Pharmacologic Therapy for Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus is a chronic metabolic disorder that results from defects in both insulin secretion and insulin action. An elevated rate of basal hepatic glucose production in the presence of hyperinsulinemia is the primary cause of fasting hyperglycemia; after a meal, impaired suppression of hepatic glucose production by insulin and decreased insulin-mediated glucose uptake by muscle contribute almost equally to postprandial hyperglycemia. In the United States, five classes of oral agents, each of which works through a different mechanism of action, are currently available to improve glycemic control in patients with type 2 diabetes. The recently completed United Kingdom Prospective Diabetes Study (UKPDS) has shown that type 2 diabetes mellitus is a progressive disorder that can be treated initially with oral agent monotherapy but will eventually require the addition of other oral agents, and that in many patients, insulin therapy will be needed to achieve targeted glycemic levels. In the UKPDS, improved glycemic control, irrespective of the agent used (sulfonylureas, metformin, or insulin), decreased the incidence of microvascular complications (retinopathy, neuropathy, and nephropathy). This review examines the goals of antihyperglycemic therapy and reviews the mechanism of action, efficacy, nonglycemic benefits, cost, and safety profile of each of the five approved classes of oral agents. A rationale for the use of these oral agents as monotherapy, in combination with each other, and in combination with insulin is provided.

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In the United States, approximately 15.6 million persons have type 2 diabetes mellitus, and about 13.4 million have impaired glucose tolerance (1). Throughout the world, the prevalence of type 2 diabetes mellitus has increased dramatically in the past two decades (1). Decreased physical activity, increasing obesity, and changes in food consumption have been implicated in this epidemic (2).

Patients with diabetes experience significant morbidity and mortality from microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (heart attacks, stroke, and peripheral vascular disease) complications. Proliferative retinopathy, macular edema, or both occur in 40% to 50% of patients with type 2 diabetes, and diabetes is the leading cause of blindness in the United States (3). The prevalence of renal disease varies considerably among ethnic populations, from 5% to 10% in white persons to 50% in Native Americans (4). Diabetes is the leading cause of end-stage renal failure, accounting for one of every three patients who enter dialysis or transplantation programs (4). Peripheral and autonomic neuropathy occur in 50% to 60% of patients with type 2 diabetes, whereas heart attacks and stroke occur two to four times more frequently in persons with diabetes than in those without the disease (5). The cost of treating diabetes and associated microvascular and macrovascular complications exceeds $100 billion per year (6).

I briefly review the pathogenesis of type 2 diabetes mellitus; provide a rationale for the importance of good glycemic control in this disease; and provide a therapeutic strategy, with a focus on oral agents alone and in combination with each other and with insulin. Indications for insulin are discussed briefly, but the major emphasis is on therapy with oral agents.

This review primarily relies on evidence-based medicine. Wherever possible, the results of large, prospective, double-blind, placebo-controlled studies published in peer-reviewed journals have been used. For several of the recently approved oral agents, I used information filed by the drug company with the U.S. Food and Drug Administration (FDA). Where controversy exists, I delineate both points of view and offer commentary that attempts to synthesize and reconcile published results. Statements that are not founded on evidence-based medicine are clearly indicated.

Pathogenesis of Type 2 Diabetes Mellitus

The appropriate treatment of any disease is based on an understanding of its pathophysiology (7). The mechanisms responsible for impaired glucose homeostasis in type 2 diabetes mellitus (**Figure 1**) are discussed briefly to provide the foundation for discussion of currently available oral agents, including their mechanism of action, efficacy, and side effects.

After ingestion of glucose, maintenance of normal glucose tolerance depends on three events that must occur in a tightly coordinated fashion: 1) stimulation of insulin secretion; 2) insulin-mediated suppression of endogenous (primarily hepatic) glucose production by the resultant hyperinsulinemia; and

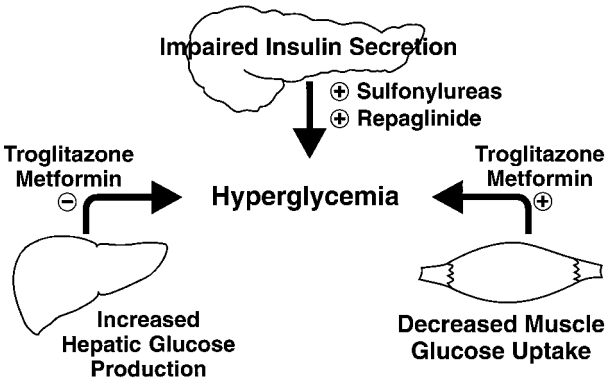

Figure 1. Pathogenesis of type 2 diabetes mellitus. Sites of action of oral agents are indicated. A negative sign indicates inhibition; a positive sign indicates stimulation.

3) insulin-mediated stimulation of glucose uptake by peripheral tissues, primarily muscle. Hyperglycemia also has its own independent effect of suppressing hepatic glucose production and enhancing muscle glucose uptake, but these effects are modest compared to those of insulin.

In patients with type 2 diabetes and established fasting hyperglycemia, the rate of basal hepatic glucose production is excessive, despite plasma insulin concentrations that are increased twofold to fourfold (8) (**Figure 1**). These findings provide unequivocal evidence for hepatic resistance to insulin, and this evidence is substantiated by an impaired ability of insulin to suppress hepatic glucose production (9). Accelerated gluconeogenesis is the major abnormality responsible for the increased rate of basal hepatic glucose production (10). The increased rate of basal hepatic glucose production is closely correlated with the increase in fasting plasma glucose level (7–10). Because the fasting plasma glucose level is the major determinant of the mean day-long blood glucose level (which clinically is reflected by the hemoglobin A_{1c} [HbA_{1c}] value), it follows that agents that reduce the elevated basal rate of hepatic glucose production will be especially effective in improving glycemic control (**Figure 1**).

Muscle tissue in patients with type 2 diabetes is resistant to insulin (7, 9, 11) (**Figure 1**). Defects in insulin receptor function, insulin receptor-signal transduction pathway, glucose transport and phosphorylation, glycogen synthesis, and glucose oxidation contribute to muscle insulin resistance (7). In response to a meal, the ability of endogenously secreted insulin to augment muscle glucose uptake is markedly impaired (12, 13), and muscle insulin resistance and impaired suppression of hepatic glucose production contribute approximately equally to the excessive postprandial increase in the plasma glucose level (13). It follows that drugs that improve muscle insulin sensitivity will be effective in decreasing the excessive increase in plasma glucose level after carbohydrate ingestion (**Figure 1**).

From a quantitative standpoint, however, in diabetic patients with established fasting hyperglycemia (glucose level $>$ 7.8 mmol/L [$>$140 mg/dL]), the excessive increase in the plasma glucose level above baseline after a meal plays a much smaller role in determining the mean day-long plasma glucose concentration than does the elevated fasting plasma glucose level. This is clear from studies that have examined the mean day-long glycemic excursions in diabetic patients who consume typical mixed meals. For example, in a study by Jeppesen and colleagues (14), the fasting glucose level in diabetic patients was (10.6 mmol/L [190 mg/dL]), indicating an increase in basal glucose level of 5.6 mmol/L (100 mg/dL) above that in nondiabetic controls (5 mmol/L [90 mg/dL]). This increase above baseline was present 24 hours per day, giving a hyperglycemic index of 2400 (100 mg/dL $\times$ 24 hours). After each of three daily meals, the increase in plasma glucose concentration was greater in diabetic patients than in controls by about 1.9 mmol/L (35 mg/dL) but returned to the baseline value by 4 to 6 hours. The hyperglycemic index accounted for by the excessive increase in plasma glucose level during each meal is 525 (35 mg/dL $\times$ 3 meals $\times$ 5 hours). Thus, the contribution of postprandial hyperglycemia to day-long hyperglycemia is only 22% (525/2400).

Impaired insulin secretion also plays a major role in the pathogenesis of glucose intolerance in patients with type 2 diabetes (15). Although debate still continues about which defect—insulin resistance or impaired insulin secretion—initiates the cascade of events leading to overt diabetes mellitus, essentially all patients who have type 2 diabetes with elevated fasting plasma glucose levels have a defect in insulin secretion (15). In diabetic patients with mild fasting hyperglycemia (glucose level $<$ 7.8 mmol/L [$<$140 mg/dL]), plasma insulin levels during an oral glucose tolerance test or a mixed meal usually are elevated in absolute terms (16). However, relative to the severity of insulin resistance and prevailing hyperglycemia, even these elevated plasma insulin levels are deficient (16, 17). As the fasting plasma glucose level increases to more than 7.8 mmol/L ($>$140 mg/dL), insulin secretion decreases progressively, and essentially all diabetic patients with a fasting plasma glucose level that exceeds 10.0 to 11.1 mmol/L (180 to 200 mg/dL) have a plasma insulin response that is deficient in absolute terms (16, 17). It follows, therefore, that drugs that improve insulin secretion will be effective in treating type 2 diabetes (**Figure 1**).

In summary, patients with type 2 diabetes mellitus are characterized by defects in both insulin se-

cretion and insulin action. A recent extensive review (7) provides more detailed discussion about the pathogenesis of type 2 diabetes mellitus.

Glycemic Control and Complications

The Diabetes Control and Complications Trial (DCCT) (18) established that in type 1 diabetes mellitus, the risk for microvascular complications could be reduced by maintaining near-normal blood glucose levels with intensive insulin therapy. No glycemic threshold for the development of long-term microvascular complications was observed in the DCCT (19). As the HbA_{1c} value was reduced to less than 8.0%, the risk for microvascular complications continued to decrease (19). Until recently, no large prospective long-term study had demonstrated that improved glycemic control in patients with type 2 diabetes can prevent microvascular complications. Nonetheless, convincing arguments suggested that the DCCT results could be extrapolated to type 2 diabetes. First, retinal, renal, and neurologic anatomical lesions seem to be identical in type 1 and type 2 diabetes mellitus (3, 20, 21). Second, epidemiologic studies have shown a close association between glycemic control and microvascular complications (3, 22–24). Third, a randomized clinical trial in Japanese patients with type 2 diabetes (15) showed that attainment of near-normal glycemia with intensive insulin therapy resulted in improvements in retinopathy, nephropathy, and neuropathy similar to those observed in the DCCT. Finally, short-term prospective studies (25, 26) have shown that reduction of the plasma glucose level reduces microalbuminuria and improves nerve conduction velocity in patients with type 2 diabetes. On the basis of these arguments, most diabetes experts have concluded that the DCCT results are applicable to type 2 diabetes mellitus (27).

More definitive information on the relation between improved glycemic control and prevention of complications was recently provided by the United Kingdom Prospective Diabetes Study (UKPDS) (28, 29). In the main randomization group of the UKPDS (28), after a dietary run-in period of 3 months, 3867 patients with newly diagnosed type 2 diabetes were randomly assigned to intensive therapy with a sulfonylurea or insulin ($n = 2729$) or to conventional diet therapy ($n = 1138$). In the intensive group, the aim was to achieve a fasting plasma glucose level less than 6 mmol/L (108 mg/dL). In the sulfonylurea group, patients were switched to insulin therapy or metformin was added if the therapeutic goal was not achieved after maximum titration of the drug dose. In patients assigned to insulin treatment in whom the therapeutic goal was not met, the dose of ultralente insulin was increased progressively and regular insulin was added. In patients assigned to conventional diet treatment, the aim was to maintain a fasting plasma glucose level less than 15 mmol/L (270 mg/dL) without symptoms. If the fasting plasma glucose level exceeded 15 mmol/L (270 mg/dL) or symptoms occurred, patients were randomly assigned to receive therapy with a sulfonylurea or insulin. The median follow-up was 10.0 years; during this period, a difference in HbA_{1c} values of 0.9 percentage points (7.0% compared with 7.9%; $P < 0.001$) was maintained between the group assigned to intensive therapy and the group assigned to conventional therapy (**Figure 2**). This difference was associated with a significant 25% risk reduction ($P = 0.009$) in combined microvascular end points (eye, kidney, and nerve) compared with the conventionally treated group. No difference in combined macrovascular end points between the two groups was observed, although there was a tendency toward fewer myocardial infarctions in the group assigned to intensive therapy.

In addition to the 2729 patients with type 2 diabetes assigned to intensive therapy and the 1138 patients assigned to conventional therapy, 342 overweight patients were randomly assigned to intensive treatment with metformin (29). These 342 patients

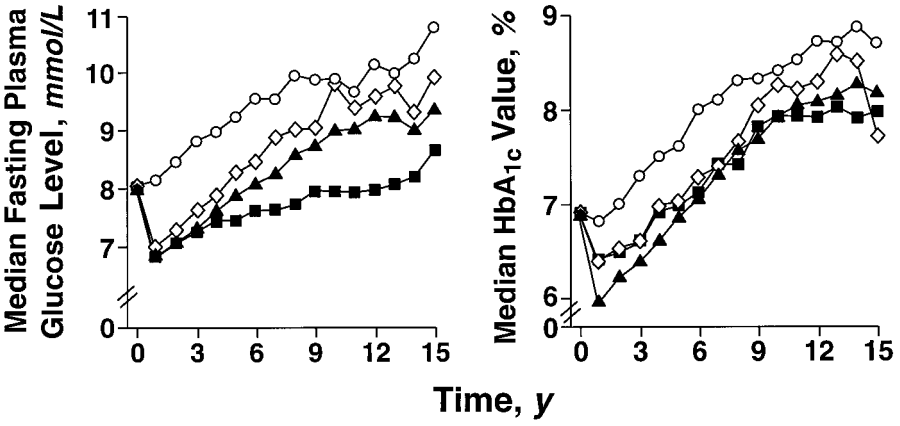

Figure 2. Time-related change in median fasting plasma glucose level (*left*) and median hemoglobin A_{1c} (HbA_{1c}) (*right*) in patients with type 2 diabetes treated with sulfonylureas (*triangles*), metformin (*diamonds*), insulin (*squares*), or conventional (diet) therapy (*circles*). The number of patients followed for more than 11 years drops off markedly. The curves for chlorpropamide and glibenclamide have been combined into one sulfonylurea curve for ease of presentation. Redrawn from references 28 and 29.

were compared with 411 overweight diabetic patients receiving conventional therapy and with 951 overweight diabetic patients receiving intensive therapy (of whom 542 were receiving sulfonylureas and 409 were receiving insulin). The median follow-up in this group was 10.7 years; during this time, a difference in the HbA_{1c} value of 0.6 percentage points (7.4% compared with 8.0%; $P < 0.001$) was maintained between the group assigned to metformin therapy and the group assigned to conventional therapy (**Figure 2**). The magnitude of reduction (29%) in the risk for microvascular complications in the metformin-treated group was similar to that in patients treated intensively with insulin or sulfonylureas, but it did not reach statistical significance (**Figure 3**). Patients assigned to intensive blood glucose control with metformin had a 32% lower risk ($P = 0.002$) for any diabetes-related end point, a 36% lower risk ($P = 0.021$) for death from any cause, a 42% reduction in diabetes-related death ($P = 0.11$), a 39% lower risk ($P = 0.010$) for myocardial infarction, and a 41% lower risk ($P = 0.032$) for stroke compared with patients who received conventional treatment (**Figure 3**). The risk reduction for any diabetes-related end point ($P = 0.003$) and death from any cause ($P = 0.021$) in the metformin group was significantly greater than that in the group assigned to intensive therapy with insulin or sulfonylureas (**Figure 3**).

In summary, the results of the UKPDS show that 1) the development of microvascular complications was similarly reduced in patients with type 2 diabetes treated with sulfonylureas, insulin, or metformin; 2) there was no threshold for the reduction in HbA_{1c} value and the development of microvascular complications; 3) in patients with type 2 diabetes assigned to intensive therapy with sulfonylureas or insulin, the incidence of macrovascular complications was not increased compared with the group assigned to conventional therapy; and 4) a decrease in macrovascular complications was seen only in patients with type 2 diabetes assigned to intensive therapy with metformin. Thus, the findings of the UKPDS are consistent with those of the DCCT (17) and the study by Ohkubo and associates (30).

On the basis of the results reviewed above, it seems most prudent to reduce blood glucose levels in patients with type 2 diabetes to as close to nor-

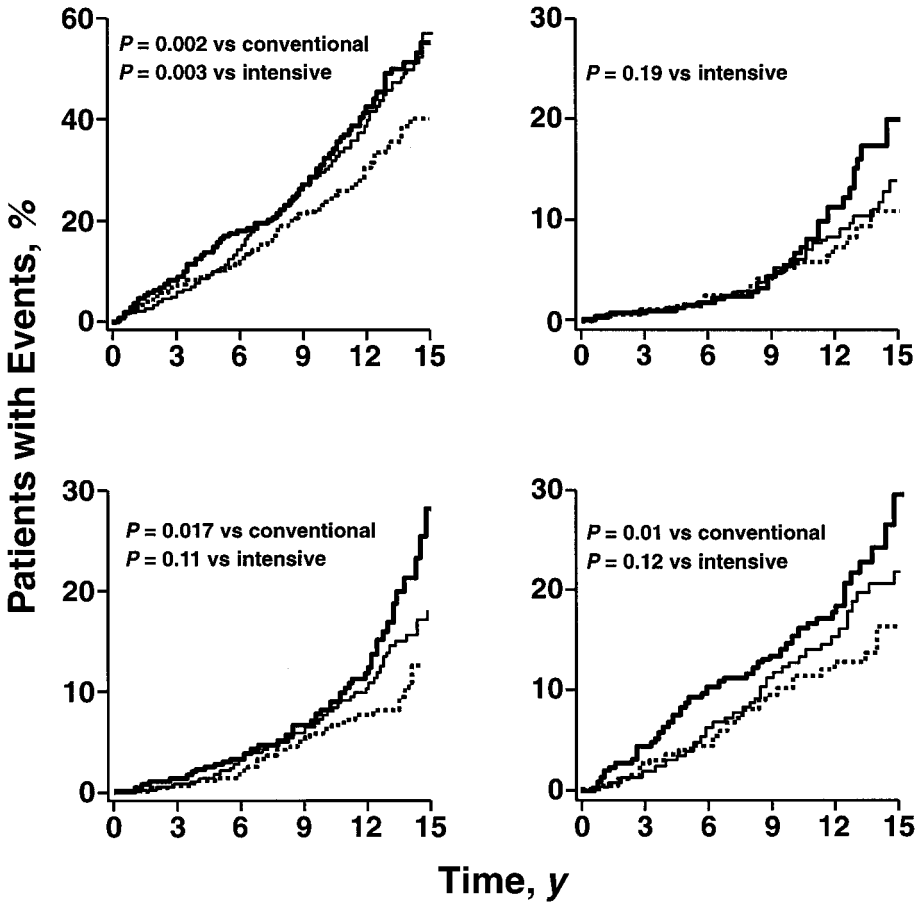

Figure 3. Effect of conventional treatment with diet (*bold solid line*), intensive treatment with sulfonylureas or insulin (*solid line*), and metformin therapy (*dashed line*) on any diabetes-related end point (*top left*), diabetes-related death (*bottom left*), microvascular complications (*top right*), and myocardial infarction (*bottom right*). *P* values represent differences between metformin and other therapies. Redrawn from references 28 and 29.

mal as possible while avoiding symptomatic hypoglycemia. Effective treatment will require the combined use of diet, exercise, oral agents, and insulin.

Diagnostic Criteria and Therapeutic Goals

On the basis of results from long-term prospective epidemiologic studies showing that 10% to 15% of persons with a fasting plasma glucose level of 7 mmol/L or more (≥126 mg/dL) develop diabetic retinopathy within 10 years of follow-up, an expert committee convened by the American Diabetes Association recommended that diabetes be diagnosed when the fasting plasma glucose level is 7 mmol/L or more (126 mg/dL) (24). This fasting plasma glucose level is consistent with a 2-hour plasma glucose level of 11.1 mmol/L or more (≥200 mg/dL) during an oral glucose tolerance test and corresponds to an HbA_{1c} value of about 6.9% (24). A random plasma glucose level of at least 11 mmol/L (≥200 mg/dL) with symptoms also establishes the diagnosis of type 2 diabetes mellitus. To definitively establish the diagnosis, one of the three previous diagnostic criteria must be confirmed.

Because hyperglycemia is believed to play an important role in the pathogenesis of microvascular complications, the American Diabetes Association has established acceptable and ideal goals for treatment of type 2 diabetes (31). Pharmacologic action is indicated if the fasting glucose level exceeds 7.8 mmol/L (>140 mg/dL), if the postprandial glucose level exceeds 8.9 mmol/L (160 mg/dL), or if the HbA_{1c} value exceeds 8.0%. On the basis of the results of the UKPDS (27, 28) and the DCCT (19), I believe that treatment should be initiated if the HbA_{1c} value is 7.0%, not 8.0% (**Figure 2**), because both the UKPDS and DCCT (8, 28) showed that treatment of diabetic patients with HbA_{1c} values in the range of 6% to 7% is associated with a significant reduction in microvascular complications.

Treatment Strategy

In developing a treatment strategy for patients with type 2 diabetes, it must be remembered that glucose intolerance occurs not in isolation but as part of a complex metabolic–cardiovascular syndrome that includes dyslipidemia, hypertension, obesity, clotting abnormalities, microalbuminuria, and accelerated atherosclerosis (32, 33), although not every one of these disorders occurs in every diabetic patient. Although hyperglycemia has been implicated as a risk factor for coronary artery disease (34), dyslipidemia far outweighs all other risk factors (35). Therefore, treatment of concomitant lipid abnormalities, hypertension, and other known risk factors for coronary artery disease is essential (5, 35). Long-term prospective studies have shown that treatment of hypertension (36) and dyslipidemia (37) reduces cardiac events in patients with type 2 diabetes. Most recently, the UKPDS (38) showed that improved control of blood pressure reduced not only macrovascular complications (heart attacks, strokes, and death) but also the risk for microvascular end points by 37% ($P = 0.009$). In this context, it is important that pharmacologic therapy does not aggravate associated cardiovascular risk factors and, preferably, leads to their improvement. Because obesity and physical inactivity are risk factors for coronary artery disease as well as for diabetes, the need for weight loss and exercise must be stressed when diabetes initially is diagnosed and must be reinforced throughout the natural history of the disease. Many excellent reviews on diet and exercise have been published (39, 40). If diet and exercise fail to achieve the desired level of glycemic control, pharmacologic intervention is indicated.

The UKPDS showed that type 2 diabetes mellitus is a progressive disorder (28, 29) (**Figure 2**). Although it was hoped that treatment with sulfonylureas, metformin, or insulin would halt the progressive deterioration of glycemic control, this has not turned out to be the case. After an initial and similar decrease in the HbA_{1c} value with metformin, sulfonylureas, or insulin, the rate of increase in the HbA_{1c} value was identical to that in the group treated with diet therapy. These results indicate that once overt fasting hyperglycemia has developed, the decline in glycemic control is relentless. In the UKPDS, this decline was related to deterioration of β-cell function (28). The results of the University Group Diabetes Program study (41, 42) also documented the progressive nature of type 2 diabetes mellitus. This important observation emphasizes the need for constant reassessment of the diabetic patient and appropriate adjustment of the therapeutic regimen in order to maintain the desired level of glycemic control.

From these observations about the natural history of type 2 diabetes mellitus, the following treatment strategy can be proposed for diabetic patients whose disease is inadequately controlled with diet and exercise (**Figure 4**).

1. Initiate pharmacologic therapy with an oral agent or insulin.

2. Quickly increase the dose of oral agent or insulin until adequate glycemic control is achieved. I recommend that patients be seen at 2- to 4-week intervals or more frequently during this titration phase.

3. In diabetic patients treated with an oral agent, choose a drug with glucose-lowering potency that can achieve the desired level of glycemic control when used as monotherapy. Because most patients

with type 2 diabetes are overweight and have associated cardiovascular risk factors, drugs that improve these abnormalities are preferred.

4. In diabetic patients whose disease is inadequately controlled with a single oral agent, I favor addition of a second oral agent with rapid dose titration until the desired level of glycemic control is achieved or the maximum dose is reached. Alternately, bedtime long-acting insulin can be added to oral agent monotherapy, or the patient can be switched to a mixed-split insulin regimen.

5. In diabetic patients in whom glycemic control is not achieved with combined oral agent therapy, several options are available: addition of bedtime insulin, switching to a mixed-split insulin regimen, or addition of a third oral agent.

It is important to recognize that, ultimately, most patients with type 2 diabetes will require treatment with insulin, either alone or in combination with an oral agent.

Insulin Therapy

Although the primary focus of this review is oral agents, comment about insulin is indicated because some diabetologists prefer to initiate therapy with insulin in patients with newly diagnosed type 2 diabetes. Edelman and Henry (43) published a comprehensive review of insulin therapy in type 2 diabetes mellitus. Numerous studies have shown that excellent glycemic control can be achieved with intensive insulin therapy in patients with type 2 diabetes (44, 45). An educated, compliant patient with an experienced physician can achieve excellent glycemic control with insulin therapy. However, most studies of intensive insulin therapy have been carried out in academic settings, using strict research protocols with specialty teams devoted to patient care. In such settings, one can expect decreases in HbA_{1c} value of about 2 percentage points. However, most primary care physicians do not have specialized training in insulin use and management of its complications, do not have sufficient time to follow up patients at frequent intervals to ensure appropriate adjustment of the insulin dose, and do not have diabetes specialty teams to assist them.

Hayward and coworkers (46) examined insulin therapy prescribed by general practice physicians in a large staff-model health maintenance organization. In 1738 insulin-treated patients with type 2 diabetes, the mean decrease in HbA_{1c} value was 0.9 percentage points, and 60% of patients had a HbA_{1c} value that exceeded 8.0% at 2 years. In a parallel cohort, 43% of patients with type 2 diabetes who were taking sulfonylureas had an HbA_{1c} value that exceeded 8.0%. Although one can raise criticisms about this study (46), the results do not indicate any superiority of insulin over sulfonylureas or vice versa in the general practice setting. The UKPDS (28, 29) also failed to show any advantage of insulin over oral agents or vice versa (**Figure 2**). The most commonly used insulin regimen in general practice is a single dose of long-acting insulin in the morning; dosages in excess of 80 U/d are rarely given (47). Because most patients with type 2 diabetes require an insulin dosage of at least 80 to 100 U/d and a multiple, split-dose regimen (44, 45), it is not surprising that blood glucose levels are inadequately controlled in most of these patients (46).

Weight gain and hypoglycemia are common side effects of insulin therapy (28, 29, 45, 48–50). Weight gain results from increased truncal fat (49) and is

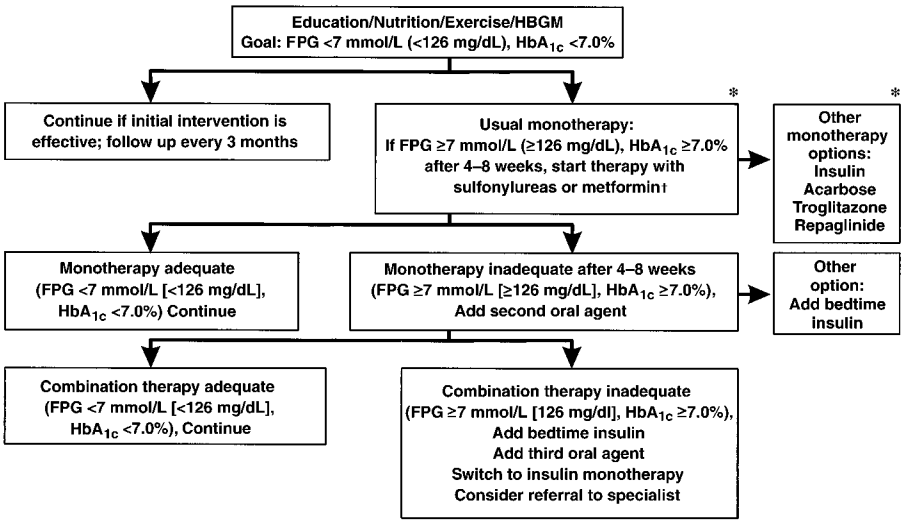

Figure 4. Pharmacologic algorithm for treatment of patients in whom type 2 diabetes is inadequately controlled with diet and exercise. *Goals and therapies must be individualized. †Preferred if the patient is obese or dyslipidemic. FPG = fasting plasma glucose level; HbA_{1c} = hemoglobin A_{1c} value; HBGM = home blood glucose monitoring.

closely related to the mean day-long plasma insulin level and daily insulin dose (45). In the UKPDS, insulin-treated obese patients with type 2 diabetes gained 4.0 kg more after 10 years than patients assigned to diet therapy ($P < 0.001$) (28). Patients assigned to sulfonylurea therapy (chlorpropamide or glibenclamide) gained 2.2 kg more, while those assigned to metformin therapy gained weight in an amount similar to that in patients assigned to diet therapy (28, 29). Because obesity is a known cause of insulin resistance (51, 52) and represents an independent risk factor for coronary artery disease, hypertension, and dyslipidemia (5, 53), weight gain is an undesirable effect of any therapy.

Hypoglycemia is another potential side effect of insulin therapy in patients with type 2 diabetes (28, 29, 45, 48–50). In the UKPDS (28, 29), after 10 years, percentages of diabetic patients with one or more major (requiring third-party assistance or hospitalization) hypoglycemic episodes were 0.5% in the sulfonylurea group, 2.3% in the insulin group ($P < 0.001$ for insulin compared with all other groups), 0% in the metformin group, and 0.1% in the diet group. The corresponding rates for any hypoglycemic reaction were 14% in the sulfonylurea group, 36% in the insulin group, 4% in the metformin group, and 1% in the diet group.

The authors of the 6-year summary of the UKPDS (50) stated that "In patients with primary diet failure, it may not be advantageous to proceed directly to insulin therapy. It is reasonable to initiate therapy with oral agents and proceed to insulin if the goal is not achieved." The 10-year summary of the UKPDS (29) concluded that metformin is appropriate first-line therapy in overweight diabetic patients because compared with insulin or sulfonylurea treatment, metformin therapy seems to decrease the risk for diabetes-related end points and results in less weight gain and fewer hypoglycemic attacks.

On the basis of the preceding discussion, I recommend initiating pharmacologic therapy with an oral agent in patients with newly diagnosed type 2 diabetes. However, insulin is indicated as initial therapy in specific patients, as follows.

1. Any patient who has type 2 diabetes, with a markedly elevated fasting plasma glucose level (>15.6 to 16.7 mmol/L [>280 to 300 mg/dL]), and ketonuria or ketonemia.

2. Symptomatic patients who have type 2 diabetes with a markedly elevated fasting plasma glucose level (>15.6 to 16.7 mmol/L [>280 to 300 mg/dL]). After 6 to 8 weeks of good glycemic control, these patients can be switched to an oral agent, or they can continue insulin therapy. A benefit of intensive insulin therapy with tight glycemic control is the reversal of glucose toxicity (54). This will improve both insulin sensitivity and insulin secretion (54) and will enhance the subsequent response to oral agent therapy (55, 56).

3. Any patient with type 2 diabetes who, after discussing the options with the primary care physician, wishes to receive insulin as initial therapy.

4. Women with gestational diabetes mellitus whose disease is not controlled with diet alone. All oral agents are contraindicated during pregnancy.

Therapeutic Algorithm for Initiation of Oral Therapy

In patients with newly diagnosed type 2 diabetes in whom insulin therapy is not indicated, I recommend that pharmacologic therapy with either a sulfonylurea or metformin be initiated as monotherapy, as long as no contraindications are present (**Figure 4**). This view, which is based on proven efficacy of, safety of, and long-term clinical experience with oral agents, is shared by other leading authorities on diabetes (28, 29, 50, 57–59), is the approach used in the UKPDS (28, 29, 59), and is consistent with the guidelines of the American Diabetes Association (60). When used as monotherapy, sulfonylureas and metformin are equally effective in decreasing plasma glucose levels, and both are more potent than other available oral agents (**Table 1**). Because metformin promotes weight loss and reduces lipid levels, it is preferred in overweight patients with type 2 diabetes and dyslipidemia. In lean patients with type 2 diabetes, therapy with either a sulfonylurea or metformin can be initiated. These recommendations are consistent with the findings of the UKPDS (28, 29). The dose of metformin or sulfonylureas can be increased over a 4- to 8-week period until the therapeutic goal (fasting plasma glucose level < 7.0 mmol/L [<126 mg/dL] and HbA_{1c} value < 7%) is achieved or the maximum dose is reached. Diet and exercise must be emphasized even after pharmacologic therapy has begun.

If monotherapy with a sulfonylurea or metformin fails to achieve the desired level of glycemic control, a second oral agent should be added, with dose escalation over 4 to 8 weeks to the maximum. Some diabetologists choose to add bedtime insulin to oral agent monotherapy rather than add a second oral agent. If combination therapy with two oral agents does not achieve the desired goal, three options are available: 1) Add bedtime insulin while maintaining therapy with one or both oral agents, 2) switch the patient to a mixed-split (short-acting plus long-acting insulin given in 2 to 4 daily injections) insulin regimen, or 3) add a third oral agent (**Figure 4**). It is important to individualize therapy on the basis of patient and physician preferences.

Specific insulin regimens to treat type 2 diabetes

Table 1. Comparison of Sulfonylureas, Repaglinide, Metformin, Troglitazone, and Acarbose When Used as Monotherapy*

Effect	Sulfonylureas and Repaglinide	Metformin	Troglitazone	Acarbose
Mechanism of action	Increase in insulin secretion	Decrease in hepatic glucose production; increase in muscle insulin sensitivity	Decrease in hepatic glucose production; increase in muscle insulin sensitivity	Decrease in GI absorption
Decrease in FPG level, *mmol/L* (*mg/dL*)	3.3–3.9 (60–70)	3.3–3.9 (60–70)	1.9–2.2 (35–40)	1.1–1.67 (20–30)
Decrease in hemoglobin A_{1c} value, *percentage points*	1.5–2.0	1.5–2.0	1.0–1.2	0.7–1.0
Triglyceride level	No effect	Decrease	Decrease	No effect
HDL cholesterol level	No effect	Slight increase	Increase	No effect
LDL cholesterol level	No effect	Decrease	Increase	No effect
Body weight	Increase	Decrease	Increase	No effect
Plasma insulin	Increase	Decrease	Decrease	No effect
Adverse events	Hypoglycemia	GI disturbances, lactic acidosis†	Anemia, hepatic toxicity‡	GI disturbances

* FPG = fasting plasma glucose, GI = gastrointestinal; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† Incidence of 0.03 cases per 1000 patient-years (rare).
‡ Severe, idiosyncratic, sometimes irreversible hepatic failure has been reported with troglitazone, but the precise incidence is unknown. Elevated liver enzyme levels occur in about 2% of patients.

are not discussed here. The reader is referred to several excellent reviews of this topic (43, 61).

Oral Agents

In the United States, five classes of oral agents are approved for the treatment of type 2 diabetes mellitus, and several new oral antidiabetic medications are being tested in humans. Oral agent therapy is indicated in any patient with type 2 diabetes in whom diet and exercise fail to achieve acceptable glycemic control (31). I examine the hypoglycemic efficacy, other beneficial effects, dosing schedule, cost, and safety of currently available antidiabetic drugs when used as monotherapy. This will be followed by a review of the use of these agents in combination with each other and with insulin.

Sulfonylureas

Mechanism of Action

Sulfonylureas have been the mainstay of antidiabetic therapy for many years. Their primary mechanism of action is enhancement of insulin secretion (**Table 1**, **Figure 1**). They initiate their action by binding to a specific sulfonylurea receptor on pancreatic β-cells (62). This closes a potassium-dependent adenosine triphosphate channel, leading to decreased potassium influx and depolarization of the β-cell membrane. This results in increased calcium flux into the β-cell, activating a cytoskeletal system that causes translocation of secretory granules to the cell surface and extrusion of insulin through exocytosis (63). Insulin released by the pancreas enters the portal vein, and the resultant portal hyperinsulinemia suppresses the elevated basal rate of hepatic glucose production. Simonson (64) and Best (65) and their colleagues were the first to demonstrate that the decrease in fasting plasma glucose level with sulfonylurea therapy was closely related to inhibition of basal hepatic glucose production. In addition, the elevated arterial insulin level enhances muscle glucose uptake, leading to a reduction in postmeal plasma glucose levels (64, 65). Although a direct effect of sulfonylurea to enhance tissue sensitivity to insulin has been suggested (66), most investigators believe that the small improvement in insulin action observed during sulfonylurea treatment (64, 65) is explained by the improvement in glucose toxicity (53).

Efficacy

The hypoglycemic potency of sulfonylureas is directly related to the starting fasting plasma glucose level (67, 68). The higher the fasting plasma glucose level, the greater its decrease from baseline. In the United States, the mean HbA_{1c} value in diabetic patients is approximately 10%, corresponding to a fasting plasma glucose level of more than 11.1 mmol/L (>200 mg/dL) (69). This value is similar to that reported in recent large clinical trials of treatment of patients with type 2 diabetes with sulfonylureas (67, 68). In such patients, one can expect the fasting plasma glucose level to decrease by 3.3 to 3.9 mmol/L (60 to 70 mg/dL) and the HbA_{1c} value to decrease by 1.5 to 2.0 percentage points (67, 68) (**Table 1**). Approximately 25% of such patients will achieve a fasting plasma glucose level less than 7.8 mmol/L (<140 mg/dL) (the current American Diabetes Association goal) and should be considered complete responders (67, 68). Factors that predict a good response include recently diagnosed diabetes, mild to moderate fasting hyperglycemia (<12.2 to 13.3 mmol/L [<220 to 240 mg/dL]), good β-cell function as reflected by a high fasting C-peptide level, no history of insulin therapy, and absence of islet cell or glutamic acid decarboxylase antibodies (69).

About 75% of patients with type 2 diabetes treated with a sulfonylurea will not reach the desired goal (fasting plasma glucose level < 7.8 mmol/L [<140 mg/dL]) and will require addition of a second oral agent or bedtime insulin. Patients in whom sulfonylurea therapy fails can be subdivided into two groups. Ten percent to 20% will have a poor initial response (decrease in fasting glucose level < 1.1 mmol/L [<20 mg/dL]) (65, 66); these patients are considered to have primary failure (70). Such patients usually have a low fasting C-peptide level and a fasting plasma glucose level that exceeds 15.5 to 16.6 mmol/L (280 to 300 mg/dL). In some of these patients, the disease represents slowly evolving type 1 diabetes (71). Fifty percent to 60% of patients with type 2 diabetes have a good initial response to sulfonylurea (decrease in fasting plasma glucose level > 1.7 mmol/L [>30 mg/dL]), but they do not reach the desired treatment goal (fasting plasma glucose level < 7.8 mmol/L [<140 mg/dL]). Such patients are considered to have partial response.

After a good initial response to sulfonylurea therapy, the secondary failure rate is about 5% to 7% per year (28, 29, 50, 72, 73), and after 10 years, most sulfonylurea-treated patients require a second oral agent (28, 29, 50, 74). Secondary treatment failure is divided into patient-related factors (weight gain, lack of exercise, failure to comply with prescribed treatment regimen, or coexisting medial disorders), therapy-related factors (use of concomitant medications that antagonize insulin action or insulin secretion, β-cell desensitization secondary to long-term sulfonylurea exposure, inadequate drug dosage, or impaired sulfonylurea absorption secondary to hyperglycemia), and disease-related problems (progression of insulin resistance and increasing insulin deficiency). It is commonly stated that the high rate of secondary failure is related to the pancreas's inability to maintain its augmented insulin secretory rate in response to long-term sulfonylurea stimulation. However, the UKPDS (28, 29, 50) has cast doubt on this theory because a similar rate of secondary failure was observed with metformin therapy. Metformin, by improving insulin sensitivity and decreasing plasma insulin levels, would have been expected to preserve β-cell function (**Figure 2**). The UKPDS results suggest that once the fasting plasma glucose level exceeds a certain value (>7.8 to 8.9 mmol/L [>140 to 160 mg/dL]), β-cell failure inexorably progresses.

Clinical trials have not demonstrated superiority of one sulfonylurea over another when given in maximally effective doses (67, 68). To the contrary, large prospective placebo-controlled trials have shown that glipizide, glyburide, and glimepiride exert equipotent glucose-lowering effects (67, 68, 70, 75). Similar results have been reported in studies comparing first- and second-generation sulfonylureas (28, 29). Although short-term studies indicate that glipizide releases insulin more rapidly than glyburide does and that glyburide suppresses hepatic glucose production more than glipizide does (76), both sulfonylureas produce similar mean day-long glycemic profiles when used long term in patients with type 2 diabetes (75).

Table 2. Currently Available Sulfonylurea Drugs

Drug (Trade Name, Manufacturer)	Daily Dosage	Duration of Action
	mg	*h*
Second-generation sulfonylureas		
Glyburide (Micronase, Pharmacia & Upjohn; (DiaBeta, Hoechst Marion Roussel)	2.5–20	16–24
Glyburide (Glynase, Pharmacia & Upjohn)	1.5–12	12–24
Glipizide		
(Glucotrol, Pfizer)	5–40*	12–24
(Glucotrol XL, Pfizer)	5–20	24
Glimepiride (Amaryl, Hoechst Marion Roussel)	1–8	16–24
First-generation sulfonylureas		
Chlorpropamide (Diabenase, Pfizer)	100–500	60
Tolazamide	100–1000	12–24
Acetohexamide (Dymelor, Eli Lilly and Co.)	250–1500	12–18
Tolbutamide	500–2500	6–12

* The maximally effective dosage is 20 mg/d, even though the drug has been approved for use with dosages up to 40 mg/d.

Other Effects

Type 2 diabetes mellitus is part of a complex metabolic–cardiovascular cluster of disorders referred to as *the insulin resistance syndrome* (the metabolic syndrome or syndrome X) (33). Because coronary artery disease represents the major cause of death in type 2 diabetes mellitus, it is desirable that any hypoglycemic agent favorably affect known cardiovascular risk factors. In most studies, sulfonylureas have been reported to have neutral or slightly beneficial effects on plasma lipid levels (67, 77) (**Table 1**). Plasma triglyceride levels decrease modestly in some studies. This hypolipidemic effect most likely represents both a direct effect of sulfonylurea on the metabolism of very-low-density lipoprotein and an indirect action of the drug secondary to reduced plasma glucose levels (77). No consistent effect of sulfonylureas on the fibrinolytic system has been described (78). Sulfonylurea therapy usually is associated with weight gain (19, 20, 39), which has been implicated as a cause of secondary drug failure (**Table 1**). However, a recent study indicates that long-acting glipizide is not associated with weight gain (67).

Dosing Schedule

Currently available sulfonylureas and their dosages are shown in **Table 2**. Other sulfonylureas

(gliclazide, gliquidone, glibornuride, and glisoxepide) are available outside the United States. Sulfonylureas are divided into first-generation and second-generation drugs. First-generation sulfonylureas have a lower binding affinity to the sulfonylurea receptor and must be given in higher doses than second-generation sulfonylureas (78). Although short-acting glipizide has been approved at a dosage of 40 mg/d, the maximally effective dosage is 20 mg/d (78). When initiating therapy, one should start with the lowest effective dose and titrate upward every 1 to 2 weeks until the desired control (fasting plasma glucose level $<$ 6.1 to 7.8 mmol/L [$<$110 to 140 mg/dL]) is achieved. Some diabetes experts use a 3- to 4-week titration interval, but there is no therapeutic advantage in waiting more than 4 weeks to increase the sulfonylurea dose. Most (75%) of the hypoglycemic action of the sulfonylurea is usually observed with a daily dose that represents half of the maximally effective dose: that is, 10 mg of glyburide or glipizide and 4 mg of glimepiride. If no hypoglycemic effect is observed with half of the maximally effective dose, it is unlikely that further dose increases will have a clinically significant effect on blood glucose level.

Safety

The frequency of adverse effects in sulfonylurea-treated patients is low (2% to 5%), and side effects typically are mild and reversible on discontinuation of therapy (78). The major adverse effect is hypoglycemia, which has been reported more commonly with the longer-acting sulfonylureas glyburide and chlorpropamide (28, 29, 50, 76, 78). The greater suppression of hepatic glucose production with glyburide (76) has been offered as an explanation for the higher incidence of hypoglycemia. Mild hypoglycemic reactions occur in about 2% to 4% of patients, and severe hypoglycemic reactions requiring hospitalization occur with a frequency of 0.2 to 0.4 cases per 1000 patient treatment years (74, 79), although the UKPDS reported a much higher incidence of sulfonylurea-related episodes of hypoglycemia (28). Because patients older than 80 years of age are at high risk for hypoglycemia (72, 79–81), short-acting sulfonylureas or repaglinide may be preferred. However, no published long-term prospective studies have compared short-acting sulfonylureas or repaglinide with long-acting sulfonylureas in elderly patients with type 2 diabetes. A recent prospective, short-term study (82) failed to find any difference in the occurrence of hypoglycemia in elderly diabetic patients ($\geq$65 years of age) treated with either glyburide or glipizide, but the number of patients studied ($n = 52$) was relatively small.

Sulfonylurea therapy should be initiated with the lowest dose. In patients with a reduced glomerular filtration rate, the risk for hypoglycemia is increased, and therapy with chlorpropamide, which is renally excreted, should be avoided. Hypoglycemia also occurs more frequently in patients who have type 2 diabetes with mild fasting hyperglycemia ($<$7.8 mmol/L [$<$140 mg/dL]), typically occurring 2 to 3 hours after breakfast or during exercise. Various drug interactions have been described, especially with first-generation sulfonylureas; these are discussed in a review by Lebovitz and Melander (78).

The results of the University Group Diabetes Program study suggested that sulfonylureas may exacerbate coronary artery disease in patients with type 2 diabetes (41, 42). However, that study has been widely criticized (83, 84), and subsequent clinical trials have not demonstrated increased cardiac mortality rates in diabetic patients treated with sulfonylureas (85–87). Moreover, the UKPDS found no increased incidence of coronary artery disease in patients with type 2 diabetes assigned to intensive therapy with sulfonylureas compared with patients receiving diet therapy (28) (**Figure 3**). This topic was the subject of a recent review (88). On the basis of currently available data—especially from the UKPDS—I believe that we should abide by the American Diabetes Association's policy statement (89): "We oppose any formal restrictions on use of the sulfonylurea agents that are based on the interpretations of the University Group Diabetes Program findings." No published clinical study demonstrates an advantage of one sulfonylurea, including glimepiride, over any other sulfonylurea with respect to coronary artery disease.

Cost

Generic sulfonylureas are the least expensive of the oral antidiabetic agents. Brand-name second-generation sulfonylureas are moderate in price (**Table 3**). If cost is the major concern, sulfonylureas are the preferred drugs of choice.

Summary

In summary, sulfonylureas are very effective glucose-lowering agents (decrease in HbA_{1c} value, 1.5 to 2.0 percentage points) that work by enhancing insulin secretion. They have no direct effect on plasma lipids, and weight gain is common with their use. The only significant side effect associated with the sulfonylureas is hypoglycemia. The sulfonylureas, especially the generic ones, are inexpensive and are the drug of choice if cost is the major consideration.

Metformin

Metformin (Glucophage, Bristol-Myers Squibb, Princeton, NJ), a biguanide that has been in clinical

use for 40 years (90), was introduced in the United States in 1995 (91). Although other biguanides, buformin and phenformin, are available outside the United States, their use has decreased dramatically. Phenformin was previously approved for use in the United States but was removed from the market because it caused lactic acidosis. Metformin, which differs structurally from phenformin, has low lipid solubility and, when used in diabetic patients with normal renal function, rarely causes lactic acidosis.

Table 3. Cost per Month (30 Days) to the Pharmacist for Commonly Used Oral Antidiabetic Agents*

Drug (Trade Name, Manufacturer)	Usual Daily Dosage	Cost
	mg	*$*
First-generation sulfonylureas		
Acetohexamide	500–750	14.18
Chlorpropamide (Diabenase, Pfizer)	250–375	1.19
Tolazamide	250–500	2.81
Tolbutamide	1000–2000	2.75
Second-generation sulfonylureas		
Glimepiride (Amaryl, Hoechst Marion Roussel)	1–4	7.06
Glipizide	10–20	3.38
(Glucotrol, Pfizer)		21.38
(Glucotrol XL, Pfizer)		10.07
Glyburide	5–20	14.95
(DiaBeta, Hoechst Marion Roussel)		20.43
(Micronase, Pharmacia & Upjohn)		22.93
(Glynase, Pharmacia & Upjohn)		20.10
Nonsulfonylureas		
Acarbose (Precose, Bayer)	150–300	41.05
Metformin (Glucophage, Bristol-Myers Squibb)	1500–2550†	48.38
Repaglinide (Prandin, Novo Nordisk)	1–4	57.12
Troglitazone (Rezulin, Parke-Davis)	400–600	147.20

* Based on the average wholesale price, derived from: Med Lett Drugs Ther. 1998;40: 55-6.
† The maximally effective dosage is 2000 mg/d.

Mechanism of Action

Metformin enhances the sensitivity of both hepatic and peripheral tissues (primarily muscle) to insulin (92–94) (**Table 1**, **Figure 1**). Metformin inhibits hepatic gluconeogenesis both in vitro (95) and in vivo (93). Evidence for an inhibitory effect on hepatic glycogenolysis has also been provided (94). The decline in basal hepatic glucose production is closely correlated with the reduction in fasting plasma glucose level (92–94, 96). Metformin also enhances muscle insulin sensitivity (90, 92–94, 96) through direct (97, 98) and indirect effects (99). At the cellular level, improved insulin action in muscle is explained by multiple actions, including increased insulin receptor tyrosine kinase activity (100), augmented GLUT4 transporter number and activity (101), and enhanced glycogen synthesis (92, 94, 96, 101). However, the primary receptor through which metformin exerts its beneficial effects in muscle and liver is yet to be identified. In a provocative study carried out in *Xenopus laevis* oocytes, a cell model used to study insulin signaling and glycogen metabolism, therapeutic concentrations of metformin enhanced insulin action through tyrosine kinase activation, increased inositol 1,4,5-triphosphate production, and augmented glycogen synthesis (98). Metformin has no direct effect on β-cell function. In metformin-treated patients with diabetes, fasting and postprandial insulin levels consistently decrease (90, 92–94, 96, 100, 101), reflecting the normal compensatory response of the pancreas to enhanced insulin sensitivity.

Efficacy

Clinical trials (90, 91, 102–104) have documented that metformin therapy consistently decreases the fasting plasma glucose level by 3.3 to 3.9 mmol/L (60 to 70 mg/dL) and the HbA_{1c} value by 1.5 to 2.0 percentage points in patients with poorly controlled diabetes (**Table 1**). In a large double-blind, prospective study involving 289 diet-treated patients with type 2 diabetes (fasting plasma glucose level, 13.3 mmol/L [240 mg/dL]), metformin decreased the fasting plasma glucose level by 2.9 mmol/L (52 mg/dL) and the HbA_{1c} value by 1.4 percentage points from baseline (101). These decreases were independent of age, ethnicity, duration of diabetes, body mass index, or fasting and glucose-stimulated plasma insulin or C-peptide levels. Approximately 25% of patients with type 2 diabetes treated with metformin monotherapy achieved a fasting plasma glucose level less than 7.8 mmol/L (<140 mg/dL) and a HbA_{1c} value less than 7% (91). Similar results were reported in a recent large dose-ranging study (104) and have been confirmed in a meta-analysis (105). Thus, metformin and sulfonylureas are equally effective in reducing fasting plasma glucose and HbA_{1c} values in patients with type 2 diabetes, and both are indicated as primary therapy (**Table 1**).

Metformin therapy is effective as combination therapy with a sulfonylurea. In 423 sulfonylurea-treated patients (fasting plasma glucose level, 13.8 mmol/L [249 mg/dL]), addition of metformin decreased the fasting plasma glucose level by 3.5 mmol/L (63 mg/dL) and the HbA_{1c} value by 1.7 percentage points (91). About 25% of these patients whose disease was poorly controlled achieved a fasting plasma glucose level less than 7.8 mmol/L (<140 mg/dL) and a HbA_{1c} value less than 7% with addition of metformin therapy. These results indicate that the hypoglycemic action of metformin is completely additive to that of sulfonylureas. In sulfonylurea-treated patients with type 2 diabetes in whom the desired therapeutic goal is not reached or who experience secondary failure, it is important not to discontinue sulfonylurea therapy. The sulfonylurea is still working, but its hypoglycemic effect is too small to reduce the glucose level to the desired value. In such cases, sulfonylurea therapy should be continued and metformin should be added. Discon-

Table 4. Dosage Range and Duration of Action of Nonsulfonylurea Oral Agents

Drug (Trade Name, Manufacturer)	Daily Dosage, *mg*	Duration of Action
Metformin (Glucophage, Bristol-Myers Squibb)	500–2000	>3–4 wk
Troglitazone (Rezulin, Parke-Davis)	200–600	>3–4 wk
Acarbose (Precose, Bayer)	25 once daily to 50–75 three times daily	~4 h*
Repaglinide (Prandin, Novo Nordisk)	1.5–16	4–6 h
Rosiglitazone (Avandia, SmithKline Beecham)	2–8	>3–4 wk
Pioglitazone (Actose, Takeda America)	15–45	>3–4 wk

* Refers to the postprandial period, after meal ingestion.

tinuation of sulfonylurea therapy and substitution of metformin (or another oral agent) will not decrease the plasma glucose level below that observed with sulfonylurea monotherapy (68, 91, 104).

As with sulfonylurea therapy, the decrease in fasting plasma glucose level from baseline with metformin therapy is highly correlated with the starting fasting plasma glucose level (91). The hypoglycemic action of metformin increases linearly, even at very high fasting plasma glucose levels (>16.7 mmol/L [>300 mg/dL]). In diabetic patients with a fasting plasma glucose level of 16.7 mmol/L or more (≥300 mg/dL), the mean decrease in the fasting plasma glucose level is about 6.7 mmol/L (120 mg/dL) (91). This observation is predictable because metformin inhibits hepatic glucose production and the magnitude of fasting hyperglycemia is primarily determined by the increased basal rate of hepatic glucose production. In contrast, when the fasting plasma glucose level exceeds 16.7 mmol/L (>300 mg/dL), insulin secretion is severely impaired and the pancreatic response to sulfonylureas often is poor (70, 75).

Other Effects

When used as monotherapy or with a sulfonylurea, metformin decreases plasma triglyceride and low-density lipoprotein (LDL) cholesterol levels by 10% to 15% (14, 90–92, 106) (**Table 1**), reduces postprandial hyperlipemia (14), decreases plasma free fatty acid levels, and decreases free fatty acid oxidation (14, 106, 107). The magnitude of the decrease in plasma triglyceride concentration is related to the fasting triglyceride level (91) and is independent of changes in the plasma glucose level (14, 91, 106). Consistent with this, metformin reduces triglyceride levels in nondiabetic patients with hypertriglyceridemia (108). High-density lipoprotein (HDL) cholesterol levels either do not change or increase slightly after metformin therapy (14, 90, 92, 106, 109, 110). Elevated plasminogen activator inhibitor-1 levels are decreased with metformin therapy in patients with and those without diabetes (109–111). Weight gain does not occur in patients with type 2 diabetes who receive metformin alone or in combination with other oral agents or insulin (28, 29, 50, 91, 102–104). Most studies show modest weight loss—2 to 3 kg—during the first 6 months of treatment (90–93, 101, 102, 104, 109) (**Table 1**). In a 1-year randomized, double-blind trial in 457 nondiabetic patients with android (male type, or abdominal) obesity, metformin also caused significant weight loss (112).

Dosing Schedule

The starting metformin dosage is 500 mg twice daily, given with the two largest meals to minimize gastrointestinal side effects (**Table 4**). The fasting plasma glucose level begins to decrease within 3 to 5 days after therapy is started and reaches a nadir within 1 to 2 weeks. The dosage should be increased by 500 mg/d every 2 weeks until the desired therapeutic goal is achieved or a maximum dosage of 2000 mg/d is reached (91, 104). Eighty percent to 85% of the maximal glucose-lowering effect is observed with a daily dose of 1500 mg (104).

Safety

Gastrointestinal side effects, including abdominal discomfort and diarrhea, are the most common adverse events, occurring in 20% to 30% of patients (91, 104). These side effects usually are mild and transient and can be minimized by slow titration. If symptoms occur during titration, one should return to the previous metformin dose at which no symptoms were encountered and wait at least 2 weeks before increasing the dose. Less than 4% to 5% of patients cannot tolerate metformin therapy (91). Metformin can interfere with vitamin B_{12} absorption, but this is rarely of clinical significance. Because metformin does not increase insulin secretion, biochemically documented hypoglycemia is rare in diabetic patients treated with metformin alone (28, 29, 50, 91).

Although uncommon, lactic acidosis has been reported with a frequency of 3 cases per 100 000 patient-years (90, 113, 114). No cases of lactic acidosis with metformin therapy were observed in the UKPDS (29). A similar incidence has been reported in U.S. surveillance studies (11). ^{14}C-lactate turnover studies have demonstrated that when used in therapeutic doses, metformin does not interfere with lactate metabolism (96) or increase basal plasma lactate levels (91). Lactic acidosis is rare in the absence of other serious medical disorders, including renal insufficiency, severe tissue hypoperfusion, cardiogenic or septic shock, pulmonary insufficiency with hypoxemia, or severe liver disease (90, 91, 113–115). In these situations, it is difficult to discern

whether the lactic acidosis is due to the severe underlying medical disorder or to metformin therapy.

Metformin therapy is contraindicated in patients with renal and hepatic disease, respiratory insufficiency, any hypoxemic condition, severe infection, and alcohol abuse. Impaired renal function is an especially important contraindication to metformin use because the drug is excreted through the kidneys. If the serum creatinine concentration is more than 124 μmol/L (1.4 mg/dL) in women or more than 133 μmol/L (1.5 mg/dL) in men, metformin should not be administered. In patients with reduced muscle mass, such as elderly patients, the serum creatinine concentration may underestimate the glomerular filtration rate, and creatinine clearance should be determined. If the creatinine clearance is less than 1.00 to 1.17 mL/s, metformin should not be given. Metformin should not be used in diabetic patients with congestive heart failure requiring pharmacologic therapy because in this situation, decreased renal perfusion and glomerular filtration rate can impair metformin excretion. In elderly patients, especially those older than 80 years of age, an age-related decrease in glomerular filtration rate is often seen. In such patients, it is advisable to measure the creatinine clearance before starting metformin therapy and to use the minimum dose required to achieve the desired level of glycemic control.

Diabetic patients, especially those with proteinuria and reduced glomerular filtration rate, are at increased risk for acute renal failure after administration of radiocontrast dye. If dye-induced renal failure is not recognized and metformin therapy is continued, plasma metformin levels will increase progressively, and lactic acidosis may occur. In diabetic patients who present with an acute medical illness that requires administration of radiocontrast dye, the study should be performed and further metformin doses should be withheld until normal renal function has been documented by serum creatinine measurement 24 to 48 hours after the procedure.

In the UKPDS (29), metformin monotherapy was associated with a highly significant decrease in the risk for macrovascular complications, including myocardial infarction, stroke, and death. However, these results have been questioned because of findings in a substudy of 537 patients with poorly controlled type 2 diabetes who had been treated with sulfonylureas for 7.1 years and who were randomly assigned to receive either metformin with continued sulfonylurea treatment ($n = 268$) or continued sulfonylurea monotherapy ($n = 269$). After a mean follow-up of 4 years, the investigators reported a 96% increase in the risk for diabetes-related death ($P = 0.04$) in the group receiving sulfonylureas plus metformin compared with the group that continued receiving sulfonylurea monotherapy. Although the absolute numbers of heart attacks (33 and 31) and strokes (15 and 13) were very similar in the two groups, more patients in the sulfonylurea plus metformin group experienced a fatal heart attack or stroke. The authors pointed out that in the substudy, the number of patients and events was small and the duration of combination therapy was short. A more relevant question is whether the relative increase in heart attack and stroke mortality resulted from an increased number of deaths in the sulfonylurea plus metformin group or to a decrease in the number of deaths in the sulfonylurea monotherapy group. This question was addressed in a subsequent analysis by Turner and colleagues (116), who found that all of the relative increase in mortality observed in the patients who received sulfonylurea plus metformin compared with those who received sulfonylurea alone resulted from a significant reduction in the expected number of deaths in the latter group; there was no increase in mortality in the sulfonylurea plus metformin group. In absolute terms, the number of fatal heart attacks actually decreased in the sulfonylurea plus metformin group compared with the expected number of deaths (116). The investigators also performed a meta-analysis of all patients receiving sulfonylurea plus metformin in the UKPDS and reported significant reductions in all diabetes-related end points and for myocardial infarction.

Cost

The cost of metformin is about twice that of a second-generation sulfonylurea, slightly less than that of acarbose and repaglinide, and one third that of troglitazone (**Table 3**).

Summary

In summary, metformin is very effective in decreasing the plasma glucose level (decrease in HbA_{1c} value, 1.5 to 2.0 percentage points); it also reduces plasma triglyceride and LDL cholesterol levels. Metformin works by suppressing basal hepatic glucose production and enhancing insulin sensitivity in muscle. Metformin is the only oral antidiabetic agent that, when used as monotherapy, has been shown to reduce macrovascular complications. Most patients treated with metformin lose weight or fail to gain weight. The most common side effects are related to gastrointestinal disturbances. Lactic acidosis is a very rare complication of metformin therapy, and this biguanide is absolutely contraindicated in diabetic patients with impaired renal function.

Acarbose

Acarbose (Precose, Bayer, West Haven, Connecticut), an α-glucosidase inhibitor, was introduced in the United States about 3 years ago. A second α-glucosidase inhibitor, miglitol (Glyset, Pharmacia & Upjohn, Kalamazoo, Michigan), was recently approved by the FDA, but it does not seem to have any significant advantages over acarbose.

Mechanism of Action

Acarbose competitively inhibits the ability of enzymes (maltase, isomaltase, sucrase, and glucoamylase) in the small intestinal brush border to break down oligosaccharides and disaccharides into monosaccharides (117–119). Acarbose has a slight (about 10%) inhibitory effect on lactase (118, 119). By delaying digestion of carbohydrates, it shifts their absorption to more distal parts of the small intestine and colon. The drug does not cause malabsorption. By slowing the digestive/absorptive process, acarbose retards glucose entry into the systemic circulation, allowing the β-cell ample time to augment insulin secretion in response to the blunted increase in plasma glucose level. Acarbose does not reverse any pathophysiologic abnormalities in patients with type 2 diabetes (**Figure 1**).

Efficacy

Clinical trials (117–123) have shown that the hypoglycemic potency of acarbose is less than that of sulfonylureas and metformin (**Table 1**). As monotherapy, acarbose decreases the fasting plasma glucose level by 1.4 to 1.7 mmol/L (25 to 30 mg/dL) and the HbA_{1c} value by 0.7% to 1.0% (117–123). Acarbose primarily affects the postprandial plasma glucose level, which is decreased by 2.2 to 2.8 mmol/L (40 to 50 mg/dL) after meal ingestion (117–123). The reduction in postprandial plasma glucose level occurs without change or with a slight decrease in the plasma insulin level. This hypoglycemic profile of acarbose dictates its clinical indications. The drug is most useful in patients with new-onset type 2 diabetes who have mild fasting hyperglycemia and in diabetic patients who are taking a sulfonylurea or metformin and require an additional reduction in fasting plasma glucose level of 1.4 to 1.7 mmol/L (25 to 30 mg/dL), because this is the typical reduction in fasting plasma glucose level reported in clinical trials of acarbose (117–123). Acarbose is also indicated in diabetic patients with predominant postprandial hyperglycemia. These patients can be recognized by measuring the postprandial glucose level under defined conditions or by documenting a mildly elevated fasting plasma glucose level (6.1 to 7.8 mmol/L [110 to 140 mg/dL]) with a disproportionately increased HbA_{1c} value (>8%).

Other Effects

Some studies have reported a modest decrease in plasma triglyceride levels (122, 123) without a change in LDL or HDL cholesterol levels with acarbose. Body weight does not significantly change with acarbose monotherapy (**Table 1**).

Dosing Schedule

Acarbose therapy should be initiated with a low dose, 25 mg once or twice daily, to minimize gastrointestinal side effects (**Table 4**). In my clinical experience, when acarbose therapy is being initiated, the drug is best given with the smallest meals to minimize gastrointestinal side effects. Acarbose must be ingested with the first bite of food because the drug must be present in the small bowel with food to be effective. It is recommended that the acarbose dose be increased by 25 mg/d every 2 to 4 weeks to minimize gastrointestinal side effects. The maximum dosage is 75 to 100 mg twice or three times daily, although many diabetic patients experience adverse gastrointestinal side effects at these doses. Because acarbose works by interfering with starch digestion and absorption, its effectiveness is diminished in patients with low carbohydrate intake.

Safety

Gastrointestinal side effects, including bloating, abdominal discomfort, diarrhea, and flatulence, occur in up to 30% of diabetic patients treated with acarbose, but these effects tend to diminish with continued drug use. Initiation of therapy with a low dose and slow titration helps to minimize these adverse effects. With very high dosages of acarbose—200 to 300 mg three times daily—elevated serum aminotransferase levels have been reported. Abnormal results on liver function tests return to normal when therapy with the drug is discontinued (117, 119). Acarbose is contraindicated in patients with inflammatory bowel disease, a plasma creatinine concentration more than 177 μmol/L (>2.0 mg/dL), or cirrhosis.

Hypoglycemia does not occur in diabetic patients taking acarbose. However, if hypoglycemia occurs when acarbose is used simultaneously with a sulfonylurea, recovery will be retarded if carbohydrate is orally administered. Ingestion of pure glucose is advised in diabetic patients who experience hypoglycemia while taking acarbose.

Cost

The cost for an average daily dose of acarbose is about twice that of a brand-name sulfonylurea and slightly less than that of metformin (**Table 3**).

Summary

In summary, the major effect of acarbose is to decrease postprandial glucose levels. The respective decreases in fasting plasma glucose and HbA_{1c} values are 25 to 30 mg/dL and 0.5 to 1.0 percentage points. Acarbose works by interfering with carbohydrate digestion and delaying gastrointestinal absorption of glucose. It does not cause weight gain and does not significantly affect plasma lipid levels. The major side effects of acarbose are related to the gastrointestinal tract.

Troglitazone

Troglitazone (Rezulin, Parke-Davis, Morris Plains, New Jersey) belongs to a class of drugs referred to as the thiazolidinediones (124, 125). Two other thiazolidinediones, pioglitazone (Actos, Takeda America, Princeton, New Jersey) and rosiglitazone (Avandia, SmithKline Beecham, Philadelphia, Pennsylvania), were recently reviewed by the FDA, and available results indicate that their hypoglycemic potency is at least equal to that of troglitazone (126, 127).

Mechanism of Action

The glucose-lowering effect of troglitazone and other thiazolidinediones is related to the drugs' ability to enhance insulin sensitivity (124, 128, 129) (**Table 1**, **Figure 1**). Like metformin, troglitazone affects both liver and muscle (124, 128–131). The original mechanistic study by Sutter and colleagues (129) showed that in every patient with type 2 diabetes treated with troglitazone, peripheral (muscle) sensitivity to insulin improved. However, only patients in whom hepatic glucose production decreased experienced a decrease in fasting plasma glucose level (129). Sironi and associates (130) reported similar results. In contrast, in a double-blind, placebo-controlled trial, troglitazone uniformly increased peripheral insulin sensitivity while affecting hepatic insulin sensitivity only modestly (128). In vitro studies have shown that a major effect of troglitazone is the inhibition of gluconeogenesis in isolated hepatocytes (132). Troglitazone also improves insulin sensitivity in adipose tissue (133). Thiazolidinediones bind to a novel receptor called the peroxisome proliferator activated receptor γ, leading to increased glucose transporter expression (124). A stimulatory effect of thiazolidinediones to increase the number of adipocytes is well established (125, 134, 135) and explains, in large part, the weight gain and reduction in circulating free fatty acid levels (128) observed with all thiazolidinedione therapy. It is likely that part of troglitazone's stimulatory effect on muscle glucose metabolism and inhibitory action on hepatic glucose production is secondary to the decrease in plasma free fatty acid levels and associated inhibition of free fatty acid oxidation (125, 128).

Efficacy

Six published trials have examined troglitazone monotherapy in patients with poorly controlled type 2 diabetes (**Table 1**). In 284 diet-treated Japanese patients, 400 mg of troglitazone per day reduced fasting plasma glucose and HbA_{1c} values by 1.6 mmol/L (23 mg/dL) and 0.6 percentage points, respectively (136). In a large European trial (137) that included 329 patients with type 2 diabetes, 600 mg of troglitazone per day caused a modest reduction of 1.6 mmol/L (29 mg/dL) in fasting plasma glucose levels; the HbA_{1c} value did not change significantly from baseline. In a 48-week open-label study, troglitazone decreased the fasting plasma glucose level by 2.2 mmol/L (40 mg/dL) and the HbA_{1c} value by 0.5 percentage points (138). In a double-blind, placebo-controlled, dose-response study (139) carried out in 70 diet-treated patients with type 2 diabetes who received 200, 400, and 600 mg of troglitazone per day or placebo for 26 weeks, the mean decreases in fasting plasma glucose and HbA_{1c} values at the highest dosage were 2.7 mmol/L (48 mg/dL) and 0.9 percentage points, respectively. In a study by the same group (140), sulfonylurea therapy was discontinued for 2 weeks and troglitazone therapy was started in 95 patients with diabetes. In patients receiving 600 mg of troglitazone per day, the HbA_{1c} and fasting plasma glucose values increased by 1.2 percentage points and 0.8 mmol/L (15 mg/dL), respectively. In a 12-week study involving 95 diet-treated patients, 600 mg of troglitazone per day decreased fasting plasma glucose and HbA_{1c} values by 2.1 mmol/L (38 mg/dL) and 0.8 percentage points, respectively (data on file with Parke-Davis). In a study involving 93 patients with type 2 diabetes treated with 600 mg of troglitazone per day for 6 months (128), fasting plasma glucose levels decreased by 2.5 mmol/L (45 mg/dL), but the HbA_{1c} value did not decrease.

Taken collectively, the above studies show respective mean reductions in fasting plasma glucose and HbA_{1c} values of 1.9 mmol/L (34 mg/dL) and 0.6 percentage points and indicate that troglitazone monotherapy is less effective than either sulfonylureas or metformin (**Table 1**). This was confirmed in a study (140) in which 76 patients were switched from glyburide therapy to treatment with troglitazone (600 mg/d) for 52 weeks. During this period, the HbA_{1c} value increased by 0.93 percentage points above baseline, showing that maximum-dose troglitazone therapy is significantly less effective than glyburide. About 25% of diet-treated patients with type 2 diabetes experience no glucose-lowering effect with troglitazone (primary treatment failure)

(124, 129, 137). Nonresponders can be predicted by a low fasting C-peptide concentration (<1.5 ng/dL) (124).

Rosiglitazone and pioglitazone seem to be at least as effective as troglitazone. Data on file with the FDA demonstrate that when these agents are used as monotherapy in drug-naive diabetic patients, the HbA_{1c} value decreases by about 1.2 to 1.5 percentage points after 26 weeks of treatment. Rosiglitazone has been approved as monotherapy and for combination with metformin. Clinical trials examining combination therapy with rosiglitazone plus sulfonylureas and rosiglitazone plus insulin have been completed and submitted to the FDA. It is expected that pioglitazone will soon be approved as monotherapy and for combination with sulfonylureas, metformin, and insulin. More detailed information on these two new thiazolidinediones were presented at the annual meeting of the American Diabetes Association in June 1999.

Other Effects

Troglitazone consistently reduces plasma triglyceride levels by 10% to 20% and increases HDL cholesterol levels by 5% to 10% (128, 129, 136, 138). However, most studies have reported a 10% to 15% increase in LDL cholesterol levels (136–138) (**Table 2**). This side effect is undesirable because hypercholesterolemia is a major risk factor for coronary artery disease, and patients with type 2 diabetes are already at increased risk for heart attack and stroke. Small decreases in blood pressure have been noted in some studies (138). A small but significant weight gain is observed in diabetic patients treated with troglitazone alone for 12 weeks or longer (136, 137) (**Table 1**). However, more significant increases in body weight occur when troglitazone is combined with a sulfonylurea or insulin (140, 141). Similar results for plasma lipid levels, blood pressure, and weight gain have been reported to the FDA (data on file with Parke-Davis).

When used as monotherapy, pioglitazone decreases the plasma triglyceride level by about 0.57 mmol/L (50 mg/dL); rosiglitazone has no clinically significant effect on plasma triglyceride levels (data on file with the FDA). Both pioglitazone and rosiglitazone increase plasma LDL cholesterol and HDL cholesterol levels by (data on file with FDA). After 26 weeks, the increase in HDL cholesterol level was 0.18 to 0.20 mmol/L (7 to 8 mg/dL) with both pioglitazone and rosiglitazone. The LDL cholesterol level increased by 0.13 mmol/L (5 mg/dL) with pioglitazone and 0.26 to 0.39 mmol/L (10 to 15 mg/dL) with rosiglitazone. Like troglitazone, both pioglitazone and rosiglitazone significantly increase body weight (increase of 3 to 4.6 kg and 2 to 3 kg, respectively; data on file with FDA).

Dosing Schedule

The starting troglitazone dosage (for monotherapy) is 400 mg/d (**Table 4**). The fasting plasma glucose level begins to decrease within 5 to 7 days but does not achieve its nadir until at least 3 to 4 weeks. Six to 8 weeks should be allowed before increasing the troglitazone dosage to its maximum, 600 mg/d. Alternately, therapy can be initiated with a dosage of 600 mg/d. When used as combination therapy with sulfonylureas or with sulfonylurea plus metformin (troglitazone is not approved for combination therapy with metformin), the starting dosage is 200 mg/d.

The recommended starting dosages of pioglitazone and rosiglitazone are 15 mg once daily and 2 mg once daily, respectively (**Table 4**). The dosage should be increased every 3 to 4 weeks to a maximum of 45 mg once daily for pioglitazone and 8 mg once daily (or 4 mg twice daily) for rosiglitazone.

Safety

When troglitazone was first introduced in the United States, 1.9% of diabetic patients who received this drug were reported to experience an increase in alanine aminotransferase (ALT) levels to levels that were more than three times the upper limit of normal, with two cases of reversible jaundice. Subsequently, several cases of severe liver toxicity have been reported (142), and there have been at least 43 cases of acute hepatic failure, with 28 reported deaths from liver failure in troglitazone-treated patients. In a recent safety review, the FDA indicated that the actual number of cases of liver toxicity was probably significantly underestimated because many cases are not reported. At the same safety meeting, the Endocrine Advisory Committee to the FDA recommended that the indication for troglitazone as monotherapy for the treatment of type 2 diabetes be removed. The FDA has agreed, stating that troglitazone should not be used as monotherapy in patients with type 2 diabetes. However, if a diabetic patient is receiving troglitazone as monotherapy and liver function is normal, therapy with the drug can be continued. Because of concerns about liver toxicity, the FDA has added a warning statement to the package insert. Troglitazone therapy should not be started if the ALT level is more than 50% above the upper limit of normal. After troglitazone therapy is started, the ALT level should be measured monthly for the first 12 months and periodically thereafter. If the ALT level increases to more than 1.5 to 2 times the upper limit of normal, monitoring should be repeated weekly until it reverts to normal. If the ALT level continues to increase and reaches values that are more than three times the upper limit of normal in follow-up visits, troglitazone therapy should be discontinued.

Across all clinical trials, diabetic patients treated with troglitazone experienced a decrease in the plasma hemoglobin level of 3% to 4%. This has been attributed to the dilutional effect of fluid retention and expansion of the plasma volume. Edema has been reported in 5% of troglitazone-treated patients, and troglitazone is contraindicated in diabetic patients with New York Heart Association class III or IV cardiac status.

The incidence of elevated liver enzyme levels in diabetic patients treated with pioglitazone and rosiglitazone are 0.25% and 0.2%, respectively (data on file with FDA). These incidences of abnormal liver enzyme levels were similar to those in patients who received placebo. No cases of acute liver failure or severe liver dysfunction were observed in either pioglitazone-treated or rosiglitazone-treated patients. Consequently, the FDA has recommended that the ALT level be measured every other month for the first year in rosiglitazone- and pioglitazone-treated patients.

Cost

Troglitazone is the most expensive oral antidiabetic agent on the U.S. market, costing three times more than metformin and four times more than brand-name sulfonylureas (**Table 3**).

Summary

In summary, troglitazone monotherapy is only modestly effective in reducing plasma glucose levels (decrease in HbA_{1c} value, 1.0 percentage point). Troglitazone works by improving insulin sensitivity in muscle and, to a much lesser extent, in the liver. Troglitazone decreases plasma triglyceride levels, but its use is associated with weight gain and an increase in LDL cholesterol levels. Liver toxicity is a significant concern with troglitazone, and monthly monitoring of liver function is required once therapy with the drug begins. Troglitazone is the most expensive of the oral agents.

Repaglinide

Repaglinide (Prandin, Novo Nordisk, Princeton, New Jersey) is a benzoic acid derivative that stimulates insulin secretion and is approved by the FDA for the treatment of type 2 diabetes.

Mechanism of Action

Repaglinide is a nonsulfonylurea insulin secretagogue (**Figure 1**) that requires the presence of glucose for its action and works by closing an adenosine triphosphatase–dependent potassium channel (143). At least two and possibly three repaglinide receptor binding sites have been found on β-cells (143). One of these is the sulfonylurea receptor. It is not currently known whether the insulin stimulatory effect of repaglinide is additive to that of a sulfonylurea.

Efficacy

When used as monotherapy, the decreases in fasting plasma glucose and HbA_{1c} values are similar to those observed with sulfonylureas (144, 145). In diet-treated patients with type 2 diabetes who had not previously been exposed to oral agents, 1 mg of repaglinide three times daily decreased the HbA_{1c} value by 1.7 to 1.8 percentage points from baseline (144, 145). Repaglinide at a dosage of 4 mg/d produced a similar decrease in the HbA_{1c} value from baseline (1.9 percentage points) (144). In a double-blind, randomized, parallel-group study, repaglinide and glyburide produced equivalent decreases in HbA_{1c} values over 1 year (145). The glucose-lowering effect of repaglinide is completely additive to that of metformin (146). The HbA_{1c} value decreased by 1.4 percentage points, from 8.3% to 6.9%.

Other Effects

Repaglinide has no significant effect on plasma lipid levels. In patients switched from sulfonylurea therapy to repaglinide therapy, no weight was gained. In drug-naive patients treated with repaglinide, body weight increased by about 3% (5 to 6 lb) (147).

Dosing Schedule

Repaglinide is rapidly absorbed (0.5 to 1 hours) and displays rapid plasma elimination (half-life $<$ 1 hour). Because of its pharmacokinetic behavior, its administration results in a rapid but brief release of insulin. The starting dosage of repaglinide is 0.5 mg three times daily, given 15 minutes before each meal (**Table 4**). Dose increases can be made weekly to a maximum daily dose of 16 mg. A repaglinide dosage of 1 mg three times daily produces 90% of the maximal glucose-lowering effect (144). Because 90% of repaglinide is recovered in the feces, it is not contraindicated in patients with renal insufficiency. In patients with liver disease, a slower titration schedule is recommended.

Safety

Hypoglycemia was the only adverse effect noted with increased frequency in patients who received repaglinide compared with those who received placebo. In diabetic patients treated for 1 year with repaglinide ($n = 1228$) or sulfonylurea ($n = 498$), fewer hypoglycemic episodes (16% compared with 20%; P value not significant) and fewer severe hypoglycemic reactions were observed in the repaglinide group (data on file with Novo Nordisk).

Cost

Repaglinide is about 2.5 times more expensive than brand-name sulfonylureas and slightly more expensive than metformin (**Table 3**).

Summary

In summary, repaglinide is very effective in reducing plasma glucose levels (decrease in HbA_{1c} value, 1.5 to 2.0 percentage points). It works by augmenting insulin secretion. Repaglinide has no direct effect on plasma lipids. Weight gain and hypoglycemia are side effects of repaglinide therapy, but some evidence suggests that less hypoglycemia occurs with repaglinide than with sulfonylureas. However, repaglinide is considerably more expensive than sulfonylureas.

Combination Therapy with Oral Agents

When a maximal dose of metformin (91) or sulfonylurea (67, 68) is used as monotherapy, about 25% of patients with type 2 diabetes with a starting fasting plasma glucose level of 12.2 to 13.3 mmol/L (220 to 240 mg/dL) will achieve an acceptable level of glycemic control according to American Diabetes Association guidelines (fasting plasma glucose level $<$ 7.8 mmol/L [$<$140 mg/dL] and HbA_{1c} value $<$ 8.0%). Similar values for the percentage of diabetic patients reaching the therapeutic goal with troglitazone are not available from the published literature. However, because the hypoglycemic effect of troglitazone monotherapy (128, 129, 136–138) is less than that of therapy with either metformin or sulfonylureas, one can anticipate that a smaller percentage of patients will reach the desired therapeutic goal. An even smaller percentage of patients with type 2 diabetes will achieve acceptable glycemic control with acarbose therapy (117, 120–123). Therefore, most patients with type 2 diabetes will require combination therapy to reach an acceptable level of glycemic control. Moreover, because type 2 diabetes mellitus is a progressive disease (28, 29, 41, 42, 50, 59) (**Figure 2**), even patients with a good initial response to oral agents eventually will require a second (or third) medication.

The most commonly used combination therapy is metformin plus a sulfonylurea (58, 59, 103, 148). Addition of a sulfonylurea to metformin therapy gives an additive glucose-lowering effect (102, 103, 149). Similarly, addition of metformin to sulfonylurea therapy gives an additive response, both with respect to glucose-lowering (101, 103, 149–152) and lipid-lowering (91, 103) effects. Hermann and colleagues (103) provided clinical validation of this approach in 144 diet-treated patients with poorly controlled (fasting plasma glucose level, 13.3 mmol/L [240 mg/dL]) type 2 diabetes who were randomly assigned to therapy with metformin, glyburide, or primary combination treatment with metformin plus glyburide. Doses were titrated upward to achieve a fasting plasma glucose level less than 6.7 mmol/L (121 mg/dL). All diabetic patients initially treated with monotherapy required addition of the second oral agent. After 6 months, decreases in HbA_{1c} and fasting blood glucose values were similar among patients who received metformin plus glyburide (2.3 percentage points and 6.1 mmol/L [110 mg/dL]), those who received glyburide plus metformin (2.0 percentage points and 4.8 mmol/L [86 mg/dL]), and those who received combination therapy from the start (2.2 percentage points and 6.1 mmol/L [110 mg/dL]). Fifty percent of the entire group achieved a fasting blood glucose level less than 7 mmol/L (112 mg/dL), and all patients had an HbA_{1c} value less than 7%. No weight was gained in any group.

In the largest published study of combination therapy, 422 patients with poorly controlled type 2 diabetes (fasting plasma glucose level, 249 mg/dL) with glyburide were randomly assigned to have metformin or placebo added to their regimen (91). In the placebo group, fasting plasma glucose and HbA_{1c} values increased by 14 mg/dL and 0.2 percentage points, respectively, after 29 weeks. In the metformin-treated group, fasting plasma glucose and HbA_{1c} values decreased by 63 mg/dL and 1.7 percentage points, respectively. Similar decreases were observed with metformin monotherapy in patients with poorly controlled diet-treated type 2 diabetes.

Numerous studies (119, 122, 152–155) have shown that addition of acarbose to sulfonylureas or to metformin therapy provides an additive effect.

Two published studies have examined the effect of troglitazone (600 mg/d) when added to sulfonylurea therapy in patients with poorly controlled type 2 diabetes (140, 156). In the study by Iwamoto and colleagues (156), the mean decreases from baseline in fasting plasma glucose and HbA_{1c} values were 1.6 mmol/L (29 mg/dL) and 0.7 percentage points, respectively. In patients with poorly controlled type 2 diabetes (fasting plasma glucose level, 12.2 mmol/L [224 mg/dL]) who received 12 mg of micronized glyburide per day (Glynase, Pharmacia & Upjohn, Kalamazoo, Michigan), addition of troglitazone (600 mg/d) decreased fasting plasma glucose and HbA_{1c} values by 3.1 mmol/L (56 mg/dL) and 1.7 percentage points from baseline (140). These results are similar to those observed with metformin plus glyburide (91) and are much better than those obtained with troglitazone monotherapy (128, 136–139). However, patients treated with troglitazone plus glyburide experienced a 13.1-pound weight gain and a significant increase (up to 13%) in LDL cholesterol levels. In a recent report involving a small

number of patients with type 2 diabetes, the effect of troglitazone was found to be additive to that of metformin (157).

If combination therapy with metformin and sulfonylurea fails to produce acceptable glycemic control, several options are available (**Figure 4**): 1) addition of bedtime neutral protamine Hagedorn (NPH) insulin while maintaining therapy with oral agents, 2) institution of a regimen consisting of multiple insulin injections, or 3) addition of troglitazone or acarbose to a regimen of sulfonylurea plus metformin. Although triple oral therapy (acarbose or troglitazone plus combined metformin and sulfonylurea therapy) has not been examined formally, one might expect their effects to be additive on the basis of results from a single retrospective study (158). Although some diabetes experts might consider institution of a multiple-injection insulin regimen if satisfactory glycemic control is not attained with combined metformin–sulfonylurea therapy, I recommend addition of bedtime insulin and continuation of metformin therapy. This approach is supported by results from a study by Yki-Järvinen and colleagues (159). When insulin is used as monotherapy, large dosages (>80 to 100 U/d) are required to achieve normoglycemia, and significant weight gain commonly occurs (28, 29, 45, 48, 50, 51, 159, 160). Because combination therapy with bedtime insulin and oral agents effectively reduces elevated plasma glucose levels, requires considerably less insulin (thereby minimizing weight gain [159–162]), and often allows for fewer insulin injections per day (163), I favor this approach.

Combination Therapy with Bedtime Insulin Plus Oral Agents

The effectiveness of bedtime insulin therapy in patients with type 2 diabetes in whom acceptable glycemic control does not occur with oral agents alone or in combination is well documented. In such patients, the elevated fasting plasma glucose level is caused by incomplete suppression of basal hepatic glucose production by sulfonylurea or metformin (64, 65, 96, 106). Although the sulfonylurea or metformin is still working, it is not producing the desired hypoglycemic effect. Bedtime insulin takes advantage of the differential sensitivity of hepatic compared with peripheral tissues to insulin (7, 9). Low doses of insulin effectively suppress hepatic glucose production and have a much smaller effect on stimulating muscle glucose uptake (164). By giving a modest dose of intermediate-acting insulin (such as NPH insulin) at bedtime, the elevated basal rate of hepatic glucose production can be reduced to normal, and the likelihood of hypoglycemia will decrease because muscle glucose uptake is only minimally stimulated.

A meta-analysis of 16 randomized, placebo-controlled trials comparing sulfonylureas plus insulin with placebo plus insulin showed significantly lower fasting plasma glucose and HbA_{1c} values, a lower daily insulin dose, and absence of weight gain in patients who received bedtime insulin plus daytime sulfonylurea (161). Similar findings have been reported in other rigorously designed trials (164–166). However, these studies were not designed to examine the superiority of bedtime intermediate-acting insulin over a mixed-split insulin regimen. Two large, well-designed trials have addressed this question. In the Finnish Multicenter Insulin Study (160), 153 patients with type 2 diabetes that was poorly controlled by sulfonylurea therapy were randomly assigned to treatment with sulfonylurea alone, sulfonylurea plus NPH insulin given at 7 a.m., sulfonylurea plus NPH insulin given at 9 p.m., NPH plus regular insulin given before breakfast and dinner, or NPH insulin given at 9 p.m. and regular insulin given with each meal. All insulin regimens improved glycemic control similarly, but the insulin dose was 50% to 60% lower in the two groups that received sulfonylurea plus once-daily NPH insulin. Bedtime insulin plus sulfonylurea caused significantly less weight gain and a 50% lower level of day-long serum free insulin. Similar results were reported in a Swedish study of patients with type 2 diabetes poorly controlled with glyburide who were subsequently randomly assigned to receive bedtime NPH insulin or a multiple-dose insulin regimen (162). In patients with type 2 diabetes that was inadequately controlled with metformin alone, addition of bedtime NPH insulin compared with switching to a multiple-insulin injection regimen produced equivalent glycemic control (167). However, the group that received metformin plus bedtime NPH insulin required 50% less insulin and experienced no weight gain.

In summary, addition of bedtime intermediate-acting insulin to either sulfonylurea or metformin monotherapy is a safe and effective way of normalizing the day-long glycemic profile while minimizing weight gain and reducing the insulin dose by 50% to 60% compared with a multiple-injection insulin regimen.

Several well-designed studies have compared addition of a second oral agent with addition of bedtime insulin in patients with poorly controlled type 2 diabetes receiving oral agent monotherapy. Combined oral agent therapy (metformin plus sulfonylurea) was as effective in achieving glycemic control as addition of bedtime NPH insulin to a sulfonylurea (166, 168–170). An advantage of the metformin–sulfonylurea combination was less weight gain (or even weight loss) and improvement in dyslipidemia.

Hermann and colleagues (103) showed that in most patients with newly diagnosed type 2 diabetes (fasting plasma glucose level, 12.2 to 13.3 mmol/L [220 to 240 mg/dL]), blood glucose levels can be controlled with combined sulfonylurea-metformin therapy. Similar findings were reported in the UKPDS (28, 59). In diabetic patients receiving sulfonylurea plus metformin in whom the desired therapeutic goal is not reached, options include addition of a third oral agent (troglitazone or acarbose) (158), addition of bedtime NPH insulin, or switching to a multiple insulin injection regimen.

The last two options were explored in a study by Yki-Järvinen and colleagues (159). Ninety-six patients with type 2 diabetes that was poorly controlled with sulfonylureas, metformin, or both were randomly assigned to receive one of the following: bedtime NPH insulin plus glibenclamide (15 mg/d), bedtime NPH insulin plus metformin (2 g/d), bedtime NPH insulin plus metformin plus sulfonylurea, or bedtime NPH insulin plus morning NPH insulin. After 1 year, glycemic control was substantially better in the group receiving bedtime insulin plus metformin (mean change in HbA_{1c} value, -2.5 ± 0.4 percentage points) than in all other groups, including the group receiving bedtime insulin, sulfonylurea, and metformin (mean change in HbA_{1c} value, -1.9 ± 0.4 percentage points). Better control in the group that received bedtime insulin plus metformin was attributed to the absence of significant weight gain (0.9 kg at one year). In contrast, mean weight gain was 3.9 kg in the insulin plus sulfonylurea group; 3.6 kg in the insulin, sulfonylurea, and metformin group; and 4.6 kg in the bedtime insulin plus morning insulin group.

In summary, a rational approach to therapy in patients with type 2 diabetes is to begin therapy with a sulfonylurea or metformin and add another oral agent if the desired glycemic control is not achieved (**Figure 4**). If additional therapy is required, bedtime NPH insulin or a third oral agent can be added. Alternately, the patient can be switched to a mixed-split insulin regimen. Because insulin monotherapy requires high doses, which usually are associated with weight gain, I favor addition of bedtime NPH insulin while maintaining therapy with an oral agent.

Addition of Oral Hypoglycemic Agents in Insulin-Treated Patients with Type 2 Diabetes

It is common to encounter patients with poorly controlled type 2 diabetes who are taking large doses of insulin. Both troglitazone and metformin have received FDA approval for use in these patients. The primary therapeutic goal is to improve the day-long glycemic profile (HbA_{1c} value $< 7\ \%$). A secondary treatment goal is to reduce the insulin dose, the number of insulin injections, or both, but this should not be attempted until the primary goal has been achieved. In a large prospective study of 234 patients with poorly controlled type 2 diabetes, 600 mg of troglitazone per day decreased the fasting plasma glucose level by 2.7 mmol/L (49 mg/dL), the HbA_{1c} value by 1.4 percentage points, and the insulin dose by 29% (140). Similar observations were reported by Buse and associates (171). However, in both of these studies, troglitazone therapy was associated with significant increases in body weight and LDL cholesterol level.

Metformin has also been widely used to improve glycemic control in insulin-treated patients with type 2 diabetes. In a study by Giuliano and coworkers (172), 50 insulin-treated patients with poorly controlled type 2 diabetes were randomly assigned to receive metformin or placebo for 6 months. In the metformin-treated group, HbA_{1c} values decreased by 1.9 percentage points, fasting plasma glucose levels decreased by 5.1 mmol/L (92 mg/dL), and insulin dose was reduced by 24%. Two recent double-blind, placebo-controlled studies performed in insulin-treated patients with poorly controlled type 2 diabetes also showed significant improvements in glycemic control and reductions in the insulin dose and number of injections (163, 173). In all three of these studies (163, 172, 173), body weight decreased significantly or did not increase, and levels of LDL and total cholesterol decreased. Bell and associates (174) initiated combination therapy with metformin plus sulfonylurea in 55 insulin-treated patients with poorly controlled type 2 diabetes; they were able to completely withdraw insulin therapy in 42 of 55 (76%) patients. After 1 year, HbA_{1c} values decreased by 1.3 percentage points in these 42 patients, and body weight declined by 2.3 kg. These results indicate that adding metformin therapy to insulin therapy in patients with poorly controlled type 2 diabetes is very effective in improving glycemic control and reducing insulin requirements.

Addition of acarbose to the therapy for insulin-treated patients with type 2 diabetes has been examined (120, 175) but reductions in HbA_{1c} values (0.4 to 0.7 percentage points) and daily insulin doses (0% to 10%) are modest compared with those achieved with addition of troglitazone or metformin.

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