

Pioglitazone/Metformin

A Viewpoint by Marc Rendell

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Metformin is the primary agent for treatment of obese patients with diabetes mellitus. The maximum daily dose appears to be 3000mg, although is limited to 2500mg in the US. Metformin lowers glucose levels by reducing hepatic gluconeogenesis and has favourable effects on lipid levels and other markers of cardiovascular disease. No single oral hypoglycaemic agent achieves the optimal level of glycaemic control in most patients with type 2 diabetes, and combined therapy with multiple agents or insulin is usually required to achieve the typical goal of a glycosylated haemoglobin (HbA_{1c}) level of 6.5%. Various combination agents are now available, using metformin as the base treatment. These combination agents include rosiglitazone and the sulphonylureas glipizide and glyburide. Recently, a tablet combining metformin with pioglitazone has come on the market.

Certainly, the dual effects of a thiazolidinedione, which lowers peripheral and hepatic insulin resistance, and metformin are desirable in providing glucose lowering without the danger of hypoglycaemia. Analysis of multiple studies suggests that the addition of a thiazolidinedione to metformin

treatment lowers HbA_{1c} by at least an additional percentage point.

Certainly, all pharmaceutical agents have potential adverse effects; combination agents combine the adverse effects of the components. Metformin causes significant gastrointestinal discomfort in at least 10% of patients and is contraindicated in patients with renal failure and congestive heart failure. Rosiglitazone and pioglitazone both cause weight gain, through both fluid retention and promotion of adipose cell activity. Anaemia also occurs, probably resulting from haemodilution. The risks of combined therapy remain to be fully elucidated. Patients with congestive heart failure and with renal failure should not receive this combined agent.

Conversely, there may be a benefit in reduction of a number of the side effects of the individual agents by using the combination. For example, the gastrointestinal adverse effects of metformin may be lessened by using a lower dose together with an add-on thiazolidinedione. Furthermore, the use of metformin may mitigate the weight gain that occurs with use of a thiazolidinedione alone. The most important question, which may be answered shortly by a major study with rosiglitazone, is whether a thiazolidinedione slows the deterioration of insulin secretory capacity, which occurs in most patients with type 2 diabetes over time. If conclusive data support this concept, the use of these agents will grow. ▲