Rosiglitazone (Avandia) and pioglitazone (Actos) and heart failure

Reason for posting: Health Canada issued an advisory on Nov. 30, 2001,[1] after receiving an increasing number of reports of congestive heart failure (CHF), pulmonary edema and pleural effusion suspected to be associated with the diabetic agents rosiglitazone and pioglitazone. Letters to health professionals were also issued by the respective manufacturers, GlaxoSmithKline and Eli Lilly Canada.[2,3]

Between March 2000 and February 2001, 38 domestic reports of suspected serious adverse drug reactions associated with rosiglitazone were received by the Canadian Adverse Reaction Monitoring Program (CADRMP), including 8 reports of heart failure. In 5 of these cases, the onset of heart failure occurred within 3 days to 6 weeks after rosiglitazone therapy had been started.[4]

Between August 2000 and August 2001, the CADRMP received 9 reports of serious adverse reactions associated with pioglitazone, including one case of CHF and one of pulmonary edema requiring hospital care; both patients recovered after the therapy was discontinued and appropriate medical therapy instituted.[3]

There are now changes in the product monographs for both drugs indicating that they should not be prescribed to patients with acute heart failure and that their use should be discontinued if heart failure develops.[5,6] As well, the pioglitazone monograph states that patients with New York Heart Association (NYHA) class II cardiac functional status or worse should not receive the drug, and the rosiglitazone monograph states that patients with NYHA class III or IV status should not receive the drug.

The drugs: Both drugs are thiazolidinediones (glitazones) and are used as adjuncts to diet and exercise to reduce insulin resistance in nonpregnant, adult patients with type 2 diabetes mellitus, and in patients with polycystic ovary syndrome. When used alone, neither agent is associated with hypoglycemia.

Rosiglitazone can be used as monotherapy or in combination with metformin or a sulfonylurea. It is not indicated for use with insulin, because unpublished trials have pointed to increased rates of heart failure and other cardiovascular events when the 2 are combined.[2]

Pioglitazone is to be used as monotherapy. It is not indicated for use in combination with other oral antidiabetic agents or insulin because the safety and efficacy of combination therapy has not been established.[6] Unpublished studies indicate that the incidence of edema is higher among patients receiving a combination of pioglitazone and insulin than among those receiving placebo and insulin.[7]

Both rosiglitazone and pioglitazone are known to be associated with persistent edema, weight gain (due in part to fluid retention and subcutaneous adipose accumulations) and mild anemia. Although no causality of hepatocellular dysfunction has been established for either drug, these medications are contraindicated in patients with active liver disease; liver enzymes should be monitored in other patients because of the association between liver failure and another thiazolidinedione (troglitazone) that is not available in Canada.

Women with polycystic ovary syndrome who take these medications may require contraception, as correction of their insulin insensitivity can lead to resumption of ovulation. The product monographs provide additional details.[5,6]

What to do: Diabetes is a risk factor for heart disease and CHF. Patients should be warned that thiazolidinedione medications such as rosiglitazone and pioglitazone may lead to the development or exacerbation of CHF. Patients in whom edema, shortness of breath, weight gain, fatigue or weakness develops should seek medical attention promptly. If the symptoms are related to heart failure, thiazolidinedione therapy should be discontinued. Rosiglitazone and pioglitazone should not be prescribed in combination with insulin, and they should not be prescribed to patients with NYHA class II, III or IV cardiac functional status (even though the product monograph for rosiglitazone states that patients with class III or IV cardiac status should not be given the drug[5]). (Note: Patients with NYHA class II cardiac status have cardiac disease that slightly limits their physical activity; they are comfortable at rest, but ordinary physical activity causes fatigue, palpitations, dyspnea or angina.[8])

Eric Wooltorton
Editorial Fellow
CMAJ

References

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