Metformin: A New Treatment Option for Non–Insulin-Dependent Diabetes Mellitus

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Metformin is a biguanide that can used alone or in combination with sulfonylureas or insulin in the treatment of non–insulin-dependent diabetes mellitus (NIDDM). Since biguanides do not increase pancreatic insulin secretion, they are referred to as antihyperglycemic agents, as opposed to hypoglycemic agents. Biguanides reduce hyperglycemia by increasing insulin sensitivity, decreasing glucose absorption, and inhibiting hepatic gluconeogenesis.

Advantages of metformin include achieving glycemic control without exacerbating weight gain or hyperinsulinemia and beneficially affecting serum cholesterol concentrations. Although metformin has the potential to cause lactic acidosis, the incidence is significantly lower compared with phenformin.

Risk factors for lactic acidosis include renal serum creatinine >1.5 mg/dL and cardiovascular, pulmonary, and hepatic disease.

Metformin should be temporarily discontinued prior to surgery and before administration of radiologic intravenous contrast, and in patients with sepsis, severe gastrointestinal disease, trauma, and acute cardiovascular events.

Key words. Metformin; biguanide; diabetes mellitus, non–insulin-dependent; acidosis, lactic; hyperinsulinism. (*J Fam Pract 1996; 42:612-618*)

Metformin, a biguanide, has been approved by the Food and Drug Administration (FDA) for the treatment of non–insulin-dependent diabetes mellitus (NIDDM). Metformin is manufactured by the French pharmaceutical company Lipha S.A., with marketing rights in the United States granted to Bristol-Myers Squibb.[1] Biguanides are not new entities. Two such agents, phenformin and metformin, were introduced in Europe in 1957.[2] Phenformin was available in the United States until 1977, when it was removed from the market because of incidences of fatal lactic acidosis.[2] Biguanides have a unique mechanism of action and are referred to as antihyperglycemic agents, as opposed to hypoglycemic agents, a term used to describe sulfonylureas.[2–6] Metformin was reconsidered for the US market because of its unique mechanism of action; a lower risk of lactic acidosis, compared with phenformin; and its successful use in over 90 countries.[6]

Mechanism of Action

Biguanides are distinctly different from oral sulfonylureas in that they do not stimulate pancreatic insulin secretion, and therefore do not directly cause hypoglycemia.[7] Metformin has several proposed mechanisms of action: decreased intestinal glucose absorption, increased peripheral glucose uptake, increased insulin-mediated glucose uptake, and decreased hepatic glucose production.[8–10] Suppression of hepatic glucose production and increased peripheral insulin sensitivity appear to be the major mechanisms of action by which glycemic control is restored.[4,6,7,11]

Effect on Cardiovascular Risk Factors

Encouraging beneficial effects of metformin on cardiovascular risk factors have been observed; however, clinical

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significance has yet to be determined. Patients with NIDDM may have an increased prevalence of dyslipidemias (elevated, small, dense, low-density lipoprotein [LDL]), high triglycerides, reduced high-density lipoprotein [HDL]), which may predispose them to cardiovascular disease.[12–16] Metformin reduces total serum cholesterol concentrations and increases HDL, and markedly diminishes triglycerides, independent of improved glycemic control. Clinically significant effects of metformin have not been demonstrated in all trials.[17] In a small population of NIDDM patients receiving metformin, a decrease in total cholesterol (17%), triglycerides (45%), and LDL (24%) and an increase in HDL (17%) were observed.[18] Less dramatic improvement was observed when a combination of metformin-glyburide was compared with glyburide alone. The combination reduced total cholesterol by 4%, triglycerides by 8%, LDL by 6%, and increased HDL by 3%; with glyburide therapy, total cholesterol increased by 1%, total triglycerides by 4%, LDL by 3%, and HDL by 1%.[19] Suppression of intestinal cholesterol biosynthesis is the suggested mechanism by which metformin alters lipid concentrations.[2]

Obesity is also prevalent among patients with NIDDM and may diminish insulin receptor sensitivity, which can further impair glycemic control.[20,21] Treatment with oral sulfonylureas and insulin often results in weight gain, further exacerbating obesity, insulin resistance, hyperglycemia, and hyperinsulinemia.[22,23] Unlike oral sulfonylureas and insulin, metformin has been associated with significant weight loss or lack of weight gain.[11,22] Stumvoll et al[11] determined that weight loss associated with metformin involves mainly the loss of adipose tissue.

Controversial epidemiological evidence suggests an association between increased serum insulin levels (hyperinsulinemia) and cardiovascular disease.[24–29] Further research is required to determine whether hyperinsulinemia is a contributing factor or an indicator of cardiovascular disease.[30,31] The use of aggressive high-dose insulin in patients with NIDDM who are still capable of producing endogenous insulin may result in an increase in cardiovascular disease.[32] The Veterans Affairs cooperative trials in NIDDM observed an increase in cardiac events in NIDDM patients receiving more aggressive insulin therapy. Further analysis of these results is being conducted.[32,33] Metformin has been demonstrated to decrease hyperinsulinemia and reduce the requirements of exogenous therapeutic insulin.[22,34] Additional studies are required to determine whether metformin is more effective in reducing cardiovascular events than insulin or oral sulfonylureas.[22]

Factors that affect coagulation are also altered by metformin. Increased tissue plasminogen activator, decreased plasminogen activator inhibitor, and decreased platelet aggregation have been observed.[35,36] It is unknown whether these beneficial effects are directly attributable to metformin or result from improvement in glycemic control or other metabolic activity.

Pharmacokinetics

Approximately 50% to 60% of the oral dose of metformin is absorbed systemically.[1,2] A proportionally greater amount of metformin will be absorbed with a smaller dose as a result of saturable absorption.[4] Administration with food delays the onset of action and decreases peak concentrations and total area under the curve.[1] Metformin is not metabolized to any significant degree.[4] Twenty percent to 30% of the drug is recovered in the feces, but it is primarily eliminated unchanged by the kidneys by means of tubular secretion. Renal insufficiency impairs elimination, increasing the risk of adverse events, particularly lactic acidosis. The half-life of metformin is approximately 6 hours in patients with normal renal function.

Clinical Studies

Metformin vs Placebo

To determine the effectiveness of metformin as first-line therapy for NIDDM, 289 obese patients with NIDDM poorly controlled with diet were randomized to receive metformin (n=143) or placebo (n=146) for 29 weeks.[37] Mean fasting glucose and HbA_{1c} were significantly lower in patients receiving metformin than in patients taking placebo (189 mg/dL vs 244 mg/dL [$P<.001$] and 7.1% vs 8.6% [$P<.001$], respectively). Fasting plasma insulin and C-peptide concentrations did not change. Total cholesterol, LDL, and triglyceride concentrations decreased in patients receiving metformin and did not change in patients receving placebo. Seventy-eight percent of patients randomized to receive metformin required the maximal dose of 2550 mg/d to achieve glycemic control.

Metformin vs Glyburide vs Metformin-Glyburide

A second study involved 788 obese patients with NIDDM poorly controlled with diet and glyburide 10 mg twice daily.[37] Six hundred thirty-two patients were randomized to glyburide (n=209), metformin (n=210), or the combination glyburide-metformin (n=213). At the end of 29 weeks, patients receiving the combination glyburide-metformin achieved lower mean fasting glucose

levels and HbA_{1c}, compared with those receiving either glyburide or metformin alone (187 mg/dL vs 261 mg/dL vs 255 mg/dL [$P<.001$], and 7.1% vs 8.7% vs 9.3% [$P<.001$], respectively). Total cholesterol, LDL, and triglycerides were significantly lower in the combination glyburide-metformin and metformin alone compared with the glyburide group. Mean weight decreased by 3.8 kg in the metformin group and increased by 0.4 kg in the combination group ($P<.001$). No significant weight change was observed in the glyburide group. Mild symptoms of hypoglycemia were described in 18% of patients in the combination glyburide-metformin group and in 3% and 2% of the glyburide and metformin groups, respectively. Ninety percent of the patients in the metformin and 70% in the metformin-glyburide group required 2500 mg of metformin daily. Mean fasting lactate levels did not change during the treatment period. This study suggests that substituting maximal-dose glyburide with metformin alone did not improve glycemic control. However, the combination of glyburide and metformin beneficially improved mean fasting glucose, HbA_{1c}, and cholesterol concentrations, compared with either drug alone.

Combination Metformin-Sulfonylurea vs Insulin-Sulfonylurea

Klein randomized 50 patients with NIDDM who failed oral sulfonylurea therapy to receive combination therapy with metformin-sulfonylurea or insulin-sulfonylurea.[38] At 12 months, similar glycemic control (fasting glucose) was obtained between the metformin-sulfonylurea and insulin-sulfonylurea combinations (180 mg/dL and 170 mg/dL, respectively). Fasting total serum insulin remained unchanged in the metformin group and increased in the insulin group from a baseline of 13.8 to 21.2 mU/mL [$P<.05$]). Therefore, patients failing on oral sulfonylureas can achieve glycemic control with the addition of metformin, and initiation of insulin therapy can be delayed.

Combination Metformin-Insulin vs Insulin

Guigliano et al randomized 50 obese patients with NIDDM who were poorly controlled on insulin (88 to 90 units/day) and had a HbA_{1c} of at least 12% to receive combination metformin-insulin or placebo-insulin.[34] Mean HbA_{1c} and fasting glucose decreased significantly from 11.7% to 9.8% and from 260 to 180 mg/dL, respectively, in the metformin-insulin group ($P<.05$). No change occurred in the placebo-insulin group. Mean exogenous insulin requirements in the metformin group decreased 22%, from 90 to 70 units/day ($P<.05$), with no reduction in the placebo group. Fasting insulin plasma levels decreased in the metformin group from 24 to 17 mU/mL ($P<.05$), with no change in the placebo group. The addition of metformin enabled patients to maintain similar glycemic control and reduce the exogenous insulin requirements without exacerbating hyperinsulinemia.

The United Kingdom Prospective Diabetes Study (UKPDS) is designed to determine the benefits of diet therapy, oral sulfonylureas, insulin, and metformin in maintaining glycemic control and in preventing NIDDM complications, including cardiovascular outcomes, over an 11-year period of follow-up.[39] The UKPDS results will assist in determining whether achievement of glycemic control decreases cardiovascular mortality and morbidity associated with NIDDM. The UKPDS also has a shorter term objective of determining the relative efficacy of treatment 3 years from the diagnosis of NIDDM.[22] Over 6000 newly diagnosed NIDDM patients were screened, and those meeting the inclusion criteria (n=2769) were stratified for obesity. All participants received diet therapy. Non-obese participants were randomized to receive either diet alone, chlorpropamide, glyburide, or Ultralente insulin with or without regular insulin. Metformin was included as a randomization option for the obese participants (>120% ideal body weight). Fasting glucose, glycosylated hemoglobin, fasting insulin concentration, body weight, compliance, and episodes of hypoglycemia were measured. Efficacy data after 3 years on 2520 patients are as follows: (1) mean fasting glucose was significantly lower in all groups compared with diet therapy ($P<.001$); (2) patients on drug therapy experienced significant weight gain compared with diet alone ($P<.001$) (mean weight gain: diet, 1.7 kg; chlorpropamide, 3.5 kg; glyburide, 4.8 kg; and insulin, 4.8 kg); and (3) fasting insulin concentrations increased compared with diet alone ($P<.001$) (mean increase in fasting plasma insulin concentration: diet, 0.1 mU/mL; chlorpropamide, 0.9 mU/mL; glyburide,1.2 mU/mL; and insulin, 2.4 mU/mL). In obese patients, metformin therapy resulted in glycemic control similar to that of insulin but without weight gain and with decreased fasting insulin concentration (mean decrease, 2.5 mU/mL).

Results of the UKPDS reported at 6 years continue to demonstrate lack of weight gain and reduction in hyperinsulinemia in obese patients randomized to metformin.[40] In patients receiving sulfonylurea or insulin, weight gain increased by 6 kg and 4 kg, respectively, compared with an increase of only 2 kg in the diet therapy group ($P<.001$). No significant increase in weight gain was observed in obese patients randomized to metformin compared with those on diet therapy. Fasting insulin plasma concentrations increased in the sulfonylurea and

insulin groups by 0.9 mU/L and 3.8 mU/L, compared with the diet therapy group ($P<.001$), and decreased by 2.1 mU/mL in the metformin group, compared with the diet therapy group ($P<.01$).

Side Effects and Adverse Reactions

The most common adverse effects caused by metformin, occuring in 5% to 20% of patients, include gastrointestinal bloating and discomfort, anorexia, nausea, metallic taste, and diarrhea.[2,41] The incidence of gastrointestinal adverse effects can be reduced if metformin is taken with meals and the dose is titrated slowly. Impairment in the absorption of vitamin B_{12} occurs but rarely causes megaloblastic anemia.[42] It is recommended, however, that patients taking metformin receive periodic measurements of hemoglobin, hematocrit, and red blood cells.[1]

Lactic acidosis is the most serious adverse effect. Biguanides may decrease the hepatic clearance and increase the production of lactic acid.[4] Lactic acidosis becomes a risk when patients have preexisting disease states that allow for lactate acid accumulation, ie, decreased acid elimination (renal or hepatic failure) or increased acid production (hypoxia).[4] Metformin differs from phenformin in that metformin does not increase the release of lactate from the muscle.[11] The risk of lactic acidosis with metformin is significantly lower than with phenformin and may be attributed to the shorter half-life and poor hepatic metabolism of metformin. Although the risk of lactic acidosis is lower with metformin (0.03 cases/1000 patient years, with 0.015 fatal cases/1000 patient years)[1] (unpublished data. Food and Drug Administration. Endocrinologic and metabolism drugs advisory committee meeting; March 19, 1994) as compared with phenformin (0.25 to 4 cases/1000 patient years),[43] metformin is capable of causing lactic acidosis and is contraindicated in patients who are at increased risk (Table 1). European data indicate that 80% of cases of metformin-induced lactic acidosis occurred in patients with renal insufficiency.[44] Among more than 600,000 patients who have received metformin in Canada, only 28 patients developed lactic acidosis, all of whom had underlying organ disease in which metformin was contraindicated.[45]

Lactic acidosis has a mortality rate of up to 50% and should be regarded as a medical emergency requiring hospitalization. Metformin-related lactic acidosis is characterized by metformin serum concentrations >5 μg/mL, blood lactate concentration of >5 mmol/L, decreased blood pH, and electrolyte disturbances with an increased anion gap. Symptoms of lactic acidosis include somnolence, confusion, shortness of breath, nausea, abdominal discomfort, dizziness, fatigue, muscle pain, and bradyarrhythmia. Treatment is hydration and correction of the metabolic acidosis. Hemodialysis can increase the elimination of the biguanide and correct the acidosis.[1]

Table 1. Risk Factors for Metformin-Induced Lactic Acidosis

Contraindications for metformin
Renal insufficiency
Hepatic disease
Severe cardiovascular disease
Severe pulmonary disease
Temporary discontinuation of metformin
Radiographic intravenous contrast medium
Infections, septicemia
Surgery, trauma
Acute myocardial infarction, angina
Stroke
Dehydration
Severe gastrointestinal illness
Drug interactions with metformin
Oral sulfonylureas/insulin
Alcohol
Cimetidine
Nifedipine
Cationic drugs (eg, ranitidine, triamterene, trimethoprim)
Nephrotoxic drugs
Aggressive use of diuretics

Data in this table adapted from Hermann LS, Melander A. Biguanides: basic aspects and clinical use. In: Alberti KGMM, DeFronzo RA, Keen H, et al, eds. International textbook of diabetes mellitus. New York, NY: John Wiley & Sons 1992; 773-95, and Luft D, Schmulling RM, Eggstein M. Lactic acidosis in biguanide-treated diabetes: a review of 330 cases. Diabetologia 1978; 14:76-87.

It is currently recommended that metformin not be prescribed for male patients with serum creatinine greater than 1.5 mg/dL or for female patients with 1.4 mg/dL and in patients with hepatic disease.[1] These recommendations are stringent and limit the use of metformin in many patients with NIDDM. The FDA has required that phase IV postmarketing studies be conducted to better define metformin dosing guidelines for patients with renal insufficiency. Metformin should be temporarily discontinued in patients who develop dehydration, sudden gastrointestinal disease, acute myocardial infarction, cardiovascular collapse, or septicemia.[1] Discontinuation of metformin is recommended 48 hours before and 48 hours after surgery or a diagnostic study involving the administration of intravenous contrast medium.[1]

Drug Interactions

Metformin will potentiate the hypoglycemic effects when used in combination with both oral sulfonylureas or exogenous insulin. Concomitant administration of nephrotoxic agents that decrease renal elimination of metformin, eg, aminoglycosides, amphotericin, intravenous radiologic contrast medium, chemotherapeutic agents, high-dose nonsteroidal anti-inflammatory drugs (NSAIDs), should

Table 2. Costs of Oral Antidiabetic Agents

Oral Antidiabetic Agent* Generic (Trade) Name	Average Wholesale Price per 100 ($)	Dose	Estimated Monthly Cost ($)†
Metformin (Glucophage)	48.60 (500 mg)/81.60 (850 mg)	500–850 mg bid	29.00–49.00
		500–850 mg tid	44.00–73.00
Glipizide	30.67 (5 mg)/56.31 (10 mg)	5–10 mg qd	9.00–17.00
		10–20 mg bid	34.00–68.00
(Glucotrol XL)	30.67 (5 mg)/60.69 (10 mg)	5–20 mg qd	9.00–36.00
Glyburide	50.93 (5 mg)	5–10 mg qd	15.00–31.00
		5–10 mg bid	31.00–61.00
(DiaBeta)	58.90 (5 mg)	5–10 mg qd	18.00–35.00
		5–10 mg bid	35.00–71.00
(Micronase)	54.49 (5 mg)	5–10 mg qd	16.00–33.00
		5–10 mg bid	33.00–66.00
(Glynase PresTab)	47.00 (3 mg)	3–6 mg qd	14.00–28.00
	70.49 (6 mg)	3–6 mg bid	21.00–42.00
Chlorpropamide	8.45 (100 mg)/12.30 (250 mg)	250–750 mg qd	4.00–11.00
(Diabinese)	36.71 (100 mg)/77.65 (250 mg)	250–750 mg qd	23.00–70.00
Tolazamide	11.00 (100 mg)/26.95 (250 mg)/51.50 (500 mg)	100 mg qd–500 mg bid	3.00–31.00
(Tolinase)	30.20 (100 mg)/63.78 (250 mg)/97.89 (500 mg)	100 mg qd–500 mg bid	9.00–59.00
Tolbutamide	12.40 (500 mg)	250 mg qd–1000 mg bid	2.00–15.00
(Orinase)	28.87 (500 mg)	250 mg qd–1000 mg bid	4.00–35.00

**Information on drugs comes from* Facts and comparisons, loose-leaf drug information service. *St. Louis, Mo: Facts and Comparisons, Inc, 1992, 1995.*
†Estimated monthly cost is based on wholesale price, derived from microfiche updated monthly from McKesson, San Francisco, Calif, Sept 1995.
Bid denotes twice daily; tid, three times daily; qd, once daily; XL, extended release.

be avoided. Cationic agents, such as ranitidine, cimetidine, triamterene, and trimethoprim, given in combination with metformin, may cause metformin levels to increase by competing for the renal tubular secretion of metformin.[1] A dose reduction in metformin is recommended when used concomitantly with these agents. Caution is particularly advisable with the concomitant use of cimetidine and metformin, as cimetidine increases metformin concentrations by 40%. Since diuretics can cause dehydration, metformin should be used carefully in patients undergoing aggressive diuresis. Alcohol has been shown to increase the risk of lactic acidosis when metformin is coadministered in high doses. Alcohol use should be avoided and metformin prescribed with discretion to habitual alcohol drinkers.

Dosage, Administration, and Cost

Metformin is available in 500-mg and 850-mg unscored tablets. Recommended starting dose is 500 mg twice daily, titrated gradually (no sooner than every 2 to 3 weeks) until glycemic control is obtained, or a maximum of 850 mg three times daily is reached. Haupt et al[46] obtained glycemic control in obese patients with NIDDM using metformin 850 to 1700 mg/d in addition to an oral sulfonylurea. In studies by DeFronzo,[37] however, maximal doses of metformin alone and in combination with an oral sulfonylurea therapy were required. Maintaining the dosage regimen of metformin at 500 mg two to three times daily will reduce the cost and possibly the risk of lactic acidosis. The cost of metmin at maximal dosing is higher then a second-geneion oral sulfonylurea (Table 2).

Conclusions

Treatment of patients with NIDDM typica begins with maintenance of lifestyle modifications, idiet, physical activity, and weight reduction, followed bral sulfonylureas and insulin therapy.[47] It is importa to maintain and enhance early education efforts in regard to lifestyle modifications, which are the cornerstone therapy of NIDDM. Approximately 60% to 70% of patients with NIDDM will have an initial satisfactory response to oral sulfonylureas.[48,49] Unfortunately, these agents tend to become less effective over time at an annual failure rate ranging from 5% to 10%.[47,48] Insulin, alone or in combination with oral sulfonylurea, has been the traditional second step. Several reports have documented that after oral sulfonylureas fail to maintain glycemic control, the addition of bedtime NPH insulin achieves glycemic control similar to that of twice-daily NPH insulin.[49–51] The combination regimen of insulin plus oral sulfonylureas also allows for utilization of less insulin and avoids an additional subcutaneous injection.

Metformin should be considered first-line therapy in obese patients with newly diagnosed NIDDM and normal renal function. The major role of metformin will be as a supplement to oral sulfonylureas following primary failure. The optimal dose of oral sulfonylureas in combina-

Table 3. Benefits and Disadvantages of Metformin

Benefits of Metformin	Disadvantages of Metformin
• Additive glycemic control when combined with oral sulphonylureas or insulin	• Risk of lactic acidosis (contraindicated in patients with renal insufficiency)
• May delay the initiation of insulin therapy after oral sulphonylurea failure	• Associated with nausea and gastrointestinal disturbances
• Decreases triglycerides, increases high-density lipoprotein	• Expense
• Weight loss or lack of weight gain	• Short half-life requiring multiple daily dosing (twice to three times daily)
• Reduction in hyperinsulinemia	

tion with metformin requires further investigation; however, either glyburide 10 mg/d or glipizide 20 mg/d is a reasonable choice. Metformin serves as an intermediate step before initiating insulin therapy. Metformin can be used in combination with insulin therapy in an attempt to reduce the total exogenous insulin dose, improve glycemic control, and reduce hyperinsulinemia. The benefits of metformin are summarized in Table 3. The need for multiple daily dosing, associated gastrointestinal intolerance, expense, and risk of lactic acidosis are limiting aspects of treatment with metformin. The risk of lactic acidosis may preclude the use of metformin in patients who have the most to gain: those with concomitant renal insufficiency or severe cardiovascular disease who have poor glycemic control, despite receiving large doses of insulin. Metformin has been shown to achieve glycemic control, promote weight reduction (or lack of weight gain), improve serum cholesterol concentrations, reduce requirements for exogenous insulin therapy, and reduce hyperinsulinemia.

The recommended dose of metformin is 500 mg to a maximum of 2550 mg per day in three divided doses. Patients taking metformin should receive regular evaluations of renal function and vitamin B_{12} levels, and education regarding the warning signs of lactic acidosis. The use of metformin is not recommended in patients with significant renal insufficiency and should be prescribed cautiously in patients with risk factors predisposing them to lactic acidosis.

Cardiovascular complications of NIDDM are related to hyperglycemia and, possibly, hyperinsulinemia.[52] Therefore, management of NIDDM should consider not only maintaining glycemic control but also reducing risk factors for cardiovascular disease. The approval of metformin provides an alternative treatment of hyperglycemia that increases insulin sensitivity, reduces hyperglycemia, and improves risk factors for cardiovascular disease without stimulating endogenous insulin secretion.

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