Metformin

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Why all the commotion about metformin, a drug that has been in use in most industrialized countries around the world since 1957? A conference in March sponsored by Bristol-Meyers Squibb addressed a number of issues surrounding the use of metformin, which has just been made available in the U.S.

Metformin appears to be serendipitously entering the U.S. market at a time when we are concentrating more on the adverse consequences of NIDDM. As reviewed by James Gavin of Chevy Chase, MD, the direct cost of diabetes is 5.8% of total personal health care expenditures in U.S., even though diabetes is diagnosed in only 2.8% of the population. By other calculations, one-seventh of U.S. health care dollars are spent on people with diabetes. Part of the challenge discussed at the conference is the need not only to control blood glucose, but also to reduce and control other cardiovascular risk factors, for which metformin may have specific advantages.

Donald Simonson of Boston reviewed a number of aspects of the pharmacology and use of the drug, which enhances the rate of glucose uptake and utilization in insulin-sensitive tissues such as muscle. In vitro studies suggest that metformin acts at the level of insulin receptor binding, glucose transport, and nonoxidative glucose metabolism (glycogen formation). It may reduce intestinal glucose absorption and/or decrease food intake, and insulin secretion is not stimulated. Enhancement of insulin sensitivity is seen more consistently in obese than in lean individuals with NIDDM, perhaps because of the loss of appetite and weight loss that accompanies treatment. This theme of an additional potential benefit of metformin in obesity was brought up by a number of the speakers in the conference. Other benefits include improvement in dyslipidemia, with an increase in HDL cholesterol, a fall in triglyceride, and, often, a fall in LDL cholesterol levels. There may be partial reversal of the hypercoagulant states associated with NIDDM and perhaps a decrease in blood pressure levels.

Side effects are primarily of gastrointestinal discomfort, with nausea, loss of appetite, and a metallic taste being common. Many patients experience diarrhea, particularly upon initiation of treatment, so that starting with low dosages is prudent. Vitamin B_{12} levels are reduced, although this is rarely associated with evidence of deficiency states. Cimetidine and, perhaps, other H2 antagonists increase metformin levels by competing for renal tubular excretion, and the drug should be used with caution when administered with other agents eliminated by the kidneys, particularly intravenous X-ray contrast media. IDDM, pregnancy, alcohol abuse, B_{12} or folate deficiency, and any severe medical illnesses are other contraindications, and the drug should probably be temporarily discontinued in the setting of an acute hospitalization or major surgical procedure. Metformin inhibits basal hepatic glucose production, primarily affecting gluconeogenesis rather than glycogenolysis. This may be related to the alteration in lactate metabolism which leads, albeit highly infrequently, to lactic acidosis. Lactic acidosis is one-tenth as likely as with the related biguanide, phenformin, which was withdrawn from the U.S. more than two decades ago. It is noteworthy that a population study of the Swedish experience from 1972 to 1981 showed that glyburide caused 0.19 cases of hypoglycemic coma per 1,000 patient-years, with a mortality of 0.032 per 1,000 patient-years, considerably greater than seen with metformin.

Peter Stacpoole of Gainesville, FL, discussed lactic acidosis in more detail. Whether or not associated with tissue hypoxia, this is a grave illness. Mortality was seen in 60–65% of a multicenter study population with lactate levels of 5–13.4 mmol/l, and in >90% of those with lactate >13.4 mmol/l. Simonson cautioned that the drug should not be used with renal insufficiency, hepatic disease, or hypoxia, including that seen in advanced congestive heart failure. The metformin package insert states, "Hypoxic states: with cardiovascular collapse from whatever cause. . . in patients on Glucophage therapy, it should be discontinued."

Ralph DeFronzo of San Antonio, TX, reviewed two important recently concluded multicenter trials of metformin. The first compared placebo with metformin in patients presenting with NIDDM: 146 individuals were treated with diet plus placebo, and 143 with diet plus metformin, at a maximum dose of 2.55 g/day. The blood glucose was about 250 mg/dl at baseline, with body weight about 150% of ideal levels. The fasting blood glucose increased by about 10 mg/dl with placebo but decreased by about 60 mg/dl with metformin by week 5, staying at this level through week 29. HbA_{1c} decreased 1.5% with metformin and increased 0.5% with placebo. The decline in the fasting blood glucose was greater at higher baseline fasting blood glucose levels, unlike the situation with sulfonylureas, which DeFronzo interpreted to mean that while the sulfonylurea response is insulin mediated, metformin may act by another means,

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perhaps by directly decreasing hepatic glucose production. With fasting blood glucose levels over 300 mg/dl, treatment decreased the blood glucose by about 100 mg/dl, while with fasting blood glucose levels of 180–220 mg/dl, metformin decreased these levels by about 40 mg/dl. DeFronzo reported that LDL cholesterol levels decreased by 15 mg/dl and that triglyceride levels decreased by 30 mg/dl. Lactate levels were slightly elevated at baseline and did not change during either placebo or metformin treatment.

The second study involved patients who failed to maintain glycemic control after a period of response to sulfonylurea treatment. There were three treatment arms, using glyburide alone (n = 209), metformin alone (n = 210), or both therapies (n = 213). The fasting blood glucose initially increased by about 30 mg/dl with metformin alone, which DeFronzo ascribed to "the sulfonylurea doing something [even with ostensible sulfonylurea failure]," but then returned to baseline as metformin dosages were increased. With glyburide alone, fasting blood glucose levels gradually increased by about 10 mg/dl over 29 weeks. When metformin was given in combination with glyburide, however, the fasting blood glucose level decreased by 75 mg/dl at 9 weeks, and remained about 70 mg/dl below baseline at 29 weeks. Glycohemoglobin levels decreased almost 2% with combination treatment, showed little change with metformin alone, and increased by 0.5% with glyburide alone. LDL cholesterol levels increased 4 mg/dl with glyburide and decreased 7–10 mg/dl with either metformin alone or the combination. Triglyceride levels decreased by about 20 mg/dl at week 29 with metformin alone, despite the lack of improvement in glycemic control, as well as with the combination of metformin and glyburide. Side effects of note were the much greater incidences of nausea (about 5% vs. 15%) and diarrhea (5% vs. 25%). DeFronzo summarized the benefits of metformin: it has relatively few side effects, lowers lipid, causes no weight gain or hyperinsulinemia, and works effectively in combination with sulfonylureas. When asked about combination treatment of insulin with metformin in NIDDM, he replied, "I think it needs to be looked at."

In the context of this increasing interest in metformin in the U.S., it is interesting to examine the experience of a large U.K. study assessing the effect of this drug in NIDDM, the U.K. Prospective Diabetes Study (UKPDS). David Matthews described this multicenter study, which was designed to address the question: is treatment with sulfonylurea, metformin, or insulin advantageous or disadvantageous? The study involved 3,942 newly diagnosed patients with type II diabetes who had fasting blood glucose >6.0 mmol/l on two occasions and who failed to respond to treatment with diet for 3 months. Subjects were randomized to glyburide, chlorpropamide, insulin, and a diet-only control. Metformin was administered only to a subset of 377 obese individuals, who were compared with equal numbers of obese patients randomized to the other therapies.

With metformin, fasting blood glucose and HbA_{1c} levels fell in a fashion similar to that seen with sulfonylureas and with insulin. However, Matthews commented, "You get the glycemic benefit without the downside of increased weight." Fasting insulin levels were actually lower than those seen in the diet-only group. Of concern, there was a gradual increase in fasting blood glucose and HbA_{1c} levels over time in all of the intervention groups, suggesting that "however intensively you try to treat NIDDM, it escapes control with time."

Henry Ginsberg, New York, NY, recalled Joslin's dictum, "With an excess of fat diabetes begins and from an excess of fat diabetics die," in discussing the mechanisms and consequences of atherogenesis in diabetes. An interesting round table discussion addressed the question, raised by John D. Bagade of Chicago, of whether VLDL triglyceride is atherogenic. He noted that the American Diabetes Association consensus panel recommended treatment at triglyceride levels of 150–200 mg/dl, and that he would recommend treatment at a level of about 200. Ginsberg replied that LDL is the only lipoprotein "for which we have intervention data." Similarly, Scott Grundy, Dallas, TX, reaffirmed his belief that LDL is of primary concern. Thus, at triglyceride levels <500 mg/dl, he would recommend statins, and only above this did he say he would use fibrates for initial lipid treatment. In contrast, Charles Glueck, Cincinnati, OH, recommended triglyceride treatment at a level of 200–250 mg/dl for patients with combined hypertriglyceridemia and hypercholesterolemia. Harold Lebovitz, Brooklyn, NY, recommended treatment with triglyceride levels of 150 mg/dl or at most at 200, citing epidemiological data from the Paris Prospective study analysis of individuals with diabetes, which supports this recommendation that relatively low levels of hypertriglyceridemia are atherogenic in NIDDM.

John A. Colwell, Charleston, SC, discussed the potential of metformin for benefiting individuals with NIDDM in terms of the increased risk they face for coronary heart disease (CHD). He noted that, based on the Multiple Risk Factor Intervention Trial (MRFIT) data, diabetes increases the risk of cardiovascular disease death, with zero, one, two, and three risk factors, approximately threefold. Further, he stated, there is now data suggesting that HbA_{1c} levels predict both total CHD and CHD mortality rates. These event rates are very high, increasing from 1–3%/year among newly diagnosed patients, to 5–8%/year with duration of diabetes 5–20 years, to 8–10% per year with a prior myocardial infarction, and to 10–12% per year among those who have required a lower extremity amputation. Colwell commented that the UKPDS may not be able to address the question of whether improved glycemic control decreases cardiovascular disease, as its primary endpoint was actually glycemic regulation. Furthermore, the loss of separation between the control and intervention groups suggests a further difficulty that may lead to the trial not being able to show a difference between treatment and nontreatment.

There is a great deal of information suggesting that abnormalities other than those in blood glucose are related to the increase in cardiovascular disease in NIDDM. Colwell reviewed data suggesting that NIDDM is associated with a "procoagulant state," and stated his belief that "all people with type II diabetes should be on enteric coated aspirin." He recommends this for individuals with type I diabetes with nephropathy as well. Colwell also drew attention to the VA feasibility trial, which achieved a 2% HbA_{1c} separation by using intensive insulin treatment. Major cardiovascular events were suffered by 11.5% of the standard treatment group but 21.3% of the intensive treatment group. Although this failed to be statistically significant because of the relatively small numbers of patients (about 70 in each group), it is reminiscent of the early increase in retinopathy levels seen during the first year of intensive insulin treatment and suggests a further need for caution. Thus, a form of treatment that does not increase insulin levels appears extremely attractive. Metformin, which lowers blood glucose by 20–25%, triglycerides by 20–30%, insulin by 5–10%, and plasminogen activator inhibitor (PAI-1) by 20–25%, appears to be such a potential therapy.

In further support of this idea (of metformin being of benefit for a number of abnormalities in NIDDM), Gerald M. Reaven, Stanford, CA, discussed the clinical utility of metformin in treating dyslipidemia, which he described as being "almost as common as hyperglycemia" in NIDDM. The prevalence of low HDL and high triglyceride levels was doubled in individuals with NIDDM in the Framingham study, as one of many examples. Both with sulfonylurea treatment and with metformin, these lipid abnormalities improve. Increased postprandial lipemia is, however, another lipid abnormality seen in NIDDM, for which metformin showed particular benefit in Reaven's studies. It is not yet clear whether the improvement in these associated abnormalities occurs independently of improvements in glycemia.

Simonson discussed the "BIGPRO" study, in which metformin was administered to nondiabetic subjects with central obesity. Of 324 subjects followed for 12 months, there was greater weight loss and a greater decrease in fasting insulin corrected for the weight loss, with greater decreases in t-PA antigen levels, but although triglyceride, HDL cholesterol, and blood pressure levels showed favorable trends these were not statistically significant.

Thus, a number of issues were raised of relevance to the potential benefit of metformin in decreasing complications of diabetes. In this context, it is important to consider whether there is good evidence that glycemic control is as important in NIDDM as the DCCT showed it to be in IDDM.

Ronald Klein, Madison, WI, discussed the epidemiology of diabetic retinopathy and its relation to glycemic control. In the Wisconsin Epidemiologic Study, 2,990 individuals with diabetes were examined, 1,210 whose onset was <30 years of age (Younger Onset [YO]) and 1,780 who were ≥30 years of age at diagnosis (Older Onset [OO]). At the baseline examination, background and proliferative retinopathy were found in 48 and 23% of the YO and 57 and 14% of the OO group. These data are similar to the prevalence of proliferative retinopathy among individuals with diabetes in NHANES III, 10–20% among whites and 30–40% among blacks and Hispanics. This would lead one to predict that, among the 5.8 million known individuals with diabetes in the U.S., >700,000 have proliferative retinopathy. The risk factors for retinopathy from the study were the duration of diabetes, use of insulin, presence of proteinuria, and level of glycosylated hemoglobin. There was no association with cigarette, aspirin, or diuretic use. Thus, at 15 years, approximately 90% of YO, 80% of OO taking insulin, and 60% of OO not taking insulin had retinopathy. Glycohemoglobin levels were <2 SD above the nondiabetic mean in only 7% of YO and 30% of OO. As the quartile of glycohemoglobin increased, the incidence of retinopathy increased from 82 to 95% among YO and from 55 to 95% among OO. Klein estimated the effect of a 2% decrease in glycohemoglobin in the three groups. The odds ratio decreased to about 0.6 in the YO and OO groups, with the data showing no evidence of a "point of no return." Regardless of the level of retinopathy at baseline, the rate of progression increased at higher glycohemoglobin levels. This suggests that the DCCT data can be extrapolated to NIDDM for microvascular disease, although there is as yet no clinical trial data confirming this.

Jay S. Skyler, Miami, FL, gave further information pertaining to the prevention of microvascular complications of diabetes. Recognizing that the question of whether the DCCT results apply to type II diabetes has not been answered, he reviewed a number of non-glycemia-related therapies that may reduce microvascular complications. Both in early and in late nephropathy, angiotensin-converting enzyme inhibitors have been shown to decrease microalbuminuria and to decrease the rate of deterioration of renal function. Protein-restricted diets have been shown in some studies of patients with established renal disease to help prevent deterioration in GFR. Aldose reductase inhibitors have been shown to increase nerve conduction velocity, and, in one report, to decrease microalbuminuria. Other studies have shown potential benefits of evening primrose oil, a source of γ-linoleic acid, in slowing deterioration in nerve conduction velocity, and of pentoxyphiline in preventing albuminuria. Aminoguanidine, an inhibitor of advanced glycation end product formation, is being studied in both early and late nephropathy as a potential therapeutic approach.

Part of the excitement surrounding the approval of metformin, then, is that beyond control of glycemia, it shows promise for controlling a number of complications of NIDDM. The coming use of this agent will allow us to learn whether this promise can be translated into reality.