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CME CREDIT HOURS

Troglitazone: a new antihyperglycemic agent

KEY POINTS:

Troglitazone lowers blood glucose levels by improving insulin sensitivity and inhibiting hepatic gluconeogenesis.

This drug is currently indicated in type II diabetes that cannot be controlled by diet, exercise, and insulin.

Concomitant dosages of insulin may need to be reduced, on an individualized basis.

Troglitazone should be taken with food, which increases its absorption.

ABSTRACT: Troglitazone is the first of a new family of antihyperglycemic drugs. We review its use in clinical practice.

Since 1993, when the Diabetes Control and Complications Trial demonstrated that improved glycemic control can delay or prevent microvascular complications, the Food and Drug Administration has approved several new antihyperglycemic drugs: one insulin analogue (insulin lispro) and four oral agents (acarbose, glimepiride, metformin, and troglitazone).

The newest of these oral agents is troglitazone (Rezulin), approved on January 29, 1997. It belongs to a new class of antihyperglycemic agents called thiazolidinediones. These drugs, also known as insulin sensitizers or insulin-action enhancers, decrease blood glucose levels by improving insulin sensitivity in muscle and adipose cells (by approximately 60%) and by directly inhibiting hepatic gluconeogenesis. Unlike the sulfonylureas, they do not stimulate insulin secretion by the pancreas.

WHY TREAT INSULIN RESISTANCE?

In non–insulin-dependent diabetes mellitus (NIDDM or type II diabetes), several abnormalities of insulin action and insulin secretion lead to hyperglycemia:

- Insulin resistance, thought to be the initiating defect.
- Impaired ability of insulin to prevent glycogen breakdown in the liver and to increase the transport of glucose into muscle and fatty tissues.
- Reduced insulin secretion by the pancreas, with resulting inability to control blood glucose.

The rate of glucose absorption via the gastrointestinal tract also plays a role in postprandial glucose regulation.

There is concern that hyperinsulinemia, which is observed in many patients with type II diabetes, may be associated with increased risk of macrovascular disease.

All medications used to treat diabetes work to correct one or more of these pathophysiologic states. Decreasing insulin resistance should lead to lower insulin levels, which may potentially be beneficial.

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PHARMACOKINETICS OF TROGLITAZONE

Troglitazone is rapidly absorbed from the gastrointestinal tract; peak blood levels occur within 2 to 3 hours. It should be taken with meals because food increases its absorption by 30% to 85%. Troglitazone is extensively metabolized in the liver, with approximately 85% of the radiolabeled drug eliminated in the feces and 3% eliminated in the urine. Its elimination half-life ranges from 16 to 34 hours. Steady state levels are attained within 3 to 5 days. Troglitazone is extensively bound to serum albumin (> 99%).

Because troglitazone has a low rate of elimination in the urine, patients with renal dysfunction do not need dose adjustments. Troglitazone should, however, be used cautiously in patients with hepatic disease.

Dose-response studies in 792 patients with type II diabetes found that doses of 200 to 800 mg/day resulted in decreases in fasting glucose levels of 40 to 60 mg/dL. Insulin levels fell by nearly 20% in response to doses of 400, 600, and 800 mg/day.

CLINICAL EFFECTS

In obese patients with type II diabetes, troglitazone reduces fasting and postprandial glucose levels modestly, and reduces insulin levels more markedly. It has been shown to be particularly effective in persons with insulin resistance or impaired glucose tolerance. It also appears to lower triglyceride levels by 20% and raise HDL-cholesterol levels by 10%. There does not appear to be any effect on apolipoprotein-B levels. Blood pressure levels may be slightly lowered.

In studies in patients with type II diabetes mellitus who needed exogenous insulin, those who received troglitazone had lower HbA_{1c} levels and needed significantly lower insulin doses than did patients who received placebo. In one such study, 15% of patients taking troglitazone were able to discontinue insulin therapy, and many more were able to reduce the daily frequency of insulin injections.

Troglitazone is indicated for patients with type II diabetes who take more than 30 units of insulin per day and have HbA_{1c} levels greater than 8.5% (normal: 4% to 6%). It is not indicated for type I (insulin-dependent) diabetes. Further research may support its role in managing impaired glucose tolerance or as a single-agent therapy in early type II diabetes.

SIDE EFFECTS

Troglitazone is generally well tolerated; clinical studies showed similar rates of adverse events with troglitazone and with placebo.

Hypoglycemia. Patients using insulin and troglitazone together may be at risk of hypoglycemia and may need a decrease in insulin dosage.

Drug interactions. Troglitazone may induce drug metabolism by CYP3A4 and therefore may reduce plasma concentrations of terfenadine, cyclosporine, tacrolimus, oral contraceptives, and some HMG-CoA reductase inhibitors.

Increased plasma volume. Troglitazone also increases plasma volume by 6% to 8%, but the clinical significance of this remains to be seen. Small decreases in hemoglobin (3% to 4% in drug-treated patients compared with 1% to 2% in those treated with placebo) have been reported and are felt to be clinically insignificant. Red blood cell mass itself is not changed.

DOSAGE AND ADMINISTRATION

Therapy with troglitazone should begin at a dosage of 200 mg by mouth with food once daily. The insulin dosage should be maintained. If an adequate response is not seen in 2 to 4 weeks, the troglitazone dosage should be increased to 400 mg daily. The maximum recommended dose is 600 mg daily. Insulin dosage adjustments should be individualized on the basis of clinical response.

Troglitazone is manufactured as a 200-mg and a 400-mg nonscored film-coated tablet. The average wholesale price of a month's supply is $104.40 for 200-mg tablets and $160.20 for 400-mg tablets.

Troglitazone is indicated for type II diabetics who take more than 30 units of insulin a day

PERSPECTIVE

This is an exciting time for clinicians, when an agent that counteracts the key pathogenic mechanism in type II diabetes is finally available. At present, however, troglitazone has a narrow indication. If further clinical experience demonstrates a significant improvement in HbA_{1c} values or an ability to correct impaired glucose tolerance, the role of this medication will be broader.

The use of troglitazone raises a practical question of cost vs benefit. If the only benefit of troglitazone therapy for a particular patient is a reduction in insulin dose or frequency, is

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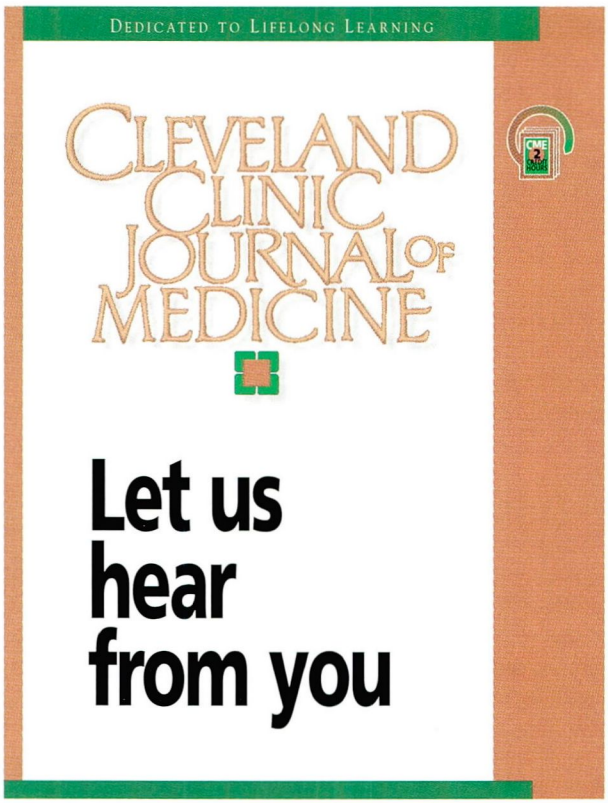

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the added cost of medication worth the benefit? (Most patients would, no doubt, wish to discontinue insulin therapy altogether.)

It would appear that if a patient is able to achieve excellent glycemic control and can discontinue insulin therapy while taking troglitazone, then troglitazone therapy should be continued. ■

SUGGESTED READING

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