

Editorial:

Thiazolidinedione, friend or foe?

Oral antidiabetic drugs, based on their mechanism of action, can be roughly divided into two groups, first which require functioning pancreatic beta cells, e.g., sulphonylureas and dipeptidyl peptidase IV (DPP-IV) inhibitors (the gliptins) and the second, which act on another target and are independent of the beta-cell function. Thiazolidinediones (TZD) fall in the second category, independent of pancreatic beta-cell function and act on adipose tissue to reduce insulin resistance. While drugs of the first group, the insulin secretagogues, are likely to fail with exhaustion of the beta-cell function, the drugs of the second group, by virtue of their independent action, are likely to work longer.¹

From the very beginning, drugs from the group of TZD have been plagued with controversies regarding their adverse effects. The first drug of the group, troglitazone, was withdrawn from the market after reports of (occasionally fatal) hepatotoxicity appeared, barely 3 years after its launch.² However, the other drugs (rosiglitazone and pioglitazone) of the group fared better and enjoyed commercial success.

Fortunes of rosiglitazone and pioglitazone, changed after a meta-analysis reported increased mortality due to vascular complications in patients who were using rosiglitazone.³ Apprehensions of poor cardiovascular safety profile led to restrictions on the use of rosiglitazone in the USA, implemented in 2010, a trend which was followed by rest of the world.⁴ In the same year it was withdrawn from the Indian market. This led to reexamination of the adverse effects of the pioglitazone. Some case reports of carcinoma of the urinary bladder⁵ became a cause for concern and led to ban on use of Pioglitazone in many countries. It was banned in India in 2013. The causative relationship could not be established and the ban was reversed after 1 year with a black box warning in India.

Ban on the use affected many patients who were using the pioglitazone and return with a black box warning, did not help the case much. Finally, last year the restriction by United States Food and Drug Administration (FDA) on use of rosiglitazone was also lifted and it sort of limped back in the market⁶. Some of the adverse effects of TZD are group-specific, while some are specific to a particular compound. Reports of hepatotoxicity of compounds other than troglitazone were uncommon. Water and sodium retention can be troublesome in patients who have had a history of cardiac failure. Any unusual weight gain or pedal edema requires corrective action in the form of reduction of dosage or complete withdrawal. Reduced bone mineral density and increased tendency of fractures have also been seen.

Results of recent research on antihyperglycemic medication have been more or less positive for the TZD. In the PRO spective pioglitAzone Clinical Trial In macroVascular Events (PRO active) trial a marginal protective effect of pioglitazone was seen on macrovascular complications among patients with type 2 diabetes mellitus (T2DM), such as myocardial infarction and recurrent stroke.⁷ TZD were part of the anti hyperglycemic therapy in most of the recent trials of glycemic control among patients with T2DM. Nineteen percent of patients in action to control cardiovascular risk in diabetes



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(ACCORD)⁸ and 17% of patients in action in diabetes and vascular disease: Preterax and diamicon MR controlled evaluation (ADVANCE) trials⁹ were on TZD.

TZD have also been used to reduce insulin resistance among nondiabetics. A recent report suggests that pioglitazone is beneficial in the obese nondiabetic, insulin resistant patients who have suffered a cerebrovascular event¹⁰. It reduced recurrence of stroke, occurrence of myocardial infarction and development of T2DM in the users of pioglitazone. Rationale of the study was that insulin resistance itself is one of the causative factors of atherosclerosis, and tackling it might be clinically useful.

So, does it mean that TZD are useful drugs and we should use these more often? Modest reduction of hyperglycemia is seen when TZD are used as the second-or third-line drug in patients with T2DM. Use of TZD often helps delay initiation of insulin in unwilling patients. Stable glycaemic control, without the added risk of hypoglycaemia is the unique selling proposition of TZD. At present these are indicated only for management of hyperglycemia in T2DM. As long as we are aware of the limitations of this class of drugs and use them judiciously, we can expect good results.

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