CME CREDIT

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BRIEF QUESTIONS AND ANSWERS ON CURRENT CLINICAL CONTROVERSIES

Q: How should patients taking the discontinued diabetes drug troglitazone be managed?

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A: I WOULD SUBSTITUTE one of the other two available thiazolidenediones—rosiglitazone (Avandia) or pioglitazone (Actos)—with the following recommendations:

- Wait at least 1 week after stopping troglitazone (Rezulin) and then check the alanine aminotransferase (ALT) level before starting one of the new agents.
- Review any potential contraindications to thiazolidenediones such as type 1 diabetes, active liver disease, an ALT level higher than 2.5 times the upper limit of normal, or heart failure.
- For patients who had been taking troglitazone 400 mg daily, substitute rosiglitazone 4 mg daily or pioglitazone 30 mg daily.
- For patients who had been taking troglitazone 600 mg daily, substitute rosiglitazone 4 mg twice daily or pioglitazone 45 mg daily.
- Continue to monitor the ALT level at approximately 3-month intervals and continuing indefinitely until the issue is clarified by the United States Food and Drug Administration (FDA).

THIAZOLIDENEDIONES: INSULIN SENSITIZERS

Troglitazone, approved for use in 1997, was the first of a relatively new class of medications called thiazolidenediones. It was followed by two other agents of the same class, rosiglitazone and pioglitazone, both approved in 1999. The thiazolidenediones appear to increase the action of insulin in skeletal muscle and adipose tissue. For this reason they are known as insulin sensitizers.

These medications are used in combination with other classes of diabetes drugs, including insulin secretagogues, metformin, and the alpha-glucosidase inhibitors.

IS LIVER TOXICITY A CLASS EFFECT?

Approximately 2.2% of patients taking troglitazone had significant liver enzyme elevations (an ALT level > 3 times the upper limit of normal). An estimated 1 in 60,000 persons taking this drug experienced idiosyncratic severe liver toxicity.[1] Approximately 60 patients have either received a liver transplant or died of liver failure attributed to taking troglitazone.

In March 2000, the FDA asked that troglitazone be withdrawn from the market, and the manufacturer complied.

The newer agents appear to be free of this side effect, or at least much safer. In clinical trials, there was no increase in frequency of ALT elevation in the drug-treated groups compared with the placebo groups.[2–4]

It is postulated that troglitazone may have had greater liver toxicity because it used tocopherol (vitamin E) for its delivery or possibly because it interacted with a subset of nuclear receptors slightly different from those for the two newer agents.

There have been two case reports of severe liver toxicity with rosiglitazone[5,6]; however, confounding variables or extenuating circumstances may have played a role.

The FDA recommends that the ALT level be monitored in patients taking the two new drugs, but does not specify at what interval. As noted above, I recommend ALT monitoring every 3 months.

With the newer agents, I recommend monitoring the ALT every 3 months

*Disclosure: The author has indicated that he serves on the speakers' bureaus of the Parke-Davis, SmithKline Beecham, Eli Lilly, Takeda, Bristol-Myers Squibb, Aventis, Pfizer, Novo-Nordisk, and Schering companies, all of which make products for diabetes care.

ARE THERE ANY DIFFERENCES BETWEEN THE TWO NEWER AGENTS?

The two newer agents appear approximately equal in efficacy. In clinical trials, each lowered hemoglobin A1c levels by 1 to 1.5 percentage points and lowered fasting blood sugar levels by 25 to 50 mg/dL.[2,4] Pioglitazone may have the additional benefit of reducing triglycerides and raising HDL cholesterol levels in patients with uncontrolled diabetes and hypertriglyceridemia.

Indications. Both rosiglitazone and pioglitazone are indicated as adjuncts to diet and exercise in patients with type 2 diabetes. Rosiglitazone is approved for use as monotherapy as well as in combination with metformin. Pioglitazone is approved for use as monotherapy as well as in combination with sulfonylureas, insulin, or metformin.

Interactions. Rosiglitazone is thought not to affect the cytochrome P450 enzyme system, whereas pioglitazone may have some effect on this system. One should therefore be cautious with concomitant use of pioglitazone with drugs such as ketoconazole that affect the cytochrome P450 isoform, CYP3A4.

Dosage. The dosage of rosiglitazone is 4 to 8 mg daily, either as a single daily dose or in two divided doses. The dosage of pioglitazone is 15 to 45 mg once daily.

REFERENCES

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