Is It Time To Introduce Metformin in the U.S.?

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A study by Nagi and Yudkin in this issue (p. 621-29) reports on the effects of metformin on insulin resistance and risk factors for cardiovascular disease in a group of NIDDM subjects. In a double-blind, placebo-controlled, crossover study of 27 NIDDM subjects, metformin therapy was associated with a 26% fall in plasma glucose; a 10% fall in plasma cholesterol, LDL cholesterol, triglycerides, and GHb; and no change in HDL cholesterol. Platelet aggregation and fibrinogen levels did not change, but PAI-1 activity did fall. The changes in glucose may have been related to an increase in the metabolic clearance of glucose, associated with improved β-cell function. Thus, it appears that metformin may have beneficial effects on glycemic regulation and on certain putative or accepted cardiovascular risk factors in NIDDM. These data generally confirm other studies and are of interest.

Is metformin an oral antidiabetic agent that should be available for general use in the U.S.? If so, what is the status of such action? If not, why not? To gain perspective on these and other issues regarding metformin, a brief historical look is in order (1).

In medieval times, it was reported that *Galega officinalis* (goat's rue or French lilac) was used as a traditional treatment for diabetes in Europe (3). The plant was found to be rich in guanidine, which was shown (by 1918) to have hypoglycemic activity (1). Guanidine, however, was too toxic for clinical use, and various derivatives (galegine, synthalin) also were found to be hepatotoxic in clinical trials. With the introduction of the sulfonylureas in the 1950s, an interest in oral agent therapy for NIDDM was rekindled, and by 1958, the biguanides metformin, phenformin, and buformin had been introduced (1). Phenformin was studied in the University Group Diabetes Program study and was associated with an increased risk for cardiovascular death (4). Reports of an increased incidence of lactic acidosis among NIDDM subjects treated with phenformin resulted in its withdrawal from the U.S. market in 1975 (5). Although metformin has been used regularly in Europe, Canada, and other countries, it has not been cleared by the FDA for clinical use in the U.S. Presumably, concerns about the checkered history of other biguanides in NIDDM treatment has led to some reticence toward tackling the issue in this country.

Metformin has been studied extensively (1,6). Interestingly, it has no blood sugar lowering effect in nondiabetic subjects, but generally is associated with a fall in fasting glucose levels of 20–30% in NIDDM individuals. In addition, postprandial glucose excursions are decreased. In combination with sulfonylureas, metformin may have an additional blood glucose lowering effect of ~20%. The main mechanism to achieve decreased glycemia in NIDDM subjects is an increase in glucose utilization. This appears to be attributable primarily to an enhancement of insulin-mediated glucose disposal (1), possibly related to an action on glucose transporters (7). Thus, the drug may decrease insulin resistance—a welcome effect for patients with NIDDM. Also interesing is that weight gain does not occur in NIDDM patients (using the drug), and, in fact, weight loss may be seen. The modest effects on plasma lipids and lipoproteins seen in this study are similar to those reported previously (1,6).

Finally, some reports suggest other effects of metformin on vascular biology in NIDDM subjects and animal models (1). Of relevance to this study are reports suggesting that metformin is associated with increased fibrinolytic activity, perhaps caused by a fall in PAI-1 activity in nondiabetic obese subjects (8). Note, however, that fibrinolytic activity was not reported in the study by Nagi et al. (this issue), and the postmetformin levels of PAI-1 were still markedly elevated. Further, platelet activation was present in this study, as indicated by high plasma levels of the platelet-specific proteins, βTBG and PF4. These elevated levels were not affected by metformin therapy. Conceivably, in vitro release of βTBG, PF4, and even PAI-1 may have occurred during blood processing. Thus, the transfer of these modest effects on putative vascular risk factors to an endorsement that this agent may affect the natural course of vascular disease in diabetes is speculative, at best. Clearly, it will take long-term prospective clinical trials to sort out these issues.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; LDL, LOW-DENSITY LIPOPROTEIN; HDL, HIGH-DENSITY LIPOPROTEIN; PAI-1, PLASMINOGEN ACTIVATOR INHIBITOR 1; FDA, FOOD AND DRUG ADMINISTRATION; BTBG, B-THROMBOGLOBULIN; PF4, PLATELET FACTOR 4; VA, VETERANS ADMINISTRATION.

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But, do we have adequate information (already) from the results of completed clinical trials with metformin to recommend its use in NIDDM patients? Although U.S. data are limited, substantial experience in other countries indicates that the glycemic benefits of metformin therapy in selected NIDDM patients outweigh the risks. The primary failure rate is ~10%, and secondary failures are ~5–10% per year (1,6). Side effects may occur in something approaching 20% of cases, however, and primarily consist of gastrointestinal upsets. Lactic acidosis may occur, particularly in individuals in hypoxic states, or if renal or hepatic function is impaired. Thus, the agent should not be used in the presence of liver or kidney disease, and must be avoided with cardiac insufficiency, alcohol abuse, pregnancy, and/or hypoxic conditions. Evidence from outside the U.S. suggests that severe complications, such as lactic acidosis, are rare with metformin use if these guidelines are followed. The reported incidence of lactic acidosis during metformin therapy is 0.027–0.084 cases/1000 patient-yr, ~10% of that reported for phenformin (0.64 cases/1000 patient-yr (2). In one Canadian study, no cases of lactic acidosis were reported (9). In one open-label study, a combined therapy of metformin with sulfonylureas appeared to be clinically effective in ~50% of patients (10). Another recent study has indicated that metformin in addition to sulfonylurea therapy in NIDDM subjects with poor glycemic control may increase insulin-stimulated glucose uptake and decrease hepatic glucose production (11).

Where do we go from here? Certainly it is a major issue in the U.S. to find a treatment for NIDDM patients who have not responded with good glycemic regulation to diet, sulfonylureas, and/or standard insulin therapy. Indeed, surveys of known NIDDM subjects under standard management often indicate fasting plasma glucose levels of ≥11 mM and HbA_{1c} levels of ≥10% (12,13). These levels are consistent with poor glycemic regulation, according to the Clinical Educational Program of the American Diabetes Association (14). But should the physician aggressively raise insulin doses in an attempt to produce normoglycemia? Will the benefits of this approach outweigh the perceived risks of hyperinsulinemia as a vascular risk factor (15), or of hypoglycemia, and/or weight gain?

We do not have answers to these questions as yet; however, two large-scale clinical trials, the U.K. study (12) and a new VA Cooperative Study (16), are attempting to answer this critical question. The VA study directly addresses the issue of the effects of intensive glycemic control with insulin on major cardiovascular events in NIDDM patients. The U.K. study—because it includes one obese NIDDM group randomized into management with metformin—may soon provide results of a multicenter study that has directly addressed the issue of the risks and benefits of metformin therapy in NIDDM subjects.

Finally, phase III clinical trials with metformin are now underway in the U.S. and are under review by the FDA. If all goes well, the manufacturers plan to submit a new drug application by early 1993. This could lead to the introduction of metformin into the U.S. market by mid-1994. Note that this timing probably will coincide with reports from the U.K. trial on the safety and efficacy of metformin therapy in NIDDM patients (12) and with the results from the Diabetes Control and Complications Trial on the effects of intensive insulin therapy on diabetic retinopathy in IDDM subjects (17).

Metformin appears to be a useful additional agent for selected NIDDM patients. It appears likely that eventually it will be available for use by U.S. physicians.

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