Role of Metformin in Treatment of Diabetes Mellitus

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Metformin, a biguanide antidiabetic agent that can be administered either alone or in combination with sulfonylureas, has been extensively used in Europe and Canada. The mechanism of action of metformin and other biguanides is not completely understood, but recent in vitro and in vivo studies suggest that metformin may act in part by both increasing the binding of insulin to its receptor and potentiating insulin action. Metformin, because of its chemical structure, does not interact with the liver and has a short half-life. Consequently, lactic acidosis, which is a rare complication of metformin, has not been associated with the proper use of this drug. In addition to its antidiabetic actions, metformin causes weight loss in obese diabetic patients and may be useful in managing associated lipid disorders.

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Most diabetic patients have non-insulin-dependent diabetes mellitus (NIDDM) (1). These patients have both pancreatic and extrapancreatic abnormalities (2). Their islets of Langerhans have an impaired ability to secrete insulin in response to either intravenous or oral glucose challenge (3,4), and their peripheral tissues are resistant to insulin (2,4–7). Insulin resistance in these patients can be demonstrated in terms of both decreased insulin-mediated glucose disposal in muscle and other tissues and abnormal suppression of hepatic glucose output (4–7).

Many of these diabetic patients are obese, and weight reduction has been shown to reduce their hyperglycemia (8). However, because stable weight reduction is difficult to achieve and is not always sufficient to induce euglycemia, drug therapy is needed in many cases. The ideal drug therapy would be to correct the defects in both insulin secretion and insulin action. The sulfonylureas are the only drugs currently available for treatment of NIDDM. However, these drugs are not initially useful in all patients, and in patients who benefit initially, the number of secondary failures is significant (9–11). Therefore, other drug therapies are needed to either complement or replace sulfonylurea therapy. Biguanides, which include metformin, phenformin, and buformin, comprise a second class of agents used to lower blood glucose levels in NIDDM patients. We review the major features of metformin, the most widely used biguanide in Europe.

CHEMISTRY AND PHARMACODYNAMICS OF BIGUANIDES

The biguanides are guanidine derivatives in which two molecules of guanidine are linked together with the elimination of an ammonia group. Guanidine itself lowers glucose activity in animals, but its toxicity prevents its clinical use (12). Alkyl diguanidines (e.g., Synthalin A) are guanidine derivatives in which the two guanidine molecules are separated by a long methylene chain. These drugs were used briefly in the 1920s, but their alleged toxicity and the advent of insulin therapy resulted in their discontinuation (12). In the 1950s, three major biguanides became available for clinical use, phenformin, metformin, and buformin. Phenformin was used successfully in the United States but was withdrawn because of associated cases of lactic acidosis (13). In contrast, metformin, which rarely causes lactic acidosis, is widely used in Europe and Canada but has not been available in the United States.

Biguanides are almost completely absorbed from the gut and bind to intestinal cells (14–16). Metformin is not metabolized in the liver, is not bound to serum proteins, and has a mean plasma half-life in humans of 1.5–2.8 h (16). Phenformin, in contrast, is metabolized by the liver and binds...
The biguanides are not truly hypoglycemic agents. They lower the elevated blood glucose levels in patients with NIDDM but do not lower the blood glucose values in non-diabetics unless there has been prolonged fasting (14,15,17). Biguanides, unlike the sulfonylureas, do not stimulate the release of insulin from the β-cells; in fact, biguanide treatment may result in lowered insulin levels (17). The major effects of biguanides are to either potentiate or mimic the actions of insulin (14,17–20).

The mechanism of action of metformin and other biguanides is not completely understood. The effects of biguanides are probably multifactorial. The following mechanisms have been suggested to be responsible for their effect of lowering elevated blood glucose concentrations: 1) increased glucose uptake into muscle (14,17–20), 2) decreased hepatic gluconeogenesis (14,17–21), and 3) decreased intestinal glucose absorption (14,17,22). In accordance with the last observations, phenformin has been reported to be more effective in normalizing abnormal oral glucose tolerance than intravenous glucose tolerance (22). Metformin, in contrast, has been reported to have little effect on glucose absorption in humans but can influence intravenous glucose tolerance (15).

Note that studies of the mechanism of action of one specific biguanide may not necessarily be applicable to all biguanides.

Studies at the cellular level indicate that metformin potentiates insulin action. The recent finding that the biguanides increase the binding of insulin to its receptor is interesting. Binding of insulin to a glycoprotein receptor on the surface of target cells is the initial step in the actions of the hormone (23–25). Subsequently, one or more intracellular effector systems (postreceptor events) are then activated to carry out the intracellular effects of insulin (23–25). Patients with NIDDM have defects in both insulin receptors and in insulin-mediated postreceptor events (7,25). In these patients, a significant decrease in the number of insulin receptors is usually detected (7,24,25). Furthermore, a decrease in the action of insulin is also detected that is generally greater than would be expected from the insulin-receptor defect alone (7,24).

In vitro studies with various cells indicate that the biguanides, at concentrations that are effective in vivo, increase insulin binding to its receptors in vitro (26–30). Studies of the effect of metformin on insulin receptors have been performed in humans. Trischitta et al. (31) reported that a 96-h treatment of six diabetic subjects completely normalized the decreased binding of insulin in circulating monocytes. No effect was seen in non-diabetic subjects (31). Lord et al. (32), in a study of eight obese diabetic patients, found that 4 wk of metformin therapy increased insulin binding by 84% in circulating erythrocytes. In four healthy volunteers, Holle et al. (27) reported that 48 h of metformin treatment increased insulin binding to circulating erythrocytes by 35%. These in vitro and in vivo studies suggest, therefore, that one action of metformin is to increase the binding of insulin to its receptor.

However, in 10 obese diabetics treated for 4 wk with metformin, glucose levels fell without a change in insulin binding to monocytes (33). In addition, other researchers have reported that metformin potentiates insulin action in vivo without changing the binding of insulin to its receptor (34). These in vivo studies suggest there may also be a postreceptor action of metformin.

Studies in vitro support this second mechanism of action. Rat adipocytes cultured 20 h in the presence of metformin (10–4 M) showed no increase in insulin binding, but metformin potentiated the actions of insulin on several cellular functions including glucose uptake, glucose oxidation, and glucose incorporation into lipids (35). Furthermore, we have found in preliminary studies with cultured hepatoma cells that metformin potentiates insulin stimulation of tyrosine aminotransferase activity at concentrations at which it does not alter insulin binding to receptors (36).

INDICATIONS FOR USE OF METFORMIN

Metformin is indicated for the treatment of NIDDM patients in whom satisfactory control of blood glucose cannot be obtained by diet alone and who have no specific contraindication to the use of biguanides (vide infra). There are three conditions for the use of biguanides as glucose-lowering agents in patients with NIDDM: as a primary drug, in combination with sulfonylureas, and after sulfonylurea failure.

Metformin has been used as the primary agent for treatment of both nonobese and obese diabetics. In a study of 216 nonobese NIDDM patients whose diet-only treatment failed, metformin was found to be equally as effective as chlorpropamide (37), a widely used sulfonylurea (9,10). In both groups, blood glucose levels fell from 17–18 mM to 8–9 mM. Metformin-treated patients lost 1.5 ± 3.8 kg, whereas chlorpropamide-treated patients gained 4.6 ± 3.9 kg. Very similar results have been reported in obese NIDDM patients (38). Lim and Khoo (39) reported that metformin was as effective as tolbutamide in treating 30 newly discovered cases of NIDDM. In his surveys of metformin, Hermann (14,40) has reported that 80% of metformin-treated patients had either good or very good responses to this drug. Blood glucose fell by 25–30% from pretreatment values.

Biguanides can also be combined with the sulfonylureas because the two agents have different modes of antidiabetic action. In a study of 228 patients, Kral and Balodimos (41) concluded that combined sulfonylurea and biguanide therapy significantly increased the number of patients who had successful oral antidiabetic therapy. One group, however, did not find that the combination therapy of metformin and sulfonylurea was beneficial (42).

When obese patients whose treatment with sulfonylureas failed were placed on a combination regimen with metformin,
>50% responded in a satisfactory manner (43). In a double-blind crossover study, Higginbotham and Martin (44) concluded that metformin significantly improved diabetic control in patients whose sulfonylurea-only treatment failed. In contrast to those treated with sulfonylureas, secondary failures are relatively rare with metformin (15,18,20). Sterne and Junien (15) found that the continued success of metformin ranged from 75 to 84% of cases.

OTHER BENEFITS OF METFORMIN THERAPY

In patients with NIDDM, metformin has beneficial weight-reducing and lipid-lowering effects. Patients often lose weight during biguanide treatment, whereas they usually gain weight during sulfonylurea treatment (15,37). Because patients with NIDDM are often obese, and obesity is a major cause of insulin resistance, this weight loss is beneficial. Usually there is an initial period of weight loss after metformin administration followed by a stable period (15). The mechanism of weight loss is unknown. Anorexia may be involved, and a direct effect on the satiety center has been proposed (15,40). Weight reduction is not related to changes in blood glucose levels but may be related in part to the reduction of hyperinsulinemia seen with metformin (15,40).

Diabetic patients often have lipid metabolism disturbances that may be favorably influenced by metformin. Metformin may directly affect very-low-density lipoprotein metabolism and may decrease hepatic triglyceride synthesis (15,18,40,45). In clinical situations, reduction of triglycerides has been observed (15,18,40,45). In rabbits, metformin inhibits the uptake of cholesterol into rabbit aorta; sulfonylureas and insulin have opposite effects (15,18,40). Metformin, therefore, may be very beneficial in NIDDM patients with associated hypertriglyceridemia and atherosclerosis.

METFORMIN AND IDDM

In addition to having beneficial effects in NIDDM, metformin may also be of benefit in IDDM. In a study with normal and obese mice, metformin increased the number of insulin receptors on hepatocytes (46). In streptozocin-treated insulinopenic mice, insulin receptors were elevated, and these receptors were not further elevated by metformin. However, metformin potentiated the action of exogenous insulin (46). Interestingly, in 14 patients with IDDM, Pagano et al. (47) reported that metformin therapy for 4–6 wk reduced insulin requirements by 25% and concomitantly increased insulin binding to circulating monocytes. In 15 patients, metformin and insulin therapy lowered glucose levels to a greater extent than did insulin alone (48). These studies suggest, therefore, that metformin can also influence insulin action at the receptor and postreceptor level in IDDM patients.

LACTIC ACIDOSIS AND OTHER SIDE EFFECTS OF METFORMIN

Lactic acidosis, a potentially lethal condition, has been reported in patients taking biguanides (13,49–51). Biguanides influence lactate metabolism, increasing both production and oxidation of lactate (13,49–51). Biguanides can raise blood lactate levels because the increase in lactate production may not be compensated by the increase in lactate oxidation (52). Patients taking biguanides have either normal or slightly elevated lactate levels (13,49–51). In most instances, patients with biguanide-associated lactic acidosis have had another disease, e.g., uremia, liver disease, alcoholism, or cardiorespiratory insufficiency (13,49–51). All of these problems are a contraindication to the administration of biguanides. Phenformin is associated with far more cases of lactic acidosis than metformin (14,45,50,51). Metformin, although as effective as phenformin in treating patients with NIDDM, has lesser effects on lactate metabolism (42,53,54).

Lactic acidosis, therefore, is not a major clinical problem with metformin (14,15,18,40,45,49–51,55). In 1977, Luft et al. (51) found that there were 330 published cases of lactic acidosis due to biguanides: 285 were associated with phenformin, 12 with metformin, and 33 with other biguanides. Bergman (56) reported that in 1975–77 in Sweden the number of prescriptions for phenformin and metformin were similar (20,192 vs. 20,548 patient-yr, respectively). However, 13 cases of lactic acidosis were seen with patients on phenformin, whereas only 1 case was seen with a patient on metformin. The relative risk of lactic acidosis was calculated to be 0.64 cases/1000 patient-yr for phenformin and only 0.05 cases for metformin (56). In France, between 1968 and 1977, there were 78 case reports of lactic acidosis in patients treated with phenformin and 17 cases in patients treated with metformin. The relative risk of lactic acidosis, calculated on the basis of the known biguanide use in France, was 0.23 (per 1000 treatment-yr) for phenformin and 0.016 for metformin (57). In Switzerland, a retrospective survey performed between 1972 and 1977 showed a relative risk of lactic acidosis of 0.40 for phenformin and 0.07 for metformin (57). All these studies clearly indicate that the risk of lactic acidosis is much lower with metformin use than with phenformin use. In addition, a better prognosis has been reported for lactic acidosis associated with metformin. Among the cases reported in France (1968–77), lactic acidosis was lethal in 30% of metformin-treated patients but in 70% of phenformin-treated patients (57). In 1979, Hermann (14) reviewed all 23 cases of metformin-associated lactic acidosis; in every case there was either a renal, liver, or cardiorespiratory contraindication to the drug. In a recent survey by Campbell (55), all 44 reported cases of lactic acidosis occurring in metformin-treated patients had strong contraindications to the use of this drug or had an overdose. In Canada, where metformin has been used for 20 yr, no case of lactic acidosis has been reported (45), which suggests that there is a low incidence of lactic acidosis associated with metformin use. In a comparison of the risk of lactic acidosis caused by metformin with the risk of severe hypoglycemia caused by chlorpropamide and other sulfonylurea agents, metformin was calculated to be safer than the sulfonylureas (55,57).

In conclusion, lactic acidosis is a very infrequent complication of metformin when administered properly. The difference in structure between phenformin and metformin may
explain the difference in toxicity (14,18,45,50,51). Because phenformin has a large phenylethyl side chain, it binds to liver and plasma proteins, and is rapidly excreted. Metformin has been reported to have other adverse effects. Gastrointestinal symptoms including nausea, discomfort, and diarrhea may occur during the initial stage of therapy (15,18,40,58). These effects are present in 5–20% of patients and are transient. With long-term therapy, vitamin B₁₂ and folic acid absorption are decreased, but macrocytic anemia has not been reported (15,40). Cutaneous allergic reactions are few (14,56).

CONCLUSION

Metformin appears to have a role in the treatment of NIDDM both as a primary and a secondary antidiabetic agent. When properly administered, metformin is a much safer drug than phenformin. Metformin is effective in both lean and obese NIDDM patients, and in particular, its use is associated with improved carbohydrate tolerance, reduced hyperinsulinemia, and weight loss. The drug does not have a high incidence of secondary failures, and it can be used in combination with sulfonylureas because both agents appear to have different mechanisms of action. Metformin does not cause hypoglycemia; rather, it lowers the elevated glucose levels seen in patients with NIDDM.

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