Learning to Use Troglitazone

The rate of change in treating type 2 diabetes is dizzying. In the last 4 years, representatives of four new classes of oral antihyperglycemic agents have been released in the U.S., and the place of each in clinical practice is being debated. Repaglinide is just entering use but is known to resemble sulfonylureas in its actions. Two other agents came with a track record. Metformin, a biguanide, had been used worldwide for years, and acarbose, an α-glucosidase inhibitor, had been studied and used in Europe before being introduced here. The fourth, troglitazone, came into use accompanied by high expectations but less information on its effectiveness and potential for adverse effects. A year after its release, we are still in the process of discovering its best clinical uses. It is time for an interim evaluation. This issue of *Diabetes Care* contains two important articles that help with such an assessment (1,2).

Troglitazone belongs to the thiazolidinedione class of drugs, which were first studied in Japan (3) and found to reduce resistance to insulin in rodents and people with type 2 diabetes. They bind to an intracellular receptor (peroxisome proliferator-activator receptor-γ [PPAR-γ]), and the resulting complex binds to nuclear sites regulating expression of various genes in muscle and adipose tissue (4). Thiazolidinediones improve the action of insulin at these tissues, presumably by this mechanism, and thus treat one of the defects underlying type 2 diabetes. In obese, insulin-resistant people without diabetes, troglitazone improves insulin-mediated glucose uptake by up to 50% (5). In people with type 2 diabetes, its effects on insulin resistance lead to better control of glucose, but early studies done in Japan (6) and Europe (7) showed less reduction of HbA_{1c} (0.5–1%) than is usually seen with sulfonylureas or metformin (1.5–2%). The modest size of this effect has been attributed to the modest obesity of patients in these studies. The average BMI was 24 in the Japanese study, not obese by U.S. standards, and 28 in the European one, reflecting ~25% excess weight. The average BMI of people with type 2 diabetes in the U.S. is 29. Because insulin resistance is strongly related to obesity, people more obese than this should benefit most from troglitazone, but this was not verified in the early studies.

Troglitazone was released in the U.S. in March 1997, at first for use only in combination with insulin and later as monotherapy or in combination with sulfonylureas, for the purpose of improving glycemic control. Since then, it has been used by at least 600,000 people in the U.S. and 200,000 in Japan (8), with clear benefits for many. During this time, several questions have arisen. What is the optimal dose? How does troglitazone's ability to reduce glucose levels in very obese patients compare with the effects of other oral agents? Can it improve medical outcomes by means other than improving glycemic control? How serious are the hepatic effects reflected by elevated liver enzymes in ~2% of individuals in the early safety and efficacy trials?

Recent publications answer some of these questions. These include reports of trials done in the U.S. in people with BMIs averaging 32–35 testing the effects of troglitazone as monotherapy (9), in combination with a sulfonylurea (1) or metformin (10), or in combination with insulin (2,11). Collectively, these studies show a dose-response relationship for improving glycemic control at least up to 600 mg daily. Accordingly, two 300-mg tablets daily is the currently recommended maximal dosage. Moreover, at full dosage in people with this degree of obesity, troglitazone seems equal to sulfonylureas (1) or metformin (10) in its ability to control glucose. This is clearly shown in the article by Horton et al. in this issue (1). Patients previously treated with full-dose glyburide were randomized to continued glyburide, troglitazone alone, or the two agents together for a year. Glyburide and troglitazone 600 mg daily resulted in equivalent glycemic control, while glyburide plus 600 mg troglitazone resulted in an HbA_{1c} that was 2.65% lower than with either alone. Thus, substituting one of these agents for the other is unlikely to improve control, but combining them is very effective and could delay the need for insulin in some cases. Interestingly, a weight gain of 13 lb accompanied the large decline in HbA_{1c}. Reduction of glycosuria certainly contributed to this, but fluid retention and other factors may have too, and the net effect was at least equal to the weight gain likely to occur with starting insulin.

The article by Buse et al. in this issue (2), together with a complementary earlier report (11), demonstrates the therapeutic power of troglitazone in combination with insulin. The study reported earlier was designed to show how much troglitazone can reduce glycemic levels in patients previously treated (ineffectively) with a fixed dose of insulin. The recent report describes reduction of insulin dosage, while glucose remained high. Neither protocol turned out exactly as planned, since reductions of both insulin dosage and HbA_{1c} occurred in each, but the clinical effects were substantial. In the first, 600 mg troglitazone reduced HbA_{1c} by 1.3% below placebo, while insulin dosage declined ~30%. In the second, 400 mg troglitazone reduced insulin dosage by 57% (versus 18% for placebo), while HbA_{1c} declined by 0.3%. These studies confirm powerful additive effects of injected insulin and troglitazone in very obese individuals. They do not, however, address a separate question, whether adding troglitazone to intensified insulin therapy can improve its ability to achieve nearly normal glycemic control.

These studies inform us about dosage and the therapeutic power of troglitazone in properly selected patients. However, other questions remain. Notably, we need more information to weigh the importance of benefits, including those that may derive from mechanisms other than better glycemic control, versus adverse effects. Although insulin resistance is clearly associated with cardiovascular events, the mechanisms underlying this association are poorly understood. Hyperglycemia, hyperinsulinemia, and disturbances of fatty acid and lipoprotein metabolism provoked by insulin resistance are leading candidates, but the relationships between them and their relative importance are unclear. The practical question is this: can reduction of insulin resistance by troglitazone or related agents reduce cardiovascular risk? Despite promising physiologic findings, no clinical study has yet shown a reduction of cardiovascular events. In addition, there are no conclusive data to support another appealing idea, that this form of therapy will slow the decline of β-cell func-

tion that accompanies the development and progression of type 2 diabetes other than by reducing glucose toxicity. We await testing of these hypotheses.

Also, we need more information on safety. As long as benefits other than reducing glucose remain hypothetical, we should hope for minimal risk. In early trials, the main adverse events were variable fluid retention, and reversible elevations of liver enzymes in 1.9% of subjects taking troglitazone compared with 0.6% of those taking placebo (8). Unfortunately, wider use has led to recognition of five cases of severe liver injury resulting in death or liver transplant associated with use of troglitazone (12). Recently, another fatality related to liver disease occurred in a large National Institutes of Health–sponsored clinical trial, prompting withdrawal of troglitazone from the trial. The clinical details of three of these six cases have recently been published (13,14), but it remains uncertain to what degree the liver injury in each case resulted from the drug, as opposed to other factors, and how many as yet unreported cases there may be. In response to these concerns, the Food and Drug Administration now recommends more rigorous testing. Serum alanine aminotransferase (ALT) levels should be measured before treatment, monthly for the next 8 months, every 2 months for the remainder of the 1st year, and periodically thereafter. Patients with ALT >1.5 times the upper limit of normal should not begin troglitazone. If levels 1.5–3 times upper normal develop during treatment, ALT should be tested weekly, and levels >3 times upper normal call for immediate discontinuation of troglitazone.

What can we conclude from this new information? Troglitazone is clearly an excellent treatment that, at least for now, lies under a shadow of concern. We know it improves insulin resistance better than other treatments, except successful weight loss, and in properly selected patients, it reduces glucose as effectively as sulfonylureas or metformin. We hope it has other benefits that remain to be verified. We must worry that the liver toxicity suspected from recent reports is indeed caused by troglitazone, and must inform prospective users of the possible risk and monitor ALT levels as recommended. We urgently need to learn whether people at risk for liver injury can be identified before treatment.

Until more is known about risks and benefits, troglitazone should be used only for patients who seem well suited and for whom alternative treatments have been considered and judged less appropriate. Specifically, monotherapy with troglitazone does not seem justified except in unusual cases. Combination with a sulfonylurea or insulin is seldom appropriate in people who are nonobese or mildly obese, but can be very effective for those who are very obese and resistant to insulin. When troglitazone is combined with insulin, the goal of treatment should be to reduce glucose rather than insulin dosage. When it is prescribed, the patient must be informed of possible risks, and follow-up with ALT should be performed.

Stepping back, we should consider how this recent experience reflects on the process of introducing new drugs to clinical use in general. So many agents are being developed, and they are tested, approved, and marketed so quickly that a mismatch between the public's expectations and the medical community's ability to prescribe skillfully may often occur. Beyond the few large safety and efficacy trials now required by the FDA for approval, we need smaller studies defining an agent's best clinical uses and timely publication of both kinds of data in peer-reviewed publications before market pressures lead to widespread use. When safety concerns arise, analyses should be published as quickly as possible. How else can we make good clinical decisions?

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