2C8 and CYP3A4. In animal studies, metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (a keto derivative of pioglitazone) are pharmacologically active. Metabolites M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady state, serum concentrations of metabolites M-III and M-IV are equal to or greater than serum concentrations of pioglitazone.

The plasma half-life ranges from 3 to 4 h for rosiglitazone, and is 3–7 h for pioglitazone and 16–24 h for pioglitazone metabolites.

CLINICAL USE AND EFFICACY

Rosiglitazone is approved for use alone and in combination with metformin and sulfonylureas. In two US placebo-controlled clinical trials in patients with type 2 diabetes, 4 mg/day of rosiglitazone for 26 weeks improved FPG by 25–35 mg/dl and HbA1c by 0.3%, and 8 mg/day for 26 weeks improved FPG by 42–55 mg/dl

and HbA1c by 0.7%, relative to baseline (22). In these studies, rosiglitazone was generally more effective in reducing FPG and HBA1c when administered in divided doses twice daily than when administered once daily. However, for HbA1C, the difference between the 4-mg once-daily dose and the 2-mg twice-daily dose was not statistically significant.

In another US study, when compared directly to maximum stable doses of glyburide, rosiglitazone reduced FPG by 25 mg/dl at 4 mg/day and by 41 mg/dl at 8 mg/day, whereas glyburide at 15 mg/day reduced FPG by 30 mg/dl (22). Although the initial fall in FPG was greater with glyburide, the improvement in glycemic control with rosiglitazone was maintained through week 52 of the study. Importantly, in patients treated with rosiglitazone, levels of C-peptide, insulin, and proinsulin were significantly reduced, whereas the levels increased in the glyburide-treated patients.

The addition of rosiglitazone at 2–8 mg/day to existing sulfonylurea, metformin, or insulin therapy also achieves further reductions in fasting plasma glucose and HbA1c (22–24). In a double-blind, placebo-controlled trial, 348 patients with type 2 diabetes were randomized to receive 2500 mg/day of metformin plus either placebo, 4 mg/day of rosiglitazone, or 8 mg/day of rosiglitazone. After 26 weeks, FPG levels were 40 mg/dl lower in the 4-mg metformin-rosiglitazone group than in the metformin-placebo group, and 53 mg/dl lower in the 8-mg rosiglitazone group compared with placebo. Mean HbA1C levels were 1.0% lower with the 4-mg dose and 1.2% lower in the 8-mg dose. Of patients receiving 8 mg/day of metformin-rosiglitazone, 28.1% achieved an HbA1C level of $<7\%$. In addition, beta-cell function as measured by the homeostasis model assessment (HOMA) improved significantly with metformin-rosiglitazone therapy in a dose-dependent manner (25). The combination of rosiglitazone (2 mg twice daily) and sulfonylurea decreased FPG by 44 mg/dl and HbA1C by 1.0%, and in combination with insulin, rosiglitazone at 4 mg twice daily reduced FPG by 55 mg/dl and HbA1C by 1.3% (26).

The other currently marketed thiazolidinedione, pioglitazone, is the only glitazone approved by the FDA for use as monotherapy and in combination with sulfonylureas, metformin, and insulin. In the absence of head-to-head studies, it is not possible to evaluate which glitazone is more potent in clinical use. Pioglitazone has been demonstrated to improve glycemia when used as monotherapy (27). In US studies, after 26 weeks, pioglitazone reduced mean FPG levels by 30 mg/dl at 15 mg/day, by 32 mg/dl at 30 mg/day, and by 56 mg/dl at 45 mg/day, compared with an increase of 9 mg/dl in the placebo group. Concurrent with FPG, the HbA1C levels also decreased by 0.3% with pioglitazone at 15 mg and 30 mg daily and decreased 0.9% with pioglitazone at 45 mg daily. HbA1C levels increased 0.7% in the placebo group (28).

In another double-blind study, pioglitazone at 15 mg daily, when added to a sulfonylurea regimen, reduced FPG by 39 mg/dl and reduced HbA1C by 0.9% after 16 weeks of therapy. At 30 mg pioglitazone per day, the pioglitazone-sulfonylurea combination reduced FPG by 58 mg/dl and reduced HbA1C by 1.3%. In the placebo group, there was an increase of 6 mg/dl in the FPG and 0.1% in the HbA1C (29).

Pioglitazone is also useful in combination with metformin. In a large 16-week study, compared with placebo, pioglitazone at 30 mg daily significantly reduced mean FPG levels (by 38 mg/dl) and HbA1c levels (by 0.8%) (30). Another use for pioglitazone is in the treatment of patients on insulin therapy. In a 16-week study, Rubin et al demonstrated that the administration of pioglitazone at 15 mg and 30 mg daily to patients receiving a median dose of 60.5 units of insulin resulted in mean FPG reductions of 36 mg/dl and 49 mg/dl and HbA1C reductions of 0.7% and 1.0%, respectively, compared with placebo (31).

OTHER BENEFICIAL EFFECTS

The glitazones have been shown to have beneficial effects not only on peripheral insulin sensitivity, hepatic glucose metabolism, and lipid metabolism but also on endothelial function, atherogenesis, fibrinolysis, ovarian steroidogenesis, and cancer cell apoptosis (5, 32–34).

Effects on Insulin Sensitivity

Most of the human studies on the insulin-sensitizing effects of the thiazolidinediones in vivo were done with troglitazone, which is no longer available. These studies documented troglitazone's in vivo effects on peripheral insulin action not only in patients with type 2 diabetes but also in other insulin-resistant states such as impaired glucose tolerance, polycystic ovary disease, previous gestational diabetes, and Werner's syndrome (5). Some of these studies used the euglycemic clamp and the frequently sampled intravenous glucose tolerance test (FSIGTT) to quantify changes of insulin sensitivity; other studies used less direct methods, including the insulin tolerance test and the intravenous or oral glucose tolerance test to assess troglitazone's effects on insulin resistance. In all studies, troglitazone in doses ranging from 200 to 600 mg/day enhanced insulin-mediated peripheral glucose utilization in both obese and lean subjects by ∼30%–100%.

Two studies from Japan document the insulin-sensitizing effects of pioglitazone in patients with type 2 diabetes. One double-blind, placebo-controlled clinical trial evaluated the effect of pioglitazone on insulin resistance in patients with type 2 diabetes (35). Insulin sensitivity [measured as insulin-stimulated glucose disposal (Rd) by the hyperinsulinemic clamp technique] and splanchnic glucose uptake (SGU) both increased significantly after three months of pioglitazone treatment. Placebo treatment produced no significant changes in either Rd or SGU. The authors concluded that pioglitazone is effective in ameliorating insulin resistance in type 2 diabetes by enhancing SGU as well as peripheral glucose uptake. Another Japanese study (36) also evaluated the effect of pioglitazone on insulin-stimulated Rd in 20 patients with type 2 diabetes. After oral administration of pioglitazone (30 mg/day) for three months, in addition to improvement in glycemic control and fasting insulin and C-peptide levels and lipid levels, the Rd significantly improved

by more than 50%. In this study, the change in Rd before and after pioglitazone administration correlated with baseline values of FPG ($\rho = 0.633$), serum insulin ($\rho = 0.653$) and BMI ($\rho = 0.456$).

Effects on Lipids

In type 2 diabetes, the major quantitative change in lipid levels is an elevation in triglyceride-rich lipoproteins and a decrease in high-density lipoprotein (HDL) cholesterol concentrations. Interestingly, low-density lipoprotein (LDL) cholesterol levels are often similar to those in the general population (37). However, qualitative changes in the composition of the LDL molecule, including an increase in small, dense LDL particles that are prone to glycation and oxidation, tend to make the molecule more atherogenic (37). This diabetic dyslipidemic profile is closely related to underlying insulin resistance and is likely be at least partly responsible for the increased cardiovascular morbidity and mortality in type 2 diabetics (38).

By improving glucose tolerance and reducing insulin resistance, the glitazones may favorably influence diabetic dyslipidemia. However, from the data presently available, there appear to be differences in the lipid-modifying abilities of the various glitazones. Pioglitazone has been shown to lower triglycerides by ~9% and increase HDL levels by ~12%–19% (39). Troglitazone has also been shown to lower triglyceride levels ~15%–20% and increase HDL cholesterol levels ~5%–8% (5). Reduction in triglyceride levels appears to result from several mechanisms, including reduced free fatty acid (FFA) substrate availability, decreased hepatic triglyceride synthesis, and enhanced peripheral clearance. In the case of rosiglitazone, despite a significant decrease in FFA levels of up to 22%, initial studies indicate no significant lowering of triglycerides, although HDL levels do increase by up to 19%. The reasons for this are not yet clear.

In addition, with all the glitazones so far, there is an increase in LDL cholesterol levels, which is cause for concern. In the case of troglitazone, it has been shown that this increase in LDL cholesterol of ~10% occurred without change in atherogenic apolipoprotein B levels (5). Moreover, following troglitazone treatment, the LDL particles became larger, more buoyant, and less prone to oxidative modification (40, 41). Data on LDL particle size and apolipoprotein B levels are still not available for rosiglitazone and pioglitazone. Long-term follow-up will be needed to see if the rise in LDL has an adverse impact on atherosclerosis and cardiovascular mortality or is offset by the potentially favorable effects on particle size.

One report (42) found a significant increase in Lp(a) levels after 4 weeks of troglitazone treatment at 400 mg/day in a small group of ten type 2 diabetic subjects (despite significant improvements in glucose and insulin sensitivity parameters). No change was found in a control group of sulfonylurea-treated patients. This increase in Lp(a) levels persisted for 12 weeks after discontinuation of troglitazone treatment and then returned to baseline values. Since Lp(a) may be associated with the development of coronary artery disease, larger, long-term studies are needed to confirm and evaluate the significance of elevated Lp(a) levels in thiazolidinedione-treated diabetic patients.

Vascular Effects

The prevalence of hypertension in diabetics is 1.5- to 2-fold higher than in nondiabetic individuals (43), and hypertension is one of the components of the insulin resistance syndrome. In type 2 diabetes and other insulin-resistant states, insulin-induced vasodilation is impaired (44), and it is possible that by enhancing insulin action, the thiazolidinediones may enhance the tonic vasodilator response to insulin and thereby reduce peripheral vascular resistance and blood pressure. Additionally, by reducing hyperinsulinemia and plasma insulin levels, these agents may reduce the potential blood-pressure–raising actions of insulin, such as renal sodium retention and increased sympathetic activity (45). Limited data suggest that the glitazones may have beneficial effects on blood pressure. In early studies, troglitazone at 800 mg/day over 48 weeks significantly reduced diastolic blood pressure by 6.5 mm Hg (8%) (46). Rosiglitazone 4 at mg twice a day over 52 weeks has also been associated with significant decreases in systolic blood pressure (3.5 mmHg) and diastolic blood pressure (2.7 mmHg) (47). No data are yet available for pioglitazone.

Anti-Atherogenic Effects

Increased concentrations and activity of plasminogen activator inhibitor–1 (PAI-1) are known to be associated with a prothrombotic state. Levels of PAI-1 are increased in patients with type 2 diabetes and are strongly correlated with body mass index, insulin resistance, and fasting levels of insulin, triglycerides, and HDL (48). So far, only troglitazone has been shown to reduce PAI-1 to near-normal levels in diabetic patients (48). Pioglitazone decreases PAI-1 levels in cultured human umbilical vein endothelial cells (49). No data are available for rosiglitazone.

Platelet aggregation is also increased in diabetic subjects (50). Troglitazone has been shown to have potent inhibitory effects on human platelet aggregation via suppression of thrombin-induced activation of phosphoinositide signaling in platelets (51). This effect was not reproducible with pioglitazone and hence may have been due to troglitazone's unique structure, which includes the α-tocopherol (vitamin E) moiety.

Another factor that is correlated with the pathogenesis and progression of atherosclerosis and restenosis is the proliferation and migration of vascular smooth muscle cells (VSMCs) from the media to the intima. Troglitazone and pioglitazone both inhibited VSMC growth and migration in preclinical studies (52–55). Also, improvements in vascular reactivity have been shown for troglitazone in human and animal studies and for pioglitazone in animal studies (in vitro only) (56, 57).

Intimal-medial thickness (IMT), a measure of atherosclerotic progression, is correlated with insulin levels in patients with and without type 2 diabetes (58, 59). In clinical trials, troglitazone reduced intimal hyperplasia in type 2 diabetes patients with and without coronary stent implants (58, 60). Effects were seen in as little as three months and were more profound than in previously reported data for pravastatin, an HMG-CoA reductase inhibitor (61, 62). Pioglitazone has shown

similar results in animal studies (63). Some evidence suggests that IMT is negatively related to insulin sensitivity (64), and it is possible that the reduction in insulin resistance after troglitazone treatment was related to the regression of both carotid and coronary IMT. This effect of troglitazone, if confirmed with the other available glitazones and shown to persist long-term, could be highly beneficial, delaying or preventing development of the accelerated atherosclerosis of type 2 diabetes.

Effects on Insulin Secretion

An elevated ratio of proinsulin to immunoreactive insulin is often present in type 2 diabetes and may reflect dysfunctional beta-cell processing of the prohormone and associated reduced beta-cell secretory capacity (65). One study found that 52 weeks of rosiglitazone therapy significantly decreased the proinsulin/immunoreactive insulin ratio (66). Troglitazone therapy was also associated with a decrease in this ratio, which suggests direct effects on the beta cell (65).

Effects on Cancer Cells

There is preliminary evidence that the thiazolidinediones, through their action on PPAR-γ, may have adverse effects on cancer cells. Estrogen biosynthesis is catalyzed by aromatase cytochrome P450, and adipose tissue is the major site of estrogen biosynthesis in postmenopausal women. Rubin et al (32) demonstrated in tissue culture that the PPAR-γ ligands troglitazone and rosiglitazone inhibit aromatase expression in cultured breast adipose stromal cells stimulated with oncostatin M or TNF-α plus dexamethasone in a concentration-dependent manner. This action of PPAR-γ agonism may have potential therapeutic benefit in the treatment and management of breast cancer. Takahashi et al (33) showed that human gastric cancer cells express PPAR-γ and that activation of PPAR-γ with troglitazone inhibits cell growth and induces apoptosis in gastric cancer cells. Another study obtained similar results using human lung cancer cells (34).

On the other hand, a murine model for familial adenomatous polyposis and sporadic colon cancer provides evidence that the glitazones have tumor-inducing effects. Hence, until further research clarifies this issue, these drugs are not recommended for patients in families with adenomatous polyposis coli (67). Long-term studies are needed to monitor the glitazones' effects on the development of sporadic colon tumors.

DOSAGE

The usual starting dose of rosiglitazone is 4 mg orally given as either a single dose once daily or in divided doses twice daily (22). For patients who respond inadequately after 12 weeks of initial treatment with rosiglitazone, the dose may be increased to 8 mg PO given as a single dose once daily or in divided doses twice daily. Pioglitazone therapy may be initiated at 15 mg or 30 mg PO once daily. For

patients who respond inadequately to the initial dose, the dose can be increased in increments up to a maximum of 45 mg PO once daily. Patients who have not responded adequately to monotherapy with both rosiglitazone and pioglitazone should be considered for combination therapy (22, 27).

The safety and efficacy of rosiglitazone and pioglitazone in adolescents and children have not been established (22, 27).

Patients with Hepatic Impairment

If a patient exhibits clinical or laboratory evidence of active liver disease or increased serum transaminase levels (ALT >2.5 times the upper limit of normal), neither rosiglitazone nor pioglitazone therapy should be initiated (see contraindications below) (22, 27).

Patients with Renal Impairment

There are no clinically relevant differences between the pharmacokinetics of rosiglitazone or pioglitazone in patients with normal renal function and patients with mild to severe renal impairment, or in hemodialysis-dependent patients. Hence, dosage adjustments are not required in patients with renal impairment who receive these agents alone. However, since metformin is contraindicated in patients with renal impairment, concomitant administration of rosiglitazone or pioglitazone with metformin is also contraindicated in patients with renal impairment (22, 27).

Side Effects

The glitazones increase plasma volume by 6%–7%, and edema is often associated with their use. In US clinical trials, edema has been reported more frequently in pioglitazone-treated patients than in placebo-treated patients. In monotherapy studies, edema was reported in 4.8% of pioglitazone-treated patients versus 1.2% of placebo-treated patients, and in the pioglitazone-insulin combination study, nearly 15.3% of pioglitazone-treated patients developed edema versus 7.0% of placebo-treated patients. Edema was also reported in 4.8% of patients receiving rosiglitazone versus 1.3% of patients on placebo, 1% of those on sulfonylureas, and 2.2% of those on metformin (22, 27).

Weight gain has also been reported more frequently with glitazone therapy. In the 26-week rosiglitazone clinical trials, the mean weight gain in patients treated with rosiglitazone monotherapy was 1.2 kg (on 4 mg daily) and 3.5 kg (on 8 mg daily). When administered in combination with metformin for 26 weeks, weight gain was 0.7 kg (on 4 mg daily) and 2.3 kg (on 8 mg daily). There was a mean weight loss of about 1 kg in both placebo and metformin monotherapy groups in these studies. A 52-week glyburide-controlled rosiglitazone study reported a mean weight gain of 1.75 kg (on 4 mg daily) and 2.95 kg (on 8 mg daily) for rosiglitazone-treated patients versus 1.9 kg in glyburide-treated patients. Similarly, in clinical studies, pioglitazone treatment is accompanied by weight gain

in a dose-related manner. The increase in average weight in US placebo-controlled monotherapy trials ranged from 0.5 kg to 2.8 kg for pioglitazone-treated patients, whereas placebo-treated patients' weight decreased by 1.3–1.9 kg. Patients taking a pioglitazone-sulfonylurea combination gained on average 1.9 kg (on 15 mg pioglitazone) and 2.9 kg (on 30 mg), whereas patients on a placebo-sulfonylurea combination lost on average 0.8 kg. Patients taking a pioglitazone-insulin combination gained on average 2.3 kg (on 15 mg pioglitazone) and 3.7 kg (on 30 mg), whereas the placebo-insulin group experienced no weight change. Even when pioglitazone was combined with metformin, the change in average weight was a 1.0-kg increase for patients on 30 mg of pioglitazone versus a 1.4-kg decrease for patients on placebo (22, 27).

Hemoglobin and hematocrit decrease in a dose-related fashion in patients treated with rosiglitazone and pioglitazone, alone or in combination. These changes are at least partly caused by increases in plasma volume and a dilutional effect of the glitazones. These changes occur primarily during the first 4 to 12 weeks of therapy; hemoglobin and hemocrit levels remain relatively constant thereafter. These changes have not been associated with any significant hematologic clinical effects. Reports of anemia were more frequent (7.1%) in patients treated with a combination of rosiglitazone and metformin, but lower pretreatment hemoglobin/hematocrit levels in patients taking metformin concurrently may have contributed to the higher reporting rate of anemia in these studies. US double-blind studies of pioglitazone alone and in combination reported anemia in 0.3%–1.6% of pioglitazone-treated patients and 0%–1.6% of placebo-treated patients. Rosiglitazone-treated patients also experience slight decreases in white blood cell counts, which may be related to the increased plasma volume (22, 27).

In placebo-controlled trials, 0.2% of rosiglitazone-treated patients and 0.2% of placebo-treated patients had reversible elevations in ALT (>3 times the upper limit of normal), compared with 0.5% of patients on active comparator agents. In pioglitazone studies, 0.26% of pioglitazone-treated patients and 0.25% of placebo-treated patients had ALT values >3 times the upper limit of normal. Preapproval clinical trials reported no cases of idiosyncratic drug reactions leading to hepatic failure for either rosiglitazone or pioglitazone. Overall, the incidence of withdrawals from clinical trials because of an adverse event other than hyperglycemia was similar for patients receiving placebo or a glitazone (22, 27).

Because the thiazolidinediones do not stimulate insulin secretion, they are not expected to cause hypoglycemia when used alone. However, mild to moderate hypoglycemia has been reported during combination therapy with sulfonylureas or insulin (22, 27).

Drug Interactions

There are significant differences in drug interactions among the glitazones. Both pioglitazone and troglitazone induce the cytochrome P450 isoform CYP3A4,

which is partly responsible for their metabolism. Thus, safety and efficacy could possibly be affected when pioglitazone is coadministered with other drugs metabolized by this enzyme. These include alprazolam, carbamazepine, some corticosteroids, cyclosporine, diazepam, diltiazem, erythromycin, felodipine, fexofenadine, lidocaine, lovastatin, midazolam, nifedipine, quinidine, some retroviral agents, simvastatin, tacrolimus, terfenadine, triazolam, and verapamil. In contrast, rosiglitazone has no drug interactions with any drugs metabolized by the P450 enzyme system. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8 and, to a lesser extent, CYP 2C9 (22).

Pioglitazone, but not rosiglitazone, may also reduce the bioavailability and efficacy of oral contraceptives containing ethinyl estradiol and norethindrone by induction of CYP3A4 enzymes. Thus, higher-dosage oral contraceptive formulations may be needed to increase contraceptive efficacy during pioglitazone use. Alternatively, the use of an alternative or additional method of contraception is recommended (22, 27).

Rosiglitazone had no clinically relevant effect on the steady-state pharmacokinetics of warfarin, nifedipine, digoxin, or ranitidine in healthy volunteers. Also in healthy volunteers, coadministration of pioglitazone with digoxin, glipizide, metformin, or warfarin for seven days did not alter the steady-state pharmacokinetics of these medications (22, 27).

Contraindications and Precautions

Troglitazone, the first glitazone marketed in the United States, was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, the need for liver transplants, and death, which led to its recall from clinical use in March 2000. In preclinical studies so far with rosiglitazone and pioglitazone, the incidence of hepatotoxicity and ALT elevations has been similar to placebo. Also, in clinical use to date, there have been only two reports of hepatotoxicity associated with rosiglitazone use (68, 69), and none with pioglitazone. However, rosiglitazone and pioglitazone should be used cautiously in patients with hepatic disease, since both are structurally very similar to troglitazone.

In all patients, liver enzymes should be checked before rosiglitazone or pioglitazone therapy is initiated. Glitazone therapy should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5 times the upper limit of normal). In patients with normal baseline liver enzymes, following initiation of therapy with rosiglitazone or pioglitazone, it is recommended that liver enzymes be monitored every two months for the first year and periodically thereafter. Patients with mildly elevated liver enzymes (ALT levels 1 to 2.5 times the upper limit of normal) at baseline or during therapy with rosiglitazone or pioglitazone should be evaluated to determine the cause of the elevation. Initiation or continuation of glitazone therapy in patients with mild liver-enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent

liver-enzyme monitoring, to determine if the liver-enzyme elevations resolve or worsen. If at any time ALT levels increase to >3 times the upper limit of normal in patients on therapy with rosiglitazone or pioglitazone, liver-enzyme levels should be rechecked as soon as possible. If ALT levels remain >3 times the upper limit of normal, glitazone therapy should be discontinued. If the patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or dark urine, liver enzymes should be checked. The decision whether to continue therapy with rosiglitazone or pioglitazone should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued (22, 27).

No data are available to evaluate the safety of rosiglitazone or pioglitazone in patients who experience liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. Neither rosiglitazone nor pioglitazone should be used by patients who experienced jaundice while taking troglitazone. For patients with normal hepatic enzymes who are switched from troglitazone to rosiglitazone or pioglitazone, a one-week washout is recommended before starting therapy with either drug (22, 27).

Caution should also be exercised when pioglitazone or rosiglitazone are administered to premenopausal, anovulatory females with insulin resistance, who may resume ovulation as a result of glitazone therapy. These patients may be at risk of becoming pregnant if adequate contraception is not used. Patients on pioglitazone who use oral contraceptive therapy are also at risk because of CYP3A4 enzyme induction (see above) (22, 27).

Due to increases in plasma volume, both glitazones should be used cautiously in patients with peripheral edema or early congestive heart failure. Thiazolidinediones, including rosiglitazone, have caused preload-induced cardiac hypertrophy in preclinical studies. In two ongoing echocardiographic clinical studies (a 52-week study using rosiglitazone 4 mg PO twice daily and a 26-week study using rosiglitazone 8 mg PO once daily) in patients with type 2 diabetes, no deleterious alterations in cardiac structure or function were observed. These studies were designed to detect a change in left ventricular mass of 10% or more. Patients with severe congestive heart failure, defined as New York Heart Association (NYHA) functional Class III and IV, were not studied. As a result, patients with NYHA Class III or IV heart failure should not receive glitazones unless the expected benefit is judged to outweigh the potential risk (22, 27).

Rosiglitazone and pioglitazone are contraindicated in pregnancy. Although animal data suggest no teratogenic effects, there are no adequate and well-controlled studies in pregnant women. Also, since it is unknown whether these drugs are secreted in human milk, they should not be administered to breast-feeding women (22, 27).

Thiazolidinediones are active only in the presence of insulin. They should not be used to treat either diabetic ketoacidosis or type 1 diabetes (22, 27).

Newer Oral Agents

Several new thiazolidinedione and non-thiazolidinedione PPAR-γ and PPAR-α agonists are undergoing clinical studies for the treatment of type 2 diabetes (70). They include GI 262570, JTT 501, KRP 297, and BM 17.0744. In animal models of insulin resistance, JTT 501 treatment has favorable effects on insulin signaling and considerably improves insulin-induced *GLUT4* translocation and glucose uptake in rat adipocytes. JTT 501 possesses an isoxazolidinedione rather than a thiazolidinedione structure and also has potent triglyceride-lowering activity because it inhibits triglyceride secretion from the liver and enhances triglyceride disposal in peripheral tissues (71). Some thiazolidinediones, such as MCC-555 and L-764486, are only weak PPAR-γ ligands, but still retain significant antidiabetic properties. They are PPAR-γ modulators rather than agonists and can behave as full or partial agonists or antagonists, depending on cell type and sequence-recognition site (70).

CONCLUSION

The thiazolidinediones are a unique new class of oral antidiabetic agents that exert direct effects on the mechanisms of insulin resistance, which is a major pathophysiologic abnormality in type 2 diabetes. The glitazones exert direct insulinomimetic as well as insulin-sensitizing effects by binding to intracellular nuclear receptors and regulating the expression of numerous genes that affect carbohydrate and lipid metabolism. In addition to hyperglycemia, type 2 diabetics often exhibit several other components of the insulin resistance syndrome (also called the cardiovascular dysmetabolic syndrome), including dyslipidemia, hypertension, vasculopathy, and hypercoagulation, which lead to accelerated cardiovascular morbidity and mortality. Since their main action is to reduce insulin resistance, the thiazolidinediones may be uniquely able to influence these metabolic abnormalities. Thus, both rosiglitazone and pioglitazone have the potential not only to reduce glycemia and insulin requirements in type 2 diabetics but also to improve other components of the insulin resistance syndrome, including dyslipidemia and hypertension, and thereby may be able to prevent or delay premature atherosclerotic cardiovascular disease, morbidity, and death. However, long-term studies are needed to determine whether these agents fulfil this potential.

The ultimate objective in diabetes treatment is prevention. The Diabetes Prevention Program, a large multicenter study sponsored by the National Institutes of Health, is exploring ways to achieve this objective. The study has randomized more than 3000 subjects into an intensive lifestyle arm, a placebo arm, and a metformin-treatment arm. It is hoped that a definitive answer will be available in the year 2002.

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