Evaluating the Safety of Diabetes Drugs
Perspective of a Food and Drug Administration insider

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Problems had been festering at the Food and Drug Administration (FDA) for years (1,2). In 2004, the abscess finally broke. First came the recognition that widely used antidepressants were associated with suicide in young patients, and then came the withdrawal of Vioxx. Drugs in diabetes and metabolism have not been spared. The obesity drug Meridia and the lipid-lowering agent Crestor are two of the five drugs whose safety was challenged by FDA epidemiologist Dr. David Graham in testimony before a Senate committee (3).

Unique among drug withdrawals is the diabetes drug phenformin, which was declared an imminent hazard by Secretary Califano and was removed from the market in 1977 because of lactic acidosis (4). As was the case with Vioxx, more recent withdrawals of diabetes and metabolism drugs were done by the manufacturers. The obesity drug Redux was removed in 1997 because of heart valvulopathy (5). The diabetes drug Rezulin was removed in 2000 because of liver failure and the lipid-lowering drug Baycol in 2001 because of rhabdomyolysis (6).

But the news for diabetes drugs has not been all bad. The concern about lactic acidosis that accompanied the approval of Glucophage has been found to be greatly exaggerated (7). Despite reports of liver injury that appeared shortly after the approval of Avandia, there is little, if any, evidence that either Avandia or the related drug Actos increase the risk of liver injury over background (8).

One lesson that should be learned from these examples is that it is hazardous to make firm conclusions about the safety of a new drug. The approval of a new drug is based on safety data from a few thousand patients treated under the intense medical supervision of a clinical trial. The very patients who are likely to have side effects are often excluded from these trials. Therefore, no one should be surprised that additional problems may be uncovered when millions of unselected patients are treated under real-world conditions.

The purpose of this article is to describe the process by which FDA evaluates safety data and to provide examples that illustrate how problems have been handled. It is beyond the scope of this report to provide a comprehensive review of safety issues related to all diabetes drugs.

THE ORIGINS OF SAFETY DATA — Diabetes drugs have typically been approved based on trials involving a few thousand patients. Although some important information is derived from short-term (phase 1 and 2) trials, the most important preapproval safety data come from results of phase 3 trials. These trials generally last from 16 to 52 weeks and compare various doses of the test drug to placebo or to another drug that has already been approved. Phase 3 trials are useful for identifying safety issues that are reasonably common but not large enough to detect adverse events that are rare. In many cases, phase 3 trials generate “signals” that need to be evaluated further. The FDA may require that approval of a new drug be contingent on the manufacturer’s commitment to do additional safety studies after approval (phase 4). In some cases, these additional studies follow a design similar to a typical phase 3 trial. However, many phase 4 studies allow for a much larger patient population and often require little, if any, modification to the standard of care that patients would otherwise receive. This approach is illustrated by the COSMIC (Comparative Outcomes Study of Metformin Intervention versus Conventional) study of nearly 10,000 patients with type 2 diabetes, in which metformin was compared with usual therapy (9). This trial is discussed in a later section.

Additional safety data can also come unexpectedly from postmarketing studies designed to investigate a new or expanded indication. That repaglinide appeared to be associated with a small increase in reports of myocardial ischemia in patients taking NPH insulin is an example of such a finding. Although the FDA does not have the regulatory authority to require a change in labeling of marketed drugs, responsible manufacturers recognize the need to inform the public about potential safety issues and are willing to revise product labels to reflect new information (10).

Observational studies provide potentially important safety data. Typically, these studies show that an adverse event was more common with one treatment than with another and that the observed difference could not be explained by known risk factors. These studies lack the rigor of randomized controlled trials; therefore, causality is harder to establish. But observational studies are useful for identifying safety signals that can then be evaluated in randomized clinical trials. For example, a study by Delea et al. (11) using insurance claims found greater reporting of congestive heart failure (CHF) in patients taking thiazolidinediones (TZDs) than in patients taking other antidiabetic agents. This finding is consistent with findings from a randomized controlled trial of pioglitazone versus glyburide and will be discussed later.

Reports of adverse events sent directly to the manufacturer or the FDA are additional sources of information about marketed drugs. These reports are especially important in identifying dangers that are rare and/or unsuspected. The ex-
ample of heart valvulopathy in patients on dextenfluramine illustrates this point (5). However, this source of information about adverse events is of limited value in quantifying a risk that is already believed to exist. Because the system is voluntary, only a small proportion of adverse events are actually reported. On the other hand, publicity about an adverse event related to a new drug may itself lead to greater reporting of that event. Particularly in high-profile cases, family members and even lawyers submit reports in addition to those submitted by health care workers. The quality of information in case reports varies enormously, so that conclusions should not be drawn from simply counting them. Even in well-documented cases, it is rarely possible to establish causality because it is difficult to distinguish the effects of a drug from the effects of the underlying illness or from other injuries that may occur at random.

**EXAMPLES OF SAFETY ISSUES WITH DIABETES AND ENDOCRINE DRUGS**

**Metformin and lactic acidosis**

Although metformin had been used widely in Europe, its approval in the U.S. was undoubtedly delayed by the experience with phenformin (12). At the time of approval, it was estimated that the risk of lactic acidosis with phenformin was about 10-fold greater than that with metformin (13). As a condition of approval, the manufacturer made a “phase 4 commitment” to perform the COSMIC study. Patients were randomized to receive metformin (n = 7,227) or “usual care” (n = 1,505) with other antidiabetic agents. The results of this study have recently been published (9). There were no differences in safety outcomes between the two arms and no cases of lactic acidosis in either group. Even before publication of this trial, Salpeter et al. (14) had reviewed published reports of controlled trials involving metformin and found no cases of lactic acidosis in 36,000 patient-years of exposure. The rate of lactic acidosis in patients with type 2 diabetes appears to be similar regardless of whether they are taking metformin (15). Furthermore, the lack of correlation between lactate levels and metformin levels suggest that metformin may well be an innocent bystander in most reported cases of lactic acidosis (16,17).

In July 2004, I wrote “When metformin is used as labeled, the increased risk of lactic acidosis is either zero or so close to zero that it cannot be factored into ordinary clinical decision making” (7). What about when metformin is not used as labeled?

CHF is listed as a contraindication to the use of metformin because of the finding that patients with CHF constituted 38% of postmarketing reports of lactic acidosis associated with the use of metformin (18). However, it has never been clearly established that metformin contributes to the already increased risk of lactic acidosis in patients with CHF. Two recent studies, with a collective database of 3,000 patients, have found that metformin can be used safely in patients with CHF and may actually decrease all-cause mortality (19,20).

Masoudi et al. (19) conducted a retrospective cohort study of Medicare beneficiaries with diabetes discharged after hospitalization with a principal diagnosis of CHF. The crude 1-year mortality rates among the patients treated with metformin (24.7%) or TZD (30.1%) were significantly less (P < 0.0001) than the mortality rate (36%) among patients who received neither metformin nor a TZD. After adjustments using Cox proportional hazard models, the hazard ratio for death was 0.87 (95% CI 0.78–0.97) for metformin and 0.87 (0.80–0.94) for TZDs. The risk for readmission for recurrence of CHF was decreased by metformin (0.92 [0.92–0.99]) and increased by TZDs (1.06 [1.00–1.09]). Readmission for “metabolic acidosis” was 2.3% for metformin-treated patients, 2.2% for TZD-treated patients, and 2.6% for patients not treated with either drug. Lactic acidosis was not reported.

In this issue of *Diabetes Care*, Eurich et al. (20) evaluate the effects of metformin treatment in patients with CHF using the Saskatchewan Health database. Among patients with new-onset CHF who were started on oral antidiabetic drug(s), 33% of patients on metformin died compared with 52% on sulfonylurea monotherapy and 31% of patients on the combination. The reduction in mortality in patients treated with metformin was statistically significant. The average of age for the patients was 72 years, and there was an average follow-up of 2.5 years. Adjustments for age, chronic disease score, and concomitant medications did not change the finding of lower all-cause mortality among the metformin users. No cases of lactic acidosis were found.

When taken together, these studies provide strong evidence that metformin should no longer be contraindicated in patients with CHF.

**TZDs and liver failure**

Rezulin (troglitazone) was approved in December 1996. In the trials that led to its approval, 48 of 2,510 (1.9%) troglitazone-treated patients and 3 of 475 (0.6%) placebo-treated patients had alanine aminotransferase (ALT) levels >3× the upper limit of normal (ULN). Five troglitazone-treated patients (0.2%) had ALT values >30× ULN, of which two had jaundice (21). However, it was not until spontaneous reports of liver failure began to appear that the significance of this finding was appreciated (22). The development of liver failure and subsequent death of a patient in the National Institutes of Health–sponsored Diabetes Prevention Program provided additional evidence that irreversible liver failure could not always be prevented in patients taking Rezulin (23). Rezulin was withdrawn in March 2000. At least 66 deaths due to liver failure and eight liver transplants were reported among the 2–3 million patients that had been treated with Rezulin (8).

The other TZDs, Avandia (rosiglitazone) and Actos (pioglitazone) were approved in 1999. Although the approval trials showed no evidence of liver failure, lingering concern about the experience with Rezulin led to the recommendation that patients on Avandia and Actos be monitored for liver injury every 2 months. This recommendation was lifted when the results of postapproval trials showed that Avandia and Actos were no more likely to cause ALT elevation than other antidiabetic drugs or placebo (8).

Among patients in the Avandia development program who received rosiglitazone in blinded trials through February 2004, 23 of 7,429 (0.3%) had an ALT >3 × ULN. Among patients in the Avandia trials who did not receive rosiglitazone, 9 of 3,431 (0.3%) had an ALT >3 × ULN. Among patients in the Actos program who received pioglitazone in blinded trials through November 2003, 15 of 5,859 (0.3%) had an ALT >3 × ULN. Among patients in the Actos trials who did not receive pioglitazone, 4 of 1,073 (0.4%) had an ALT >3 × ULN. For comparison, 4 of 921 (0.4%) patients in the initial trials of Glucophage (metformin) also had an ALT >3 × ULN (24). In contrast to the findings with Rezulin,
there were no patients in any of these trials who had ALT values \(>30 \times \text{ULN}\).

Since Avandia and Actos were marketed in 1999 through 2004, >7 million patients have been treated. I believe the cases of liver failure associated with these drugs represent the background of liver failure that occurs in patients with type 2 diabetes, regardless of treatment (8). Indeed, Jick et al. (25) reported two deaths and one transplant among 44,406 patients who received an oral hypoglycemic agent in the U.K., where TZDs were not even used.

**Pioglitazone and CHF**

TZDs cause fluid retention and have been associated with edema in clinical trials. Cardiomegaly results when laboratory animals are treated with TZDs for a long period of time. It is not known whether this cardiomegaly results from chronic fluid overload or if the drug exerts a toxic effect directly on the heart (26).

During phase 3 trials, a larger proportion of patients on pioglitazone reported edema than patients on placebo. As a condition of approval, the manufacturer performed a phase 4 trial to evaluate the effects of pioglitazone on cardiac function in CHF. This study compared pioglitazone with glyburide in patients with New York Heart Association class 2 and 3 heart failure and ejection fraction \(<40\%\). Mean HbA1c was 8.8% at baseline despite treatment with antidiabetic agents. Over the course of the 24-week study, overnight hospitalization for CHF was reported by 9.9% of patients on pioglitazone compared with 4.7% on glyburide, but no difference in cardiovascular mortality was observed. These findings have been added to the label for Actos (27,28).

Although this trial satisfied the manufacturer’s phase 4 commitment, questions remain about the effect of pioglitazone and other TZDs on the heart. Although TZDs may exacerbate CHF in susceptible patients (especially patients taking insulin), no increase in mortality has been observed. If anything, there may be a decrease in mortality (19,29).

As a condition of approval of Rezulin (troglitazone), the manufacturer performed a double-blind placebo-controlled study on the effect of 600 mg troglitazone on the echocardiogram parameters in patients with class 3 and 4 heart failure. The patients had poor glyemic control on pharmacological therapy. Most patients were taking sulfonylureas; about half were taking insulin (29).

The study was terminated in March 2000 when troglitazone was withdrawn from the market. Seventy-seven patients (40 placebo and 37 troglitazone) were randomized, but only 39 patients (20 placebo and 19 troglitazone) completed the 24 weeks.

Mean (±SE) left ventricular ejection fraction at baseline was 40.5 ± 2.5% in placebo patients and 32.4 ± 2.7% in troglitazone-treated patients. The mean change from baseline to last observation was \(-0.9 ± 2.5\%\) for placebo patients and 2.0 ± 1.9% for troglitazone patients. Other echocardiographic parameters also showed little change.

Some patients treated with troglitazone experienced fluid retention, as manifested by worsening of ankle edema, pulmonary rales, and greater need for diuretics. But this was not associated with a greater risk of death. Indeed, there were fewer deaths on troglitazone than on placebo (two versus five), fewer cardiac deaths (one versus three), and fewer withdrawals because of cardiac events in patients who did not die (four versus five).

This leads to the speculation that fluid retention with TZDs may exacerbate CHF in the short term but that amelioration of insulin resistance may confer a long-term benefit.

Given the very small number of patients in the troglitazone study, one cannot draw conclusions from this study alone. But the results are consistent with those of the observational study by Maoudi et al. (19) discussed earlier. In that study, mortality rates were lower in patients treated with a TZD, but the risk for readmission for recurrence of CHF was increased. From these data, it is also reasonable to conclude that fluid retention with TZDs may exacerbate CHF in the short term but that improvement in insulin sensitivity may confer a net benefit.

**CONCLUSIONS**—An overly cautious FDA would deprive patients of important new drugs. The problem we face is how to determine if a new drug is safe based on the data that are submitted in the application. Given the limitations of most preapproval studies, no one should be surprised that additional problems may be uncovered when millions of patients are treated under real-world conditions. The best the FDA can be expected to do is to provide the public with a balanced assessment of risk and benefit and to require drug companies to perform additional safety studies as a condition of approval.

After a drug is approved, the FDA lacks the regulatory authority to require that a drug company change its product label or perform additional studies. Legislation proposed by Senator Charles Grassley may change this. But the fate of this legislation is in doubt (30). In contrast to its willingness to take bold steps in other areas, the nomination of the Acting Commissioner to be permanent Commissioner signals that the Bush administration is satisfied with business as usual at the FDA. But even without additional legislation, the FDA is hardly powerless. A request to improve the safety of a drug would hardly ever be rejected if the FDA was willing to back it up by posting its concern on the FDA website. As the work of New York’s Attorney General Eliot Spitzer has demonstrated, drug companies fear litigation more than anything else. A drug company cannot run the risk of saying “no” to the FDA in public. For better or worse, the threat of product liability litigation provides a counterbalance to the enormous influence of the pharmaceutical industry. Plaintiff’s attorneys have provided the FDA with some of the powers that Congress has withheld.

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