Effectiveness and side effects of thiazolidinediones for type 2 diabetes: real-life experience from a tertiary hospital

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Type 2 diabetes is a progressive disease. Despite ongoing lifestyle interventions and dose increments of sulfonylurea, metformin or insulin, the disease remains sub-optimally controlled in about 50% of patients 6 years after being diagnosed. This relates, in part, to the observation that neither sulfonylurea nor metformin therapy arrests the progressive decline in β-cell function seen in type 2 diabetes.1,2

The thiazolidinediones (TZDs) pioglitazone and rosiglitazone are novel insulin-sensitising antidiabetic agents that bind with high affinity to the peroxisome proliferator-activated receptor (PPAR-γ).3 Studies in animals4 and humans suggest that TZDs may help preserve β-cell function and thereby delay progression of type 2 diabetes.

A number of clinical trials have reported use of TZD as monotherapy5–8 or in combination with a sulfonylurea, metformin or insulin,9–11 and have shown significant reductions in the level of glycohaemoglobin (HbA1c) compared with placebo. However, there are few reports of effectiveness and side effects of TZDs in routine clinical use, and few studies comparing rosiglitazone and pioglitazone.12–15 We have therefore conducted a review of TZDs in clinic outpatients with type 2 diabetes whose disease was not optimally controlled with standard therapy.

METHODS

We reviewed the records of patients with type 2 diabetes who had been prescribed TZDs (15, 30 or 45 mg pioglitazone daily or 4 or 8 mg rosiglitazone daily) for at least 2 months between 1 May 2000 and 31 October 2002 through the Royal Melbourne Hospital diabetes clinic. This clinic treats about 2500 patients with type 2 diabetes each year and is staffed by 10 endocrinologists. Therapy with a TZD was commenced if the HbA1c level was greater than 8% despite appropriate lifestyle advice and drug therapy. Rosiglitazone was the sole TZD prescribed until pioglitazone became available in October 2000. As pioglitazone was the only TZD to receive Therapeutic Goods Administration approval for use in combination with insulin, after October 2000 most patients who required insulin were prescribed pioglitazone rather than rosiglitazone. In those who did not require insulin, the choice of TZD was left to the treating physician. There was no treatment crossover. All patients received lipid-lowering therapy if deemed necessary.

Baseline laboratory data were defined as the most recent value for HbA1c and lipid levels before commencement of TZD. Weight change was determined as the greatest change in weight compared with baseline during the first 6 months of TZD therapy. This study was approved by the Royal Melbourne Hospital Human Research Ethics Committee.

STATISTICAL ANALYSIS

For continuous variables, Student’s t-test was used to assess statistical significance, defined as P<0.05. Qualitative variables were assessed using the χ² test, where P<0.001 was considered significant.

RESULTS

A total of 203 patients who attended the diabetes clinic at Royal Melbourne Hospital were prescribed TZDs for two months or more between 1 May 2000 and 31 October 2002. Both pioglitazone and rosiglitazone improved glycaemic control, with a reduction in the HbA1c level of 1.02% (range, 0.85%–1.19%) and 0.96% (range, 0.81%–1.11%), respectively, in the first 6 months of therapy. Rosiglitazone was associated with a 0.45 mmol (range, 0.31–0.59 mmol) increase in cholesterol level and 0.99 mmol (range, 0.60–1.38 mmol) increase in triglyceride level, while pioglitazone was associated with insignificant declines in cholesterol and triglyceride levels. There was reduced requirement for insulin, but not for oral hypoglycaemic agent (OHA), in most patients who used these agents. Pioglitazone and rosiglitazone were associated with increased rates of hypoglycaemia (17% and 11% of patients, respectively), significant weight gain (48% and 58%) and oedema (33% and 21%). There were four cases of acute left ventricular failure and two cases of reversible liver dysfunction in patients treated with TZDs.

Conclusions: Adding pioglitazone or rosiglitazone therapy to OHA or insulin in patients with type 2 diabetes significantly improved glycaemic control. However, the use of these drugs in routine clinical practice was associated with more frequent adverse events than previously reported in clinical trials.
Before treatment there were no significant differences in age, sex, weight, HbA1c level or lipid profiles between the patients treated with pioglitazone or rosiglitazone. The mean duration of diabetes was significantly longer in the pioglitazone group than the rosiglitazone group. Half the patients in each group (50%) were receiving hypolipidaemic agents.

Glycaemic control
Both pioglitazone and rosiglitazone were associated with a significant reduction in HbA1c level of around 1% at 6 months (Box 2a). Baseline diabetes treatment did not significantly influence the effect of TZD on HbA1c level.

In a smaller population of patients for whom HbA1c level was recorded at baseline, 6 and 12 months, a similar 1% reduction was seen and sustained (Box 2b).

Effects on insulin and oral hypoglycaemic agent therapy
At baseline, insulin was prescribed to 83 patients in the pioglitazone group and 47 in the rosiglitazone group (P < 0.001). Seventy-six (59%) of these 130 patients had a reduction in their insulin dose 6 months after starting TZD therapy — four (3%) ceased insulin treatment, in 17 (13%) the insulin dose was reduced by more than 50%, in 28 (22%) it was reduced by 25%–50%, and in 27 (21%) it was reduced by up to 25%. However, 30 patients (23%) did not change insulin dose and 24 (18%) required an increase in dose after 6 months of TZD treatment.

There was little effect of TZD on oral hypoglycaemic agent (OHA) use. Of 165 patients treated with OHA or OHA and insulin, 20% had a reduction in their OHA dose, 3% ceased OHA treatment, 19% had a reduction in their OHA dose of more than 50%, 23% had a reduction of 25%–50%, and 12% had a reduction of up to 25%. However, 26% did not change their OHA dose and 29% required an increase in dose after 6 months of TZD treatment.

### 1 Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pioglitazone</th>
<th>Rosiglitazone</th>
<th>Total</th>
<th>P*</th>
</tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>107</td>
<td>96</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>64.4 (10.7)</td>
<td>64.6 (10.3)</td>
<td>64.5 (10.5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Range</td>
<td>36–86</td>
<td>41–82</td>
<td>36–86</td>
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</tr>
<tr>
<td>Sex (ratio, female : male)</td>
<td>56:51</td>
<td>53:43</td>
<td>109:94</td>
<td></td>
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<tr>
<td>Duration of diabetes mellitus (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>17.0 (7.6)</td>
<td>14.5 (17.3)</td>
<td>15.8 (7.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Range</td>
<td>3–36</td>
<td>4–33</td>
<td>3–36</td>
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<tr>
<td>Baseline weight (kg)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>84.3 (14.1)</td>
<td>82.3 (17.9)</td>
<td>83.4 (16.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Range</td>
<td>59.5–125.9</td>
<td>54.0–155.0</td>
<td>54.0–155.0</td>
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</tr>
<tr>
<td>Baseline HbA1c level (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.5 (1.6)</td>
<td>9.6 (1.5)</td>
<td>9.6 (1.6)</td>
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<tr>
<td>Range</td>
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<td>6.3–15.3</td>
<td>6.2–15.3</td>
<td></td>
</tr>
<tr>
<td>Prior treatment (No. of patients [% of total])</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oral hypoglycaemic agent</td>
<td>24 (22%)</td>
<td>49 (51%)</td>
<td>73 (36%)</td>
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</tr>
<tr>
<td>Monotherapy</td>
<td>3</td>
<td>10</td>
<td>13</td>
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<tr>
<td>Double-agent therapy</td>
<td>14</td>
<td>29</td>
<td>43</td>
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<tr>
<td>Triple-agent therapy</td>
<td>7</td>
<td>10</td>
<td>17</td>
<td></td>
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<tr>
<td>Insulin monotherapy</td>
<td>19 (18%)</td>
<td>19 (20%)</td>
<td>38 (19%)</td>
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<tr>
<td>Combination therapy†</td>
<td>64 (60%)</td>
<td>28 (29%)</td>
<td>92 (45%)</td>
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</tr>
</tbody>
</table>

* Pioglitazone versus rosiglitazone. † Oral hypoglycaemic agent plus insulin.

SD = standard deviation. HbA1c = glycohaemoglobin.

### 2 Effect of thiazolidinediones on glycohaemoglobin (HbA1c) and lipid levels

Data are shown as mean values and standard errors of the mean. * Significantly different from baseline values, calculated by the paired t test.
lin at baseline, in 26 the OHA dose had decreased, in 132 it had not changed and in seven it had increased at 6 months.

These effects of TZD on insulin and OHA therapy were not significantly different between the pioglitazone or rosiglitazone groups.

Lipids
In patients for whom data were available, statistically significant increases in total cholesterol and triglyceride levels were associated with rosiglitazone, but not pioglitazone, treatment (Box 2c and 2d).

Hypoglycaemia
Increased frequency of hypoglycaemia was noted in 18 patients in the pioglitazone group (17%) and 11 in the rosiglitazone group (11%). This difference was not significant. All episodes were mild (requiring self-administration of oral glucose) or moderate (requiring assistance to administer oral glucose). Hypoglycaemic episodes occurred in 29 patients prescribed insulin and two receiving sulfonylurea in combination with TZD.

Weight
Repeat weight measurements during the first 6 months of TZD treatment were available for 192 patients. Just over half of these experienced weight gain of more than 2 kg (Box 3). The mean gain was 2.3 kg (range, –5.0 to 19 kg) in the pioglitazone group and 2.9 kg (range, –5.0 to 11.5 kg) in the rosiglitazone group (P = 0.95). Baseline treatment for diabetes (OHA v insulin v OHA + insulin) did not correlate with degree of weight gain. However, there was significant correlation between baseline weight and weight gain at six months (Box 3).

Oedema and congestive cardiac failure
Peripheral oedema was noted in 33% of the pioglitazone group and 21% of the rosiglitazone group (difference not significant). It was severe enough to prompt withdrawal of TZD in 7% and 4%, respectively (difference not significant). The presence of peripheral oedema was not dose related.

Pulmonary oedema was noted in five patients (two taking pioglitazone and three taking rosiglitazone). Four of these had pre-existing congestive cardiac failure treated with diuretics. Pulmonary oedema prompted withdrawal of treatment in three of these patients.

Liver function tests
One patient treated with pioglitazone had asymptomatic elevation of liver enzyme levels 3 months from baseline, with alanine transaminase (ALT) at 162 U/L (normal, <35 U/L) and alkaline phosphatase (ALP) at 178 U/L (normal, 25–100 U/L). Ultrasound showed multiple gallstones and a normal liver. The liver enzyme levels returned to normal within a week of ceasing pioglitazone therapy.

One patient treated with rosiglitazone also had asymptomatic ALT elevation (385 U/L) of undetermined cause. This resolved at 12 months despite continuation of rosiglitazone.

Cessation of treatment
TZD treatment was withdrawn within 12 months in about 20% of the patients in the study (20 of 107 patients taking pioglitazone and 21 of 96 patients taking rosiglitazone). The reasons for ceasing treatment in these 41 patients were non-response (13), peripheral oedema (12), weight gain (5), pulmonary oedema (3), liver dysfunction (1), asymptomatic hyponatraemia (1) and abdominal pain (1). The reason for cessation was unclear in two patients. One patient treated with rosiglitazone died from lower-limb sepsis disease during the study period. Her clinical course was complicated by ischaemic heart disease and dialysis-dependent renal failure.

DISCUSSION
We report the effects of TZD therapy in routine Australian clinical practice. We acknowledge that the study’s retrospective, non-randomised design is a limitation.

Our study population, whose average HbA1c level was clearly elevated at 9.6%, was representative of the Australian population of people with type 2 diabetes for whom TZD therapy might be considered. While our prescribing patterns did not follow current Pharmaceutical Benefits Scheme (PBS) authority guidelines (eg, rosiglitazone was combined with insulin, TZD was used with more than one other OHA), we believe most of our patients would have met the criteria for the authority guidelines, which were developed after we started to prescribe TZDs.

Consistent with other studies,6-11,14,16,17 we have shown TZD treatment is associated
with a clinically significant reduction in HbA1c level of about 1%. It could be argued that this reduction is caused by other factors, such as increased patient compliance with diet, exercise or medication. However, our patients were not offered additional diabetes clinical care or education in conjunction with TZD treatment. Furthermore, in general, these patients were a group who, over a number of years, had had various interventions in an attempt to improve glycaemia, but remained suboptimally controlled. We therefore feel the observed reductions in HbA1c levels are real effects of TZD treatment.

We observed a significant increase in total cholesterol and triglyceride levels in patients receiving rosiglitazone, but not in those receiving pioglitazone. Previous prospective and retrospective studies have shown that rosiglitazone increases total cholesterol level, but may either increase or mildly decrease triglyceride levels. Pioglitazone has been shown to decrease both total cholesterol and triglyceride levels, a finding we did not confirm. Our results must be interpreted with caution, as patient numbers were small and we did not control for the use of lipid-lowering therapy. Given the important impact of dyslipidaemia on cardiovascular risk in type 2 diabetes, further study of the clinical significance of TZD-induced dyslipidaemia is highly desirable.

Our study also highlights the high rate of side effects associated with TZD in routine Australian practice. Hypoglycaemia was increased in about 15% of patients being treated with TZD, all of whom were also treated with either sulfonylurea and/or insulin. This rate of hypoglycaemia is much higher than previously reported in controlled trials. We strongly recommend that patients with diabetes who are treated with sulfonylurea and/or insulin are counselled about the increased risk of hypoglycaemia when starting TZD therapy.

Our results also confirm that weight gain is a significant side effect of TZD treatment. This was highly correlated with baseline body weight. Given the highly distressing nature of this side effect, it is surprising that weight gain only prompted cessation of therapy in a small proportion (2.5%) of our patients. Further study into its causes and possible prevention is needed.

The incidence of peripheral oedema of about 27% in our study was somewhat higher than the 3%–16% reported in other studies. This discrepancy may have resulted from our broader inclusion criteria or concurrent use of non-steroidal anti-inflammatory drugs and calcium-channel blockers (prescribed to 24% of all patients who experienced oedema in our study). Similarly, the 2.5% incidence of pulmonary oedema in our study was much higher than in other studies. We strongly recommend that TZD be used with great caution in patients with congestive cardiac failure and that clinical evidence of volume overload be sought when following any patient who commences TZD therapy.

Our study identified only two out of 203 patients with unexplained elevation of liver enzyme levels and no patients with permanent liver damage. These findings are insufficient to conclude that TZD treatment carries no hepatic risk. Until more safety data are available, we recommend 2-monthly liver function testing in all patients treated with TZD, as per Australian Therapeutic Goods Administration guidelines.

Our observed rate of withdrawal from TZD treatment at 12 months (20%) was also at odds with results of controlled trials of TZD therapy. This may have resulted from inclusion of older patients or patients with significant comorbid disease, such as heart failure.

In summary, treatment of type 2 diabetes with pioglitazone or rosiglitazone in a hospital outpatient setting was associated with improved glucose control in most patients. The treatment was not without significant risk of side-effects, including hypoglycaemia, weight gain and oedema, which in turn led to a high cessation rate at 12 months. Careful patient selection and follow-up and realistic treatment goals are necessary for effective use of these novel agents.

COMPETING INTERESTS

None identified.

REFERENCES


13. Khan MA, St Peter JV, Yue JL. A prospective, randomised comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. Diabetes Care 2002; 25: 708-711.


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