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Pioglitazone

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Pioglitazone is the third thiazolidinedione to be marketed in the US for the treatment of type 2 diabetes mellitus. Also called 'insulin sensitisers', thiazolidinediones activate PPAR-γ which leads to the transcription of various proteins regulating protein and lipid metabolism. These drugs improve insulin sensitivity and thereby lower blood glucose levels in people with type 2 diabetes mellitus. The main site of action of the thiazolidinediones is in skeletal muscle where they increase insulin-stimulated glucose uptake. In addition, they may decrease hepatic glucose production at high dosages.

The glucose lowering effect of pioglitazone appears similar to that of troglitazone or rosiglitazone. Pioglitazone is effective in lowering blood glucose levels as monotherapy as well as in combination with other antidiabetic agents. The efficacy of such combination therapy confirms the hypothesis that hyperglycaemia is multifactorial. Combination therapy is rapidly being accepted as an appropriate approach to the treatment of type 2 diabetes, even in the early stages of disease (before failure of monotherapy).

At least as important as the glucose lowering effect of pioglitazone is the potential for reduction with the drug, through the targeting of the multifaceted insulin resistance syndrome, of the burden of cardiovascular disease in patients with diabetes. The insulin resistance syndrome is associated with hyperinsulinaemia, hypertension, glucose intolerance, dyslipidaemia and abnormal fibrinolysis.[1] The thiazolidinediones, by directly reducing insulin resistance, have been shown to have favourable effects on all components of this syndrome.[2]

PPAR-γ is present in many tissues (including vascular tissue), and modulation of the function of these receptors may affect many other disease processes, including atherosclerosis. Most of these benefits have been shown in clinical trials of troglitazone, and *in vitro* and animal studies have demonstrated similar potential of pioglitazone for reduction of cardiovascular disease. Clinical studies in humans are needed to confirm this potential benefit, and long term trials will ultimately be required to demonstrate beneficial effects on cardiovascular outcomes. When compared with data for other thiazolidinediones, preliminary results suggest significant improvements in lipid profiles in patients treated with pioglitazone.[3]

Pioglitazone was well tolerated in clinical trials, although oedema and bodyweight gain (which are thiazolidinedione class effects) appear troublesome in a few patients.[3] However, these trials were of relatively short duration, and long term safety data are not available. Although the potential for drug interactions needs to be evaluated further, recent data have shown that pioglitazone does not alter the pharmacokinetics of oral contraceptives or hormone replacement therapy.[4] Troglitazone was recently withdrawn because of reports of severe and occasionally fatal idiosyncratic liver failure. Severe hepatotoxicity leading to liver failure or death has not been reported with pioglitazone. It is nevertheless recommended that pioglitazone should not be used in patients with active liver disease who have baseline plasma ALT levels greater than 2.5 times the upper limit of normal. Monitoring every 2 months should continue for the first year, with discontinuation of the drug in patients whose ALT levels remain 3 times the upper limit of normal or if the patient is jaundiced.

Because of the virtual epidemic of obesity and insulin resistance, pioglitazone may have an important therapeutic role, particularly if its safety and potential for cardiovascular benefit are confirmed. ▲

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