

Treatment of Non-Insulin-Dependent Diabetes Mellitus With Metformin

Robert Guthrie, MD

Background: Metformin alleviates hyperglycemia of non-insulin-dependent diabetes mellitus (NIDDM) by inhibiting hepatic glucose production and improving peripheral insulin sensitivity. In contrast to sulfonylureas, metformin does not stimulate insulin secretion, promote weight gain, exacerbate hyperinsulinemia, or cause hypoglycemia. It also favorably affects serum lipids.

Methods: A comprehensive review of the medical literature from 1968 to the present was conducted using the key words "metformin" and "non-insulin-dependent diabetes mellitus."

Results: Metformin monotherapy was superior to placebo and comparable to sulfonylureas in reducing fasting plasma glucose and glycosylated hemoglobin levels in patients with NIDDM uncontrolled by diet. Metformin and sulfonylureas, however, had diverse effects on body weight and fasting plasma insulin levels; both weight and insulin levels remained unchanged or decreased with metformin and increased with sulfonylureas. In patients with secondary sulfonylurea failure, the combination of metformin and a sulfonylurea synergistically improved glycemic control better than either drug alone and was comparable to insulin plus sulfonylurea. When hyperglycemia is uncontrolled by insulin after secondary sulfonylurea failure, limited data suggest the efficacy of metformin plus insulin. The mild, transient, self-limited gastrointestinal side effects that sometimes occur can be minimized by gradually increasing the doses and by taking metformin with food. Risk of metformin-associated lactic acidosis is low if prescribing guidelines are adhered to. Potential adverse drug interactions include hypoglycemia during concurrent sulfonylurea therapy and elevated metformin plasma concentrations when metformin is taken concomitantly with cimetidine.

Conclusions: Metformin can be used safely and effectively as first-line monotherapy in NIDDM or in combination with a sulfonylurea when monotherapy with either agent fails. It can be particularly suitable when weight gain, hyperlipidemia, and hypoglycemia are clinically important issues. (J Am Board Fam Pract 1997;10:213-21.)

Diabetes mellitus is a major health problem in the United States and contributes in large amount to the development of other severe illnesses, including coronary heart disease, retinopathy and blindness, neuropathy, and renal failure. Of the 16 million diabetic patients in the United States, nearly 90 to 95 percent have non-insulin-dependent diabetes mellitus (NIDDM).¹

Methods

A computer literature search, including a comprehensive review of the medical literature from

1968 to the present, was conducted using the key words "metformin" and "non-insulin-dependent diabetes mellitus."

Pathogenesis of NIDDM

The pathogenesis of NIDDM is incompletely understood, but it is thought to be a combination of diminished insulin sensitivity, particularly in the muscles and liver, together with decreased insulin production by pancreatic β -cells.² The primary defect might be impaired insulin secretion in lean NIDDM patients and peripheral insulin resistance in overweight NIDDM patients.² Hyperglycemia in NIDDM results from increased hepatic glucose output and reduced peripheral glucose utilization,³ the relative importance of each factor being unknown. Age, obesity, family history, and ethnicity (ie, Hispanic, Native Amer-

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From the Department of Emergency Medicine, Ohio State University, Columbus, Ohio. Address reprint requests to Robert Guthrie, MD, Ohio State University, 005 Upham Hall, 473 West 12th Ave, Columbus, OH 43210.

ican) are predominant risk factors for NIDDM, indicating the etiologic involvement of genetics and weight.

The earliest prediabetic metabolic abnormality appears to be insulin resistance, which precedes and can predict the development of impaired glucose tolerance and NIDDM.^{4,5} Initially insulin secretion can remain sufficient to compensate for insulin resistance and to maintain normoglycemia. In NIDDM insulin resistance becomes manifest as a reduced ability of insulin to inhibit hepatic glucose production and to stimulate glucose utilization by skeletal muscle.^{6,7} Insulin resistance places an increased demand on pancreatic β -cells, leading to progressive loss of β -cell function secondary to exhaustion of their secretory capacity. Even in the presence of insulin resistance, progression to NIDDM appears to require a concomitant defect in insulin secretion.²

Treatment of NIDDM

Persistent hyperglycemia leads to the microvascular and macrovascular complications of NIDDM. The goal of NIDDM therapy is, therefore, to restore blood glucose levels to as close to normal as possible (ideally fasting plasma glucose is approximately 115 mg/dL). This level is not realistic for many patients, but 115 mg/dL is the ultimate goal. Because most NIDDM patients are obese, and weight loss is associated with improved glucose and lipid metabolism, weight reduction through dietary restriction and exercise is the cornerstone of NIDDM therapy. Dietary compliance and weight reduction are frequently unsuccessful, however, making further therapy necessary. Since the 1970s, the only NIDDM therapies beyond diet and weight control have been sulfonylureas and insulin.

Sulfonylureas lower glucose primarily by increasing β -cell insulin secretion. Although frequently effective, sulfonylureas tend to promote weight gain through induction of higher insulin levels, and they can cause hypoglycemic episodes, but they are rarely associated with hypoglycemic coma. Also, approximately one third to one half of patients with newly diagnosed NIDDM cannot successfully control their glucose levels with a sulfonylurea.^{8,9}

Recently the biguanide metformin, an antihyperglycemic agent used in Europe for 30 years, has become available in the United States. Al-

though metformin is derived from the same chemical class as phenformin, unlike phenformin, metformin does not undergo hepatic metabolism, it is excreted unchanged in the urine, and it does not inhibit aerobic metabolism. The risk of metformin-induced lactic acidosis is therefore extremely low; there have been approximately 0.03 cases per 1000 patient years based on worldwide surveillance data.¹⁰ Patients can minimize the risk of lactic acidosis by strictly following prescribing instructions and avoiding known contraindications. Chemically unrelated to the sulfonylureas, metformin can be used as first-line monotherapy in NIDDM or in combination with a sulfonylurea when monotherapy with either agent has failed. Approximately 10 percent or less cannot successfully control their newly diagnosed NIDDM by metformin.¹⁰ Secondary failure rates are reported to be 5 to 10 percent each year for both metformin¹⁰ and sulfonylureas.⁸

Pharmacodynamic Properties of Metformin

The mode of action of metformin (improving peripheral sensitivity to insulin and inhibiting hepatic production of glucose) improves glucose tolerance in NIDDM patients by lowering both basal and postprandial plasma glucose levels. In contrast to the sulfonylureas, metformin neither stimulates insulin secretion nor produces hypoglycemia in either diabetic or nondiabetic patients. Rather than increasing plasma insulin levels, metformin can actually reduce insulin levels.^{11,12} Metformin can also have a beneficial effect on serum lipid profiles and might have vasoprotective properties.¹⁰

Effects on Peripheral Glucose Utilization and Metabolism

Metformin increases insulin-stimulated glucose utilization in both diabetic and nondiabetic insulin-resistant patients.^{13,14} In NIDDM patients metformin increases insulin-stimulated glucose utilization by up to 53 percent.¹⁵⁻¹⁸ This effect has been attributed predominantly to increased nonoxidative glucose disposal,^{14,19,20} such as the formation of glycogen (glycogenesis) and the incorporation of glucose into triglyceride.

Effects on Hepatic Glucose Production

Treatment with metformin (1 to 2.55 g/d) for up to 3 months reduces basal hepatic glucose production, typically by 10 to 30 percent.^{16,21-24} Sup-

pression of hepatic gluconeogenesis, in part by means of reduced free fatty acid and lipid oxidation, might be a principal action of metformin²⁵ and has been proposed as a primary cause of reduced fasting hyperglycemia in NIDDM.

Effects on Insulin Levels

Because metformin does not stimulate insulin secretion,^{11,22,26} plasma levels of insulin and its precursor C-peptide are generally unchanged or reduced during metformin therapy.^{16,27-29} Marked reductions in plasma levels of insulin^{12,23,30,31} and the insulin precursor proinsulin^{31,32} have been reported in both lean and overweight patients with NIDDM, an effect apparently secondary to metformin-induced reductions in plasma glucose. Also, metformin can greatly reduce (by more than 50 percent) fasting hyperinsulinemia in nondiabetic patients.³³

Pharmacokinetic Properties of Metformin

The pharmacokinetics of metformin are reviewed in Table 1.³⁴ Gastrointestinal absorption of metformin is complete within 6 hours of ingestion. The absolute oral bioavailability is 50 to 60 percent at doses of 0.5 to 1.5 g.^{11,35} Metformin distributes rapidly, does not bind to plasma proteins, and does not undergo hepatic metabolism or biliary excretion.³⁵ It does undergo rapid renal excretion and has a mean plasma elimination half-life of 4.0 to 8.7 hours.^{34,35} Metformin half-life correlates with creatinine clearance and is prolonged in patients who have renal impairment. The potential for excretion in breast milk or transfer across the placenta is unknown.

Metformin in NIDDM

Metformin has been evaluated in NIDDM as first-line monotherapy and in combination with sulfonylureas and insulin. Metformin is not approved by the Food and Drug Administration (FDA) for use in patients with insulin-dependent diabetes mellitus (IDDM); therefore, its use in this patient population is not recommended. In some of the clinical trials reported here, dosages of metformin greater than the FDA-approved dosage of 2.5 g/d have been used.

Metformin Monotherapy

As monotherapy metformin substantially decreases elevated blood glucose levels. It has a glu-

Table 1. Summary of the Pharmacokinetic Properties of Orally Administered Metformin.

Parameter	Range
Absolute oral bioavailability (%)	50-60
Time to reach maximum plasma concentration (h)	2.0-3.3
Maximum plasma concentration (mg/L) 850-mg dose	1.5-2.0
Area under the plasma concentration-time curve (mg/L·h) 850-mg dose	8.7-9.6
Volume of distribution (L)	63-276
Total clearance (L/h)	26.5-42.4
Renal clearance (L/h)	20.1-36.9
Plasma elimination half-life (h)	4.0-8.7

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cose-lowering activity superior to that of placebo and equivalent to that of the sulfonylureas in both overweight and lean patients with NIDDM. In controlled clinical studies of metformin monotherapy (0.5 to 3 g/d) for up to 8 months' duration, overweight and lean patients with NIDDM whose glucose levels were poorly controlled by diet alone were able to reduce their fasting blood glucose concentrations by 22 to 26 percent of pretreatment levels and their glycosylated hemoglobin (HbA_{1c}) levels by 12 to 17 percent of pretreatment levels, representing an absolute decrease of about 1.4 percent, which was a significantly greater reduction than with placebo.³⁶⁻³⁸ In studies for 3 to 12 months' duration conducted predominantly with overweight patients whose NIDDM was uncontrolled by diet alone, metformin therapy (0.5 to 3 g/d) resulted in reductions in fasting plasma glucose levels of 14 to 45 percent of pretreatment values, compared with 18 to 43 percent reductions after treatment with chlorpropamide (0.5 g/d), glyburide (3.5 to 10.5 mg/d), or glipizide (80 to 240 mg/d).³⁹⁻⁴¹

In a long-term study in nonobese patients with NIDDM uncontrolled by diet, treatment with metformin (1 to 3 g/d) or chlorpropamide (100 to 375 mg/d) for 1 year resulted in similar reductions from baseline in mean postprandial plasma glucose concentrations in patients aged between 60 and 79 years (by 51 percent and 49 percent, respectively) and in patients aged between 40 and 59 years (by 51 percent and 50 percent, respectively); more than 80 percent of patients in each age group successfully controlled their glucose concentrations using either treatment.⁴²

In a four-way comparison trial, the United Kingdom Prospective Diabetes Study (diet vs chlorpropamide vs glyburide vs insulin vs metformin), all of the active agents produced similar fasting plasma glucose and glycosylated hemoglobin values, all of which improved more than with diet alone. Metformin recipients, however, had lower insulin levels, avoided the weight gain seen with sulfonylureas or insulin, and had less frequent hypoglycemic episodes.¹²

Metformin monotherapy has beneficial effects on serum lipids. Circulating triglyceride levels were either unchanged or reduced (by up to 45 percent)²¹ during metformin monotherapy in NIDDM patients.³⁴ This reduction might be associated with a decline in the concentration of very low density lipoprotein (VLDL) triglycerides, especially in patients with pre-existing hypertriglyceridemia.^{10,43,44} A more modest reduction (up to 18 percent) in serum total cholesterol levels generally occurs during metformin monotherapy.³⁰ These reductions are suggested as being secondary to metformin-induced decreases in low-density lipoprotein (LDL) cholesterol or VLDL cholesterol levels.¹⁰ Modest reductions (8 to 25 percent) in serum LDL cholesterol levels and increases (17 percent or less) in high-density lipoprotein (HDL) cholesterol levels have also been reported after metformin therapy.^{21,36}

Unlike the sulfonylureas, which often cause weight gain, metformin monotherapy is associated with either no change or a reduction in body weight. In placebo-controlled studies conducted predominantly in overweight patients with NIDDM (mean pretreatment body mass index greater than 27 kg/m²), mean body weight was unchanged during metformin therapy.³⁶⁻³⁸ In direct comparisons with groups taking sulfonylureas, groups taking metformin showed either no change or a mean reduction in body weight of 2.7 lb (1.2 kg), whereas sulfonylurea-treated groups showed mean weight gains ranging from 6.2 to 11.6 lb (2.8 to 5.3 kg).³⁹⁻⁴¹ In nonobese patients with NIDDM, a small mean weight loss of 3.3 lb (1.5 kg) was observed following metformin therapy, whereas a mean weight gain of 10.0 lb (4.6 kg) occurred in patients who received chlorpropamide.⁴²

Metformin monotherapy does not exacerbate hyperinsulinemia. In the United Kingdom Prospective Diabetes Study of patients with newly diagnosed NIDDM, mean fasting plasma insulin

levels declined by 22 percent from pretreatment levels after 6 years of metformin monotherapy. In contrast, sulfonylurea or insulin monotherapy resulted in elevation of mean fasting plasma insulin levels (by about 11 percent) after the same treatment period.¹² In another study, patients with NIDDM unresponsive to diet were prescribed metformin monotherapy (0.85 to 3.0 g/d) for a 3- to 8-month period, and fasting plasma insulin levels decreased by 24 percent.⁴¹ In other studies, both fasting and postprandial plasma insulin levels remained unchanged.^{37,38,40,45} In contrast, glipizide (80 to 240 mg/d) and glyburide (3.5 to 10.5 mg/d) increased fasting (23 percent) and postprandial (33 percent) plasma insulin levels, respectively.^{40,41} Because metformin does not increase insulin levels, an additional important distinction from the sulfonylureas is that metformin treatment will not produce hypoglycemia.

Metformin and Sulfonylurea Combination Therapy

The complementary modes of action of metformin and the sulfonylureas allow a combination therapy that synergistically improves glycemic control after secondary failure with either drug alone. Secondary failure, which occurs in more than 60 percent of patients after 5 years of sulfonylurea therapy,⁹ is predominately due to progression of the disease.

Small randomized comparisons and a large multicenter study of patients with NIDDM who had secondary sulfonylurea failure determined that the addition of metformin was significantly more effective than the addition of placebo in controlling hyperglycemia. In one randomized study (n = 30),²⁷ a reduction in mean fasting plasma glucose of approximately 60 mg/dL was observed 5 weeks after the addition of metformin (1 g/d) to glyburide (15 to 20 mg/d) or glipizide (20 mg/d). In a large multicenter study (n = 1823),⁴⁶ glycemic control improved after the addition of metformin (850 to 2550 mg/d) to maximal doses of sulfonylureas. Mean fasting blood glucose measured in 155 patients decreased by 67.6 mg/dL (a 29 percent reduction). All of these trials reported significant improvements in hemoglobin A (HbA₁) or HbA_{1c} levels. In the large multicenter study,⁴⁶ mean HbA₁ values decreased significantly, by 1.9 percent, after 12 weeks.

More recently, DeFronzo et al³⁶ showed that metformin and sulfonylurea are synergistic when

used in combination and superior to either antihyperglycemic drug alone in patients undergoing secondary sulfonylurea failure. In their three-arm multicenter study of 632 patients with NIDDM, patients who switched from glyburide monotherapy to metformin monotherapy (0.5 to 2.5 g/d) experienced no change in fasting plasma glucose levels, whereas patients who continued with glyburide monotherapy (20 mg/d) had a further deterioration in glycemic control. In contrast to levels achieved by glyburide alone, the addition of metformin to glyburide reduced the average fasting plasma glucose level by an additional 77 mg/dL, and the average HbA_{1c} level by an additional 1.9 percent. While metformin alone does not produce hypoglycemia, combination therapy led to an increase in the symptoms of hypoglycemia.

Comparative data also show that the antihyperglycemic efficacy of metformin coadministered with glyburide was equivalent to that of insulin-containing regimens. In a 2-month study of 16 patients with NIDDM, the addition of metformin (1.5 g/d) or NPH insulin (0.15 to 0.2 IU/kg at bedtime) was compared with pre-existing glyburide monotherapy (15 mg/d).⁴⁷ The fasting plasma glucose level was reduced by 68.5 mg/dL (a 28 percent decrease) and the HbA_{1c} level by 1.5 percent (a 16 percent decrease) with metformin plus glyburide, compared with reductions in fasting plasma glucose of 82.9 mg/dL (a 33 percent decrease) and HbA_{1c} of 1.8 percent (a 19 percent decrease) with insulin plus glyburide. Body weight was unchanged in the metformin plus glyburide group, but it increased by 3 percent in the insulin plus glyburide group. No statistically significant differences were reported between the two groups. Other clinical trials have shown similar results.^{48,49}

Metformin and Insulin Combination Therapy

When secondary failure to sulfonylureas occurs, severe insulin resistance often necessitates aggressive high-dose insulin therapy, either alone or in combination with a sulfonylurea.⁵⁰ Even then glycemia often remains poorly controlled. Limited clinical data suggest that therapy with a combination of metformin plus insulin might achieve adequate glycemic control in some patients.

A randomized, double-blind, placebo-controlled 6-month study in 50 obese patients with NIDDM whose glucose levels had remained poorly controlled despite initiation of regular and

Lente insulin therapy (mean dose 90 IU/d) following secondary sulfonylurea failure showed benefits of adding metformin 1.7 g/d to insulin regimens.³⁰ Significant sustained decreases were observed in mean plasma glucose levels (from 268.4 to 176.5 mg/dL), HbA_{1c} levels (from 11.7 percent to 9.8 percent), mean fasting plasma insulin concentrations (a 30 percent decrease from baseline), and mean daily insulin dosage (a 24 percent decrease from baseline; mean decrease of 21.6 IU/d). All of the reduction in the mean daily insulin dosage occurred in patients who responded well to treatment (glucose profile less than 180 mg/dL). The body weight of all patients remained stable during the study, and there were no reports of hypoglycemia.

Long-Term Efficacy

The United Kingdom Prospective Diabetes Study¹² was established in 1977 to look at the long-term use of diet alone, insulin, metformin, or sulfonylurea therapy on the complications commonly associated with NIDDM. The final report of this study is expected in 1998 and will provide valuable information on the long-term efficacy and effect on diabetic complications of the antidiabetic regimens studied.

Safety of Metformin

Adverse Effects

Acute, self-limiting adverse effects, mainly of gastrointestinal origin (primarily diarrhea), are the most common side effects of metformin, occurring in up to 30 percent of patients. In most patients gastrointestinal symptoms are mild, transient, and dose-related; they can be minimized by taking metformin with food and by gradually increasing the dose. These symptoms typically disappear spontaneously after several weeks of treatment at a given dose and cause less than 5 percent of patients to discontinue metformin.⁴⁶ The tolerability of metformin does not appear to be modified by coadministration with a sulfonylurea.⁴⁶

During clinical trials about 7 percent of patients taking metformin had their levels of vitamin B12 decrease to subnormal without clinical manifestations. Thus, annual hematologic assessment should include monitoring for signs of vitamin B12 deficiency. Apparent deficiency can be treated by supplementing vitamin B12 or discontinuing metformin.

Lactic Acidosis

The most serious adverse effect associated with metformin is lactic acidosis. Extensive experience with metformin in Europe and Canada shows that the risk of lactic acidosis is low. Based on worldwide surveillance data, the overall incidence of metformin-associated lactic acidosis is approximately 0.03 cases per 1000 patient-years, with approximately 0.015 fatalities per 1000 patient-years.¹⁰ To put the risk of metformin-associated lactic acidosis in perspective, the mortality risk is comparable to that of sulfonylurea-induced hypoglycemic coma, anaphylaxis from penicillin, and thromboembolism from the use of oral contraceptives. Reported cases of metformin-associated lactic acidosis have primarily occurred in patients in whom the drug was contraindicated, especially those with renal impairment. Risk factors for the development of metformin-associated lactic acidosis have been described, and adherence to the prescribing guidelines will substantially minimize the risk of lactic acidosis.

Metformin, although derived from the same chemical class as phenformin, has many important structural and pharmacological differences. Phenformin was withdrawn from the market in the 1970s because of an unacceptably high incidence of lactic acidosis, particularly in patients possessing a defect that impaired hepatic metabolism of the drug. In contrast to phenformin, however, metformin is not metabolized, it is excreted rapidly in urine, it does not accumulate systemically,⁵¹ it is not lipophilic, it binds minimally to mitochondrial membranes (ie, does not inhibit aerobic metabolism), and it does not decrease glucose oxidation, resulting in a substantially reduced risk of elevating lactate levels.^{21,43,52}

Renal function must be evaluated before initiating and regularly during metformin therapy. Because renal function can be compromised in elderly patients who have normal serum creatinine measurements, metformin should be used only after renal function has been assessed and confirmed to be normal. Renal function assessment should include a measurement of 24-hour creatinine clearance or calculation of creatinine clearance, factoring for age and muscle mass. Metformin is contraindicated in patients who have renal disease or renal dysfunction (eg, as suggested by serum creatinine levels of 1.5 mg/dL and greater in men, 1.4 mg/dL or greater in

women, or abnormal creatinine clearance in either), and in patients with acute or chronic metabolic ketoacidosis. Furthermore, because iodinated radiologic contrast agents can cause renal impairment, though rarely, metformin should be temporarily discontinued before a procedure using these agents and not reinstated until normal renal function has been confirmed.

Other precautions are those that have been associated with lactic acidosis, including history of lactic acidosis, impaired hepatic function, cardiac insufficiency (cardiovascular collapse, acute congestive heart failure, acute myocardial infarction), and any other hypoxic conditions. Because alcohol is known to potentiate the effect of metformin on lactate metabolism, metformin recipients should avoid excessive acute or chronic alcohol intake. Metformin administration should be temporarily suspended for any surgical procedure until the patient's oral intake has resumed and renal function has been evaluated as normal.

Thus, with proper attention to prescribing guidelines and use of the minimal effective dose, the incidence of lactic acidosis can be minimized.

Drug Interactions

Metformin is associated with few clinically important drug interactions.⁵³ Single-dose studies have found no clinically serious pharmacokinetic interaction between metformin and glyburide, furosemide, propranolol, or ibuprofen.

Although as monotherapy metformin does not induce clinical hypoglycemia, when used in combination with sulfonylurea, hypoglycemia can result, possibly because of a synergistic action of the two agents.⁵³ Additional improvements in glycemic control occur when acarbose and metformin are coadministered⁵⁴ despite an apparent reduction in the bioavailability of metformin.⁵⁵

Although metformin does not affect cimetidine pharmacokinetics, cimetidine increases the peak concentration and area under the plasma concentration-time curve of metformin (but not the elimination half-life) by competitive inhibition of renal tubular secretion, thereby necessitating patient monitoring or dose adjustment.

Conclusions

The unique mode of action of metformin, improving peripheral insulin sensitivity and inhibiting hepatic glucose production, complements and

provides several advantages relative to the sulfonylureas. Metformin improves glucose tolerance in patients who have NIDDM without stimulating insulin secretion or exacerbating hyperinsulinemia, and it does not cause hypoglycemia. The ability of metformin to reduce hyperglycemia without raising plasma insulin concentrations is noteworthy because an association has been suggested between hyperinsulinemia and an increased risk of atherogenesis.^{56,57} Numerous studies have confirmed that the effectiveness of metformin is similar to that of the sulfonylureas. Metformin, however, also has an independent beneficial effect on serum lipid profiles and, while clinically effective in both lean and overweight NIDDM patients, stabilizes or even reduces body weight in some patients. Thus, metformin might be the appropriate first-line therapy for many NIDDM patients. The complementary modes of action of metformin and sulfonylureas allow combination therapy to improve glycemic control after secondary failure (when fasting plasma glucose exceeds 140 mg/dL) with either drug alone.

Although gastrointestinal side effects predominate with metformin therapy, they occur at the start of treatment and generally resolve spontaneously with continued treatment. Extensive experience with metformin in Europe and Canada shows that the incidence of metformin-associated lactic acidosis is rare (comparable to the risk of hypoglycemic coma with sulfonylurea therapy) and can be minimized by appropriately selecting patients according to the prescribing guidelines.

Thus, metformin is an antihyperglycemic agent with a unique mechanism of action that complements and provides several advantages relative to the sulfonylureas, particularly in patients with NIDDM in whom weight gain, hyperlipidemia, or hypoglycemia is a clinically serious issue.

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