Editorial

Have glitazones lost their sparkle?

Gillian M Shenfield, Clinical Pharmacologist, Sydney

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'All that glitters is not gold' (proverb)

The safety of new drugs has never been as well established as pharmaceutical company promotions may suggest. Health professionals and consumers have become more aware of this with the removal of widely used drugs such as rofecoxib from the market. Now the thiazolidinediones, better known as 'glitazones', are under suspicion of causing serious, previously unsuspected adverse effects. Given these concerns, what can be said about the role of thiazolidinediones in third-line therapy of poorly controlled type 2 diabetes?

There are several reasons why previously undescribed adverse effects emerge after a drug is marketed. Before a new drug is registered for use it must undergo a rigorous series of clinical trials, but the total number of patients who have been given the drug rarely exceeds 3000 before it is marketed. Inevitably any adverse effect, for example liver toxicity, occurring in fewer than 1 in 1000 people may not be detected until the drug has been more widely used. Secondly, if the drug induces an increase in a common disease, such as myocardial infarction, the effect will only be detected by appropriately designed large trials or epidemiological studies. Thirdly, the duration of early clinical trials rarely exceeds a few weeks or months and the patients included are often atypical of the population which will take the new drug for many years. Finally and increasingly, many new drugs act on cell receptors which have numerous functions in addition to the one targeted by drug therapy. Altering one function may have unintended effects on others.

All these problems apply to the glitazones which work by stimulating the peroxisome proliferator-activated receptor gamma (PPARγ). These receptors exist in most body tissues, including arteries, and mediate numerous basic functions beyond their useful effects on fat redistribution and glycaemic control. Troglitazone, the first glitazone marketed, was withdrawn from the market because of deaths due to liver failure. A closely related drug, muriglitazar, which stimulates both PPARγ and alpha receptors, increased adverse cardiovascular events. It was withdrawn by its manufacturer after rejection by the US Food and Drug Administration (FDA). Pioglitazone and rosiglitazone, the two PPARγ agonists available in Australia, do not cause serious liver damage, but do induce weight gain, fluid retention and heart failure. One study found that over 40 months the incidence of heart failure was 8.2% in patients taking thiazolidinediones compared with 5.3% in a control group.[1] The drugs are therefore contraindicated in patients with heart failure (New York Heart Association class III or IV).

Recent data suggest further associations between glitazones, cardiovascular events[2] and peripheral limb fractures.[3] Pioglitazone and rosiglitazone have been associated with an increase in peripheral fractures in postmenopausal women, particularly in the humerus, hands and feet. There is also a study suggesting that rosiglitazone may reduce bone formation and density.[4]

A meta-analysis reported a significant increase in the risk of myocardial infarction with rosiglitazone and a trend towards increased risk of death from cardiovascular causes. (Compared with other treatments, the odds ratio with rosiglitazone was 1.43 for myocardial infarction and 1.64 for death from cardiovascular causes.[2]) These findings have been challenged on methodological grounds[5], but there is sufficient doubt to warrant caution with prescribing the drug for a vulnerable diabetic population already at high risk of having cardiovascular disease.[6] Current data suggest that pioglitazone may not

In this issue…

Often the excitement around the launch of a new drug is soon tempered by the emergence of problems in practice. Mark Boyd and Sarah Pett inform us that the uptake of enfuvirtide has been limited, and Gillian Shenfield considers the adverse effects of thiazolidinediones.

Sometimes a patient has to take a drug despite its serious adverse effects. Cecilie Lander tells us that this is a particular problem for pregnant women who need treatment for epilepsy.

Antiepileptic drugs are also used in bipolar disorders, but Ajeet Singh and Michael Berk say that lithium still has an important role.

Paracetamol and ibuprofen are also old drugs which remain widely used. Sean Beggs reviews how they compare when used to relieve pain in children.

increase cardiovascular events, but the reasons for this difference are unknown.

What are the implications of these findings for managing patients with poorly controlled type 2 diabetes? Firstly, all patients should be assessed for osteoporosis and fracture risk and managed appropriately. It would be wise not to start a glitazone in anyone known to have a history of fracture or significant osteoporosis.

In Australia, patients being considered for treatment with a glitazone will already be taking metformin, a sulfonylurea or both, and will have poor glycaemic control with or without symptoms. The aim of further lowering of blood glucose concentrations is to reduce the incidence of both macro- and microvascular disease. Even better outcomes can be achieved by additionally improving the control of blood pressure.[7] These goals should have a high priority in all patients, but are the glitazones the best way to achieve them? They have been shown to slow the progression of type 2 diabetes over four years[8], but this is only a surrogate measure for long-term outcomes.

The alternative therapy in these patients is insulin. This is as effective as the glitazones on surrogate measures such as glycaemic control and has been used in long-term studies showing a reduction in cardiovascular events. All patients eligible to start a glitazone should therefore be given the choice of taking insulin. Most are scared of injections and many doctors find the thought of starting insulin therapy daunting. Once persuaded to try, it is my experience that the majority of patients admit that insulin is much easier to use than they had feared.

In patients already taking one of the glitazones the first action should be to review how successful it has been. As 25–30% of patients have no significant improvement in glycaemic control after eight weeks, they should stop the glitazone and start insulin. Patients who have had a very good improvement in glycaemic control, and have no overt heart disease, could stay on the glitazone, but be advised about the problems and have strict management for other risk factors. The patients with an intermediate response need to have the pros and cons discussed, but should be advised of the known, long-term efficacy of insulin.

These evolving problems with thiazolidinediones reinforce the fact that new is not always better. We do not have all the answers so it will be necessary to modify prescribing as more information becomes available.

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Professor Shenfield is a member of the National Prescribing Service New Drugs Working Group which oversees the writing of NPS RADAR.

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