ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (10): 839-850
0114-5916/08/0010-0839/$48.00/0

Monitoring the Safety of Pioglitazone

Results of a Prescription-Event Monitoring Study of 12 772 Patients in England

Rachna Kasliwal,[1,2] *Lynda V. Wilton*[1,2] and *Saad A.W. Shakir*[1,2]

1 Drug Safety Research Unit, Southampton, United Kingdom
2 University of Portsmouth, Portsmouth, United Kingdom

Abstract

Background: Pioglitazone is an antidiabetic drug that targets insulin resistance in patients with type 2 diabetes mellitus by stimulating the peroxisome proliferator-activated receptor (PPAR)-γ. Pioglitazone belongs to a class of drugs called thiazolidinediones (TZDs) and was launched in the UK in November 2000.

Objective: To monitor, using prescription-event monitoring, the post-marketing safety of pioglitazone, which is prescribed in primary care in England.

Methods: An observational cohort study in which patients were identified from dispensed prescriptions issued by primary-care physicians/general practitioners (GPs) between November 2000 and June 2001. Information on demographics, the use of pioglitazone, clinical event data, events suspected as adverse drug reactions, reasons for stopping the drug and cause of death (if appropriate) were collected using questionnaires posted to GPs at least 8 months after the date of first prescription for each patient. Event incidence densities (IDs) [number of first reports of an event/1000 patient-months of exposure] were calculated.

Results: The cohort comprised 12 772 patients (median age 62 years); 53.1% were males. The most frequent starting daily dose of pioglitazone was either 15 mg or 30 mg (n = 10 298). Pioglitazone/metformin was the most frequently used combination reported (n = 4029). Of the 3690 patients who stopped treatment, 1143 stopped due to reasons related to poor glycaemic control. 'Oedema/fluid retention' (n = 121) and 'weight gain' (n = 118) also appeared high on the list of reasons for discontinuing. 'Malaise/lassitude' and 'nausea/vomiting' were the most frequently reported suspected adverse drug reactions (ADRs) associated with pioglitazone. Specific clinical events considered as early onset events with pioglitazone were: 'malaise/lassitude', 'nausea/vomiting', 'dizziness', 'headache/migraine', 'diarrhoea', 'weight gain' and 'abnormal liver function test'.

Conclusion: Pioglitazone was considered to be a reasonably well tolerated drug, with the main reasons for discontinuing being related to the drug not being effective. The frequency of individual ADRs reported in this study did not exceed the frequency in the summary of product characteristics (SPC) for pioglitazone. However, amongst the frequently reported suspected ADRs, 'nausea/vomiting'

and 'diarrhoea' are not listed in the SPC. Further research is required to assess whether the risk of myocardial infarction and deaths due to cardiovascular causes is a class effect of the thiazolidinediones. Results from this study should be taken into account with other clinical and pharmacoepidemiological studies.

Background

Thiazolidinediones (TZDs) are a unique class of antidiabetic drugs that target insulin resistance in patients with type 2 diabetes mellitus by stimulating the peroxisome proliferator-activated receptor (PPAR)-γ, which regulates the transcription of genes involved in insulin action, adipocyte differentiation, lipid metabolism and inflammation.[1]

Three TZDs have been developed and marketed in the UK to date: troglitazone (launched October 1997); rosiglitazone (July 2000); and pioglitazone (November 2000). Troglitazone was withdrawn from the UK market (December 1997) within a few months of its launch, after a number of reports of severe hepatic adverse events.[2] Hepatotoxicity is not thought to be a TZD class effect,[3] the difference between troglitazone and the other two TZDs being the lack of the hepatotoxic α-tocopherol side chain in the latter two.[4] However, monitoring of liver function before starting treatment and regularly during treatment with pioglitazone is recommended.[5] A number of case reports of hepatocellular injury associated with pioglitazone,[6-10] including one case of fatal liver failure,[11] have been reported.

In addition to hepatotoxicity, there have been concerns regarding the risk of heart failure, fluid retention, weight gain and anaemia with the use of pioglitazone.[5] Although the mechanism of development of fluid retention is not fully understood, it is thought to be a TZD class effect, to be dose-dependent and to be exacerbated by concomitant insulin therapy.[12]

The PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study showed that the number of cases of heart failure requiring hospital admission was higher for pioglitazone versus placebo (6% vs 4%; p-value = 0.007).[13] Furthermore, there are published post-marketing reports of cardiac failure and pulmonary oedema in patients receiving pioglitazone, in whom the conditions resolved on discontinuing pioglitazone.[14,15] Pioglitazone is contraindicated in patients with cardiac failure or a history of cardiac failure (New York Heart Association stage I–IV).[5]

A recent meta-analysis[16] suggests that rosiglitazone may increase the risk of myocardial infarction (MI) and cardiovascular death. Another meta-analysis on pioglitazone showed a lower risk of death, MI or stroke in a diabetic population treated with this drug.[17] These findings have lead to confusion amongst researchers, physicians and patients about benefits versus risks of this class of drugs. The world-wide adult diabetic population is estimated to rise from 135 million in 1995 to 300 million in 2025 and, therefore, the safety surveillance of antidiabetic agents has become extremely important.[18] Therefore, the Drug Safety Research Unit (DSRU) has conducted this safety study, using prescription-event monitoring (PEM) methodology in general practice in England, on the first users of pioglitazone during its immediate post-marketing period.

Methods

An observational cohort study was conducted in England, using the PEM technique described in more detail previously.[19]

Prescription Information and 'Green Form' Questionnaires

Patients were identified by means of data from dispensed National Health Service prescriptions for pioglitazone, issued by primary care physicians/general practitioners (GPs) in England between November 2000 and June 2001. This prescription information was supplied in confidence to the DRSU by the Prescription Pricing Authority (now the Prescription Pricing Division, which is a part of the National Health Service Business Services Authority). A simple 'green form' questionnaire was sent to the prescribing GP approximately 8 months following the first prescription identified by the DSRU for each patient. The green form requested information (outcome data) on any events that had occurred since the initiation of pioglitazone. The term 'event', as used in PEM, is defined as, "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint that was considered of sufficient importance to enter in the patient's notes."

GPs were also requested to provide information on: patient demographics; indication for prescribing pioglitazone; dosage at the time of starting pioglitazone and at the time of the event; dates of starting and stopping treatment; if applicable, reason(s) for stopping pioglitazone; whether pioglitazone was being used with another antidiabetic drug (tick box questions – metformin/sulphonylurea/insulin/other/combination); and, if applicable, cause of death. GPs were requested to indicate if they suspected any event to be an adverse drug reaction (ADR) associated with pioglitazone and if any event had been reported to the Committee on Safety of Medicines (CSM) or the manufacturer of pioglitazone. If there was no response to the initial green form mailing, reminders were sent to GPs 2 months after the first mailing. All green forms were completed by GPs on a voluntary basis. Any green form returned with no demographic or clinical information was classified as 'void' and excluded from the study cohort and subsequent analysis.

All reported events were entered onto the DSRU database using the DSRU event dictionary that has a hierarchical structure arranged by system-organ class (SOC). The terminology used by the GP (doctor summary terms) is grouped under 'lower-level' terms, which are in turn grouped under broader, 'higher-level' terms that are linked to the respective SOCs.

Strict confidentiality of patient information was maintained throughout the study. The GPs were requested to provide a patient identification number and all communications were carried out using this number.

Follow-Up of Events

All reported pregnancies were followed-up to ascertain the outcome of pregnancy, and deaths where the cause was not specified were followed-up to ascertain the cause of death.

Incidence Density Analysis

In order to detect any early onset events with pioglitazone, the differences between incidence densities in month 1 (ID_1) and IDs in months 2–6 of treatment ($ID_{2–6}$) were calculated with 99% confidence intervals (CIs). A positive difference indicates that the ID in month 1 was higher than months 2–6. This calculation was carried out for all events occurring during the treatment period. Patient-months of exposure were based on those patients for whom either the date of stopping the drug was known or who continued to take the drug until the end of the study period.[19]

Table I. Baseline characteristics of 12 772 patients

Characteristic	Number (% of total cohort)
Age known[a]	9869 (77.3)
missing[b]	*2903 (22.7)*
Sex	
male	6777 (53.1)
missing[b]	*162 (1.2)*
Starting daily dose (mg)	
15	5703 (44.7)
30	4595 (36.0)
45	21 (0.16)
missing[b]	*2453 (19.2)*

a Median age 62 years, interquartile range 52–70 years, minimum-maximum 12–101 years.

b Missing refers to unspecified responses.

Power

The ability to detect an event is dependent on the expected incidence of the event in those exposed to the drug, the background rate in those not exposed to the drug and the total number of patients. A cohort of at least 10 000 patients would allow with 95% certainty that events not observed in the cohort occurred less frequently than one in 3333 cases.[20]

Also, a cohort of 10 000 should allow for the detection of at least three cases of an event with 85% power, if the event occurs at a rate of at least one in 2000 patients (assuming the background rate is zero).[21]

Ethics

This study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the CIOMS in collaboration with the WHO.[22] The method of study also complies with the guidelines issued by the Royal College of Physicians[23] and the Department of Health.[24]

Results

Cohort Data

A total of 213 538 prescriptions were collected and used to identify 34 151 patients who had commenced treatment with pioglitazone between November 2000 and June 2001. Of the 26 506 green forms sent, 14 490 (54.7%) were returned. Of these, on 1718 green forms (11.8%), no demographic or clinical information was provided by the GP, these were classified as void and excluded from the study. Thus, useful information was available for 12 772 patients.

Of the 12 772 patients, 6777 (53.1%) were males, the median age of the cohort was 62 years and the most frequent starting dose of pioglitazone was 15 mg. Details on baseline characteristics are given in table I. Although pioglitazone is not recommen-

Table II. Primary indication reported for prescribing pioglitazone

Primary indication	Number (% of total cohort)	% where indication was specified (n = 8812)
Diabetes mellitus or the context for prescribing an antidiabetic drug (e.g. poor glycaemic control)	8 017 (62.78)	91.0
Inadequate response/intolerance to previous antidiabetic drug	771 (6.06)	8.75
Insulin resistance syndrome/related conditions (polycystic ovarian disease/ lipodystrophy)[a]	19 (0.15)	0.21
Indications unrelated to glycaemic control[b]	3 (0.03)	0.03
Patient's request	2 (0.02)	0.02
Indication not specified	3 960 (31.01)	
Total	**12 772 (100)**	

a This includes 16 patients who were prescribed pioglitazone for insulin resistance syndrome, two female patients for polycystic ovarian disease and one patient for lipodystrophy. In another four patients, ovarian cyst (n = 2) and lipodystrophy (n = 2) were reported as secondary indications.

b This includes one patient each of: chronic obstructive pulmonary disease, psoriasis and mitochondrial myopathy.

ded in patients <18 years of age, there were three female patients (12, 13 and 17 years) and three male patients <18 years of age (two aged 16 years and one aged 17 years) in this cohort.

Prescribing Indication for Pioglitazone

Prescribing indication for pioglitazone was not specified for 3960 (31.0%) patients. Where specified (n = 8812), diabetes (or the context of prescribing an antidiabetic drug) was the major primary indication reported for prescribing pioglitazone (n = 8017; 91.0%). Details on primary indication for pioglitazone are given in table II.

Concomitant Use of Other Antidiabetic Drugs

Of the total cohort, 286 (2.2%) patients were reported to be taking pioglitazone as monotherapy. For 11 988 patients (94.0% of total cohort), at least one antidiabetic medication was reported as concomitant therapy to pioglitazone. The most frequent combinations were: pioglitazone and metformin only 33.6% (4029 of 11 988); pioglitazone and sulphonylurea only 25.0% (2984 of 11 988); and pioglitazone, metformin and sulfonylurea 18.0% (2151 of 11 988). Furthermore, insulin was used with pioglitazone, either alone or with another antidiabetic

Table III. Events most frequently reported as suspected adverse drug reactions (ADRs) to pioglitazone and the number reported to the Committee on Safety of Medicines (CSM)

Reported ADRs		Number	% of total	Reported	Frequency if labelled in SPC[5]
higher level term	lower level term		cohort	to CSM	(pioglitazone in combination with metformin/sulphonylurea)[a]
Unspecified side effects[b]	Unspecified side effects[b]	66	0.52	1	NA
Malaise, lassitude		30	0.23	0	Fatigue – uncommon: (pioglitazone + sulphonylurea)
	Malaise	19	0.15	0	
	Lassitude	11	0.10	0	
Nausea, vomiting		28	0.22	0	Not labelled
	Nausea	22	0.17	0	
	Vomiting	6	>0.1	0	
Dizziness	Dizziness	22	0.17	1	Common: (pioglitazone + sulphonylurea)
Headache, migraine	Headache	16	0.12	0	Headache – common: (pioglitazone + metformin) uncommon: (pioglitazone + sulphonylurea)
Diarrhoea	Diarrhoea	12	>0.1	1	Not labelled
Oedema		11	>0.1	1	
	Oedema	8	>0.1	1	Information in SPC from double-blind studies: oedema seen in 5.9% of patients treated with pioglitazone + sulphonylurea and in 6.0% treated with pioglitazone + metformin
	Swollen ankles	2	>0.1	0	
	Fluid retention	1	>0.1	0	
Visual defect	Visual disturbance	11	>0.1	1	Vision abnormal Common: (pioglitazone + metformin) Uncommon: (pioglitazone + sulphonylurea)
Pain joint	Pain joint	10	>0.1	0	Common: (pioglitazone + metformin)
Weight gain	Weight gain	8	>0.1	0	Common: (pioglitazone + metformin/ sulphonylurea)

a Frequency as per SPC:[5] common >1/100, <1/10; uncommon >1/1000, <1/100.

b The general practitioner did not specify the exact clinical event, but reported that the patient had adverse effects with pioglitazone.

NA = not applicable; **SPC** = summary of product characteristics.

Table IV. The 15 most frequently reported reasons for discontinuing pioglitazone

Higher level term	Lower level term	Number	% of total cohort
Diabetes mellitus, hyperglycaemia		1143	8.95
	Diabetic control impaired	947	7.41
	Glycaemic control poor	83	0.65
	Hyperglycaemia	74	0.58
	Diabetes worsened	37	0.29
	Ketoacidosis diabetic	1	0.01
	Nephropathy diabetic	1	0.01
Not effective	Not effective	831	6.51
Malaise, lassitude		150	1.17
	Malaise	114	0.89
	Lassitude	36	0.28
Patient request	Patient request	128	1.00
Oedema		121	0.95
	Oedema	73	0.57
	Fluid retention	23	0.18
	Swollen ankles	19	0.15
	Oedema face	3	0.02
	Swollen limb	3	0.02
Weight gain	Weight gain	118	0.92
Hospital referrals no admission		110	0.86
	Hospital referrals	109	0.85
	Hospital referrals: psychiatry	1	0.01
Non-compliance	Non-compliance	100	0.78
Intolerance[a]	Intolerance	96	0.75
Nausea, vomiting		90	0.70
	Nausea	68	0.53
	Vomiting	22	0.17
Dizziness	Dizziness	68	0.53
Unspecified adverse effects[a]	Unspecified adverse effects	65	0.51
Diarrhoea	Diarrhoea	64	0.50
Headache, migraine	Headache	63	0.49
Liver function test abnormal	Liver function test abnormal	63	0.49

a The general practitioner did not specify the exact clinical event, but reported that the patient had intolerance/unspecified adverse effects with pioglitazone.

drug in 441 (3.7%) patients. For the remaining 498 patients (3.9% of the total cohort), it was either not known or not specified whether pioglitazone was taken as monotherapy or in combination with another antidiabetic drug.

Events Suspected to be Adverse Drug Reactions

An event was coded as an ADR if the GP reported that the event was suspected to be due to the drug; 299 events were reported as suspected ADRs to pioglitazone in 204 patients. The clinical term most frequently reported as a suspected ADR associated with pioglitazone use was 'malaise/lassitude' (n = 30). Table III gives the most frequently reported ADRs associated with pioglitazone use and the number that were reported to the CSM. None was reported to the manufacturer of pioglitazone. All the events suspected as ADRs associated with pioglitazone (or equivalent terms) in table III are listed in

the summary of product characteristics (SPC) of pioglitazone,[5] expect for two event terms, 'nausea/vomiting' and 'diarrhoea'.

Reasons for Discontinuing Pioglitazone

Twenty-nine percent (n = 3690) of patients stopped pioglitazone during the study period. In 92.7% (n = 3420) of these patients, the reason for stopping pioglitazone was reported. As some GPs reported more than one reason for stopping pioglitazone, a total of 4010 reasons for stopping the drug were recorded. The 15 most frequently reported reasons for discontinuing pioglitazone are given in table IV. Events related to indication and 'not effective' were the most frequent.

Incidence Density Analysis

The number of events reported during treatment, together with the IDs for the first month of treatment, months 2–6 of treatment, and the overall time period are shown in table V. There were seven specific clinical events ('malaise/lassitude', 'nausea/vomiting', 'dizziness', 'headache/migraine', 'diarrhoea', 'weight gain' and 'abnormal liver function tests' [LFTs]) for which the rate of event in month 1 was significantly greater than the rate of event in months 2–6, suggesting that these were early onset events with pioglitazone (table V). Of these, except for two event terms, 'nausea/vomiting' and 'diarrhoea', all events or equivalent terms are listed in the SPC.[5]

Events of Interest

The following events were considered events of interest: 'oedema', 'weight gain', 'abnormal liver function tests', 'cardiac failure' and 'anaemia'. Frequencies for these events are presented in table VI.

A total of 118 events of abnormal LFTs were reported in 107 patients, as some patients had more than one event reported. The type of LFT deranged

Table V. Incidence densities (ID), for the first 15 clinical events reported during treatment with pioglitazone ranked in order of ID_1

Higher level term	N_1	$N_{2–6}$	ID_1	$ID_{2–6}$	$ID_1–ID_{2–6}$ (95% CI)	N_A	ID_A
Diabetes mellitus, hyperglycaemia	178	775	15.55	15.50	0.05 (−3.28, 3.37)	1479	14.03
Malaise, lassitude[a]	77	106	6.73	2.12	4.61 (2.56, 6.65)	259	2.46
Nausea, vomiting[a]	59	73	5.15	1.46	3.69 (1.91, 5.48)	167	1.58
Dizziness[a]	57	86	4.98	1.72	3.26 (1.49, 5.02)	175	1.66
Headache, migraine[a]	57	60	4.98	1.20	3.78 (2.03, 5.52)	150	1.42
Oedema	55	163	4.80	3.26	1.54 (−0.25, 3.34)	329	3.12
Diarrhoea[a]	51	82	4.45	1.64	2.81 (1.14, 4.49)	181	1.72
Intolerance[a,b]	46	46	4.02	0.92	3.10 (1.53, 4.66)	102	0.97
Weight gain[a]	41	101	3.58	2.02	1.56 (0.03, 3.09)	226	2.14
Pain joint	35	120	3.06	2.40	0.66 (−0.79, 210)	226	2.14
Pain abdomen	31	71	2.71	1.42	1.29 (−0.04, 2.61)	140	1.33
Upper respiratory tract infection	31	102	2.71	2.04	0.67 (−0.69, 2.02)	211	2.00
Lower respiratory tract infection	29	120	2.53	2.40	0.13 (−1.20, 1.47)	233	2.21
Liver function test abnormal[a]	28	48	2.45	0.96	1.50 (0.24, 2.73)	107	1.01
Unspecified adverse effects[a,b]	26	36	2.27	0.72	1.55 (0.36, 2.74)	66	0.63

a Events for which there was a positive significant difference between month 1 (ID_1) and months 2–6 ($ID_{2–6}$).

b The general practitioner did not specify the exact clinical event, but reported that the patient had intolerance/unspecified adverse effects with pioglitazone.

ID_1 = incidence density for each event during the first month of treatment; **$ID_{2–6}$** = incidence density for each event during treatment months 2–6; **$ID_1–ID_{2–6}$** = arithmetic difference between ID_1 and $ID_{2–6}$; **ID_A** = incidence density for each event for the total treatment period; **N_1** = number of first reports of each event during the first month of treatment; **$N_{2–6}$** = number of first reports of each event during treatment in months 2–6; **N_A** = number of first reports of each event during the total treatment period.

Table VI. Summary of events of interest during treatment with pioglitazone

Event	N_A (% of cohort)	N_1	ID_1	Number given as reason for stopping pioglitazone (% of total events reported)	Frequency of adverse reactions in SPC[5]
Oedema	329 (2.57)	55	4.80	121 (36.78)	Information from double-blind studies: oedema seen in 5.9% of patients treated with pioglitazone + sulphonylurea and in 6.0% treated with pioglitazone + metformin
Weight gain	226 (1.77)	41	3.58	118 (52.21)	Common[a] (pioglitazone + metformin/ sulphonylurea)
Abnormal liver function tests	107 (0.84)	28	2.45	63 (58.88)	Post-marketing experience: isolated cases of elevated liver enzymes Clinical trials: incidence of all liver and biliary adverse events, pioglitazone 1.1% and placebo 0.9%
Cardiac failure	98 (0.77)	14	1.22	25 (25.51)	Incidence of 1.1% reported when pioglitazone used with insulin
Anaemia	42 (0.33)	5	0.44	5 (11.90)	Common[a] (pioglitazone + metformin)

a Common >1/100, <1/10.

ID_1 = incidence density for each event during the first month of treatment; **N_A** = number of first reports of each event during the total treatment period; **N_1** = number of first reports of each event during the first month of treatment; **SPC** = summary of product characteristics.

is given in table VII. Of the 118 events, 36 (0.3% of cohort) events were known to be events of raised enzymes (ALT or AST) and for 47 events the GP had not specified which component of the LFT panel had been deranged.

Deaths

The total number of deaths reported in this cohort was 221 (1.73%). The cause of death was established for 160 (72.4%) of these cases. Of these 160 deaths, 152 were reported during treatment with pioglitazone, but for six patients it was not known whether they were continuing pioglitazone at the time of death. None of the deaths were attributed to pioglitazone by the reporting GP.

There were 81 deaths related to cardiovascular causes (79 patients taking pioglitazone and two not known whether taking pioglitazone at time of death). This included 48 deaths related to ischaemic heart disease/myocardial infarction (IHD/MI) [47 were during treatment with pioglitazone] and 15 deaths due to cerebrovascular accident/cerebral haemorrhage/cerebral arteriosclerosis (14 were during treatment with pioglitazone). Thus, deaths related to cardiovascular causes accounted for 36.7% (81 of 221) of all deaths in the cohort, with IHD/MI (n = 48) being the most frequently reported cause.

There were 28 patients where cardiac failure was reported as a cause of death. Of these 28, cardiac failure was the only mentioned cause of death for five patients; for the remaining patients, 14 had IHD/MI, two had hypertensive heart disease, one

Table VII. Components of the liver function test (LFT) panel reported to be abnormal

Component of LFT	Number
Raised ALT	22
Raised γ-GT	18
Raised alkaline phosphatase	10
Raised bilirubin	7
Raised AST	5
Raised AST and ALT	4
Raised AST and alkaline phosphatase	2
Raised ALT and γ-GT	2
Raised AST and γ-GT	1
Deranged LFT (component unspecified)	47
Total	**118**

γ-GT = γ-glutamyl transpeptidase.

had cardiomyopathy and six had other (non-cardiac) causes of death reported.

Pregnancies

There were two pregnancies reported to be exposed to pioglitazone. One resulted in a full-term, live born, neonate with no congenital abnormalities; this patient was exposed to pioglitazone during the first month of pregnancy.

In the second case, the exposure to pioglitazone had been in the first 6 weeks of pregnancy. The neonate was born at 32 weeks of gestation, with sirenomelia, congenital malformations associated with pulmonary hypoplasia and hyaline membrane disease. The neonate died 3 hours after birth.

Discussion

This PEM study examined the use of pioglitazone prescribed in primary-care conditions in England in 12 772 patients. This paper provides a descriptive analysis of this population with a summary of the events reported during the period in which these patients were observed.

PEM is an observational cohort technique, used for the post-marketing surveillance of newly marketed drugs. One of the major strengths of PEM is that it uses data from day-to-day clinical practice. There are no exclusion criteria, i.e. all patients in England prescribed and dispensed the study drug during the period of the study are eligible for inclusion. The PEM cohort comprises all patients for whom a completed questionnaire was returned by the GP. This resulted in a cohort with a wide age range of patients and without exclusion of those with co-morbidities or those on co-prescribed medicines. Furthermore, the methodology of PEM is non-interventional, in that it does not influence the prescribing practices of GPs, as the patients are identified from dispensed prescriptions. Another strength of the methodology is that PEM is based upon 'event' monitoring and is therefore capable of identifying signals for events that were not necessarily suspected as being ADRs associated with the drug being studied. The methodology also readily permits follow-up for additional data on events of interest and also in case of death to ascertain the cause of death.

A limitation of this study was the low response rate of 55%. However, this is similar to the average response rate of 56% for the 93 completed PEM studies in England. It is not possible to assess the effect of low-response rate on the results of this study. However, we have no reason to believe that non-response bias was differential, i.e. GPs' response to the questionnaire was affected by the event profiles of their patients.

Under-reporting of events, including serious or fatal events, is possible in PEM. Another limitation of the study, as in any observational study, is that it was not possible to estimate the degree of compliance with the prescribed medication.

The median age of the cohort was 62 years, with similar proportions of men and women. In the majority of these patients, the starting daily dose was either 15 mg or 30 mg (99.8% of specified doses), which is as per the recommendations of the SPC. The major reported indication for the use of pioglitazone was, as expected, the licensed indication of diabetes. For a few patients, unlicensed indications such as polycystic disease of the ovary and lipodystrophy were reported. Pioglitazone has been shown to improve insulin sensitivity as well as ovulation rates in women with polycystic ovary syndrome[25] and has also been tried with success in a patient with HIV-associated lipodystrophy syndrome.[26]

Although pioglitazone was not recommended as monotherapy and was contraindicated in combination with insulin at the time of launch (initial SPC [2002]),[5] in this study 2.2% and 3.7% patients were prescribed pioglitazone as monotherapy and as pioglitazone in combination with insulin, respectively. Pioglitazone was later licensed for use as monother-

apy (2003) and for use in combination with insulin (2007).[27] A high proportion (18%) of patients were prescribed triple therapy, pioglitazone with metformin and a sulphonylurea. This combination was also not licensed at the time of launch,[5] but was included in the SPC[27] in 2006.

Five events, 'oedema', 'weight gain', 'abnormal LFTs', 'cardiac failure' and 'anaemia', from the 'special warnings and precautions for use' section of the pioglitazone SPC, were considered as events of interest. None of these events were reported at a frequency higher than that given in the SPC. Of the weight gain and abnormal LFT events reported, a high proportion were reasons for stopping pioglitazone (52% and 59%, respectively).

An event was coded as an ADR if the GP reported that the event was suspected to be due to the drug. However, it should be noted that the frequency of suspected ADRs reported in this study may be an underestimate because the GPs may not always know or may not always indicate that the event was an ADR. The frequency of suspected ADRs reported did not exceed the frequency given in the SPC of pioglitazone.

Events documented as reasons for discontinuing pioglitazone are important. Although they do not imply causality, they give an indication about the extent to which a particular event may have affected the patient, in that it caused the GP or the patient to stop treatment with the drug. 'Impaired/poor control of diabetes' and 'not effective' were the most frequently reported reasons for discontinuing pioglitazone. 'Oedema' and 'weight gain' also appeared high on the list.

Signals for possible adverse events to pioglitazone were identified through analysis of IDs for each event and medical review to identify events of interest. All except two terms ('nausea/vomiting' and 'diarrhoea') that were identified as early onset adverse events associated with pioglitazone, were given in the SPC of pioglitazone.[5] 'Abnormal LFTs' and 'weight gain' were also found to be early onset adverse events associated with pioglitazone use.

Results from the PROactive study[28] suggest that pioglitazone significantly reduces the occurrence of fatal and nonfatal MI and acute coronary syndrome in high-risk patients with type 2 diabetes and previous MI, contributing to the debate generated by the rosiglitazone meta-analysis.[16] Similarly, a meta-analysis of 19 clinical trials showed a lower risk of death, MI or stroke associated with pioglitazone.[17] Furthermore, a comparative study showed that pioglitazone reduced the relative risk of hospitalization with acute MI in patients with type 2 diabetes compared with rosiglitazone.[29] Although IHD/MI were the most frequently reported causes of death in this cohort, we had no further information on these cases to enable us to assess whether the deaths were causally associated with pioglitazone use.

Of the two pregnant women reported to be exposed to pioglitazone, one pregnancy (exposed to pioglitazone for first 6 weeks) resulted in a premature neonate with sirenomelia, congenital malformations associated with pulmonary hypoplasia and hyaline membrane disease. The neonate died 3 hours after birth. Sirenomelia (meaning 'mermaid-like' habitus) is characterized by fusion of the lower extremities. It is thought to be due to deficiency of caudal development, which takes place in the third week of gestation.[30] Although its aetiology is unknown, diabetes has been suggested as one of the possible causative factors.[31] Pioglitazone has been shown to cause fetal growth restriction in animal studies,[5] but whether it could have lead to the above mentioned congenital abnormality is difficult to assess. The number of pregnancies in this study is too small to draw any conclusions on the possible effect of pioglitazone on the outcome of human pregnancy.

Conclusion

This study examined the use of pioglitazone in 12 772 patients in the community setting and reflects 'real-world' use. Pioglitazone was considered to be a reasonably well tolerated drug with the main reasons for discontinuation being reasons related to ineffectiveness. The frequency of individual ADRs reported in this study did not exceed the frequency in the SPC of pioglitazone. However, amongst the frequently reported suspected ADRs, 'nausea/vomiting' and 'diarrhoea' are not listed in the SPC. Off-label use of pioglitazone (initial SPC [2000]: use as monotherapy; with insulin; as part of triple therapy) was observed. These have been included in the SPC since launch. Further research is required to assess whether the risk of myocardial infarction and deaths due to cardiovascular causes, is a TZD class effect. Results from this study should be taken into account with other clinical and pharmacoepidemiological studies.

Acknowledgements

The Drug Safety Research Unit (DSRU) is an independent, registered charity (No. 327206) that works in association with the University of Portsmouth, UK. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The unit has received such funds from the manufacturer of pioglitazone. Prof. Shakir has participated on a data safety monitoring board for Takeda, for which he reviewed an honorarium. Drs Kasliwal and Wilton have no conflicts of interest that are directly relevant to the content of this article.

We are grateful to the primary-care physicians in England, the Prescriptions Pricing Division (a part of the National Health Service Business Services Authority) and the health authorities of England for their important participation in the PEM study for pioglitazone. We also thank Mr Shayne Freemantle and Mrs Neera Soor for data management and information technology support.

References

1. Lenhard JM. PPAR gamma/RXR as a molecular target for diabetes. Receptors Channels 2001; 7 (4): 249-58
2. Wise J. Diabetes drug withdrawn after reports of hepatic events [letter]. BMJ 1997 Dec 13; 315 (7122): 1564
3. Scheen AJ. Hepatotoxicity with thiazolidinediones: is it a class effect? Drug Saf 2001; 24 (12): 873-88
4. Tolman KG. Thiazolidinedione hepatotoxicity: a class effect? Int J Clin Pract Suppl 2000 Oct; (113): 29-34
5. Takeda Europe R & D Centre Limited. Summary of Product Characteristics for Actos (pioglitazone hydrochloride); 2000 Oct
6. May LD, Lefkowitch JH, Kram MT, et al. Mixed hepatocellular-cholestatic liver injury after pioglitazone therapy. Ann Intern Med 2002 Mar 19; 136 (6): 449-52
7. Pinto AG, Cummings OW, Chalasani N. Severe but reversible cholestatic liver injury after pioglitazone therapy [letter]. Ann Intern Med 2002 Nov 19; 137 (10): 857
8. Maeda K. Hepatocellular injury in a patient receiving pioglitazone [letter]. Ann Intern Med 2001 Aug 21; 135 (4): 306
9. Chase MP, Yarze JC. Pioglitazone-associated fulminant hepatic failure. Am J Gastroenterol 2002 Feb; 97 (2): 502-3
10. Nagasaka S, Abe T, Kawakami A, et al. Pioglitazone-induced hepatic injury in a patient previously receiving troglitazone with success. Diabet Med 2002 Apr; 19 (4): 347-8
11. Farley-Hills E, Sivasankar R, Martin M. Fatal liver failure associated with pioglitazone [letter]. BMJ 2004 Aug 21; 329 (7463): 429
12. Macfarlane DP, Fisher M. Thiazolidinediones in patients with diabetes mellitus and heart failure: implications of emerging data. Am J Cardiovasc Drugs 2006; 6 (5): 297-304
13. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005 Oct 8; 366 (9493): 1279-89
14. Jamieson A, Abousleiman Y. Thiazolidinedione-associated congestive heart failure and pulmonary edema. Mayo Clin Proc 2004 Apr; 79 (4): 571-7
15. Kermani A, Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. Mayo Clin Proc 2003 Sep; 78 (9): 1088-91
16. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007 Jun 14; 356 (24): 2457-71
17. Lincoff AM, Wolski K, Nicholls SJ, et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007 Sep 12; 298 (10): 1180-8
18. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998 Sep; 21 (9): 1414-31
19. Shakir S. Prescription-event monitoring. In: Strom BL, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd, 2005: 203-16
20. Strom B. Sample size considerations for pharmacoepidemiology studies. In: Strom B, editor. Pharmacoepidemiology. 2nd ed. Chichester: John Wiley & Sons, 1994
21. Machin D, Campbell M, Fayers P, et al. Chapter 7. Post marketing surveillance. Table 7.1. Sample sizes required to observe a single adverse reaction with a given probability and anticipated

incidence. In: Machin D, editor. Sample size tables for clinical studies. 2nd ed. Oxford: Blackwell Science Ltd, 1997: 150

22. CIOMS W. International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002 [online]. Available from URL: http://www.cioms.ch/frame_guidelines_nov_2002.htm [Accessed 2008 Jul 26]
23. Royal College of Physicians of London. Guidelines on the practice of Ethical Committees in Medical Research involving Human Subjects. 3rd ed. London: Royal College of Physicians, 1996
24. Department of Health. Supplementary operational guidelines for NHS Research Ethics Committees – November 2000. Multi-centre research in the NHS the process of ethical review when there is no local researcher [online]. Available from URL: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006696. [Accessed 2008 Jul 26]
25. Brettenthaler N, De GC, Huber PR, et al. Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004 Aug; 89 (8): 3835-40
26. Prasithsirikul W, Bunnag P. Improvement of fat redistribution, insulin resistance and hepatic fatty infiltration in HIV-associated lipodystrophy syndrome by pioglitazone: a case report. J Med Assoc Thai 2004 Feb; 87 (2): 166-72
27. Takeda UK Limited. Summary of Product Characteristics for Actos (pioglitazone hydrochloride), 2007 Aug [online]. Available from URL: http://emc.medicines.org.uk/industry/default.asp [Accessed 2008 Aug 19]
28. Erdmann E, Dormandy JA, Charbonnel B, et al. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. J Am Coll Cardiol 2007 May 1; 49 (17): 1772-80
29. Gerrits CM, Bhattacharya M, Manthena S, et al. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. Pharmacoepidemiol Drug Saf 2007 Oct; 16 (10): 1065-71
30. Larsen WJ. Human embryology. 2nd ed. New York: Churchill Livingstone Inc., 1997: 62-3
31. Reece EA, Hobbins JC. Diabetic embryopathy: pathogenesis, prenatal diagnosis and prevention. Obstet Gynecol Surv 1986 Jun; 41 (6): 325-35

Correspondence: Dr *Rachna Kasliwal*, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton, SO31 1AA, United Kingdom.
E-mail: rachnakasliwal@hotmail.com