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Safety and tolerability of pioglitazone, metformin, and gliclazide in the treatment of type 2 diabetes

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Abstract

This analysis compares the safety and tolerability of pioglitazone (a thiazolidinedione), metformin (a biguanide), and gliclazide (a sulfonylurea). Data collected from four 1-year, double-blind studies comparing treatment of over 3700 patients with type 2 diabetes with pioglitazone, metformin, or gliclazide have been combined to provide comparative tolerability and safety profiles. All treatments were well tolerated with approximately 6% of patients withdrawing from treatment because of side-effects. The side-effects profile varied between treatments, with pioglitazone being associated with edema, metformin with gastrointestinal side-effects, and gliclazide with hypoglycemia. Cardiovascular outcome was similar with all treatments, with no excess reports of cardiac failure with pioglitazone treatment. Both pioglitazone and gliclazide resulted in mean weight gain, whilst with metformin there was mean weight loss. Mean liver enzyme values decreased with pioglitazone and to a lesser extent with metformin. With gliclazide, mean liver enzyme values increased. The expected small decreases in mean hemoglobin and hematocrit seen with pioglitazone also occurred with metformin and to a lesser degree with gliclazide. The results show that all three drugs are safe, but that tolerability profiles vary. Each treatment provides an alternative therapy for type 2 diabetes, dependent on the particular needs of individual patients.

Keywords: Gliclazide; Metformin; Pioglitazone; Safety and tolerability

1. Introduction

Type 2 diabetes is a disease not only affecting glucose metabolism, but a syndrome involving amongst others, lipid disturbances and abnormal vascular function. The hypothesis first proposed by Reaven [1,2] that insulin resistance is involved in many of these abnormalities, has now gained widespread consensus.

The thiazolidinediones improve both glycemic control and specific elements of dyslipidemia in type 2 diabetes by interacting directly with the peroxisome proliferator gamma receptor to reduce insulin resistance [3]. Despite this, there has been some reluctance to prescribe these agents widely in clinical practice.

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The main reasons for this are concerns about safety of the class. The first agent, troglitazone, was withdrawn from the market because of rare, but serious hepatotoxicity in susceptible patients. In addition, edema occurs in a proportion of patients during treatment with thiazolidinediones. This has led to suggestion that fluid retention may lead to precipitation of heart failure and increased cardiovascular risk in a patient group already compromised [4].

Pioglitazone is one of two thiazolidinediones marketed in Europe shortly after the withdrawal of troglitazone [5]. Although placebo-controlled trials with this compound showed no evidence of hepatotoxicity or increased incidence of congestive heart failure [6], the trials were of relatively short-term duration and direct comparisons with other oral glucose-lowering agents were not possible.

Recently, four large 1-year, double-blind trials comparing the effects of pioglitazone treatment as monotherapy or combination therapy with either a biguanide (metformin) or a sulfonylurea (gliclazide) have been completed [7–10]. Safety data collected from these trials allow comparison of the safety and tolerability profile of pioglitazone with the older, established oral glucose-lowering agents.

2. Research design and methods

The trials were conducted in hospital or general practice centers in Europe, Canada, and Australia and recruited patients aged $\geq$35 and $\leq$75 years with inadequately controlled type 2 diabetes. All patients gave written, informed consent to participate in the study and local Ethics Committee approval was obtained for each site. The study was conducted in accordance with the Declaration of Helsinki and the requirements of Good Clinical Practice of the European Community.

Major exclusion criteria were type 1 diabetes, use of insulin, concomitant congestive heart chronic pancreatitis; familial polyposis coli; malignant disease in the previous 10 years; or myocardial infarction, transient ischemic attacks, or stroke in the previous 6 months. Patients with alanine aminotransferase (ALT) above three times the upper limit of normal (ULN) and serum creatinine $>$ 135 μmol/L were also excluded. Two studies compared pioglitazone, metformin, or gliclazide as monotherapy treatments in patients naïve to oral glucose-lowering therapy (1194 and 1250 patients, respectively) [7,8]. Two others compared combination therapy treatments. In one, pioglitazone or metformin was added to treatment of patients with type 2 diabetes inadequately controlled with a sulfonylurea (639 patients) [9]. In the other, pioglitazone or gliclazide was added to treatment of patients inadequately controlled with metformin treatment (630 patients) [10].

Patients were randomized to treatment after screening and all treatments were blinded to patient and investigator using a double-dummy technique. Treatments were force-titrated, dependent on tolerability, over the first 8–16 weeks to maximum doses of 45 mg of pioglitazone daily, 2550 mg of metformin daily and 320 mg of gliclazide daily. The dose of any medication could not be changed after this titration period. Routine safety data, including adverse events, laboratory variables, electrocardiographs (ECGs), vital signs, and body weight were collected at each of the 2-monthly visits over 1 year. Patients were instructed to adhere to a disease- and weight-orientated diet throughout the study. Dietary advice was given at baseline with the target of body weight normalization and supply of individually appropriate calories and nutrients. If body weight increased more than 5% at any stage or HbA_{1c} increased to greater than 9% after completed dose titration, patients were given further intensive dietary counselling.

To obtain an overview of comparative safety and tolerability, data from individual trials have been combined when clinically appropriate. In all other cases, data from individual trials are presented. Descriptive statistics were used to summarize changes in baseline characteristics, laboratory variables, and the reporting of adverse events. All adverse events were coded according to MedDRA® terminology and were classified according to severity (mild, moderate, or severe) and seriousness (leading to death or permanent disability or requiring hospitalization).

3. Results

3.1. Baseline data

In total, the trials randomized 3713 patients. Demographic data for pioglitazone, gliclazide, and

Table 1
Baseline demographic data and % of patients with the most commonly reported concomitant diseases at baseline

	Pioglitazone $n = 1857$	Metformin $n = 917$	Gliclazide $n = 939$
Baseline characteristics			
Age (S.D.) (years)	57 (9.4)	58 (9.1)	56 (9.4)
Male:female	55:45	56:44	58:42
Weight (S.D.) (kg)	89.2 (16.8)	88.0 (16.0)	89.6 (17.2)
BMI (S.D.) (kg/m^2)	31.4 (5.3)	30.9 (5.1)	31.2 (5.4)
Duration of diabetes (S.D.) (years)	4.2 (4.8)	4.4 (4.9)	3.8 (4.4)
HbA_{1C} (S.D.) (%)	8.7 (1.0)	8.7 (0.9)	8.6 (1.0)
Fasting glucose (S.D.) (mmol/L)	11.4 (2.8)	11.5 (2.8)	11.2 (2.8)
Percentage of patients with the most commonly reported concomitant diseases at baseline			
Vascular (including hypertension)	58.8%	58.6%	55.1%
Musculoskeletal/connective tissue	20.2%	17.2%	20.7%
Cardiac	16.2%	15.4%	13.0%
Nervous system	8.7%	8.7%	12.1%
Gastrointestinal	8.2%	7.5%	12.7%
Hepatobiliary	5.9%	4.5%	4.9%

metformin patients (regardless of use as monotherapy or combination therapy) and the most commonly reported concomitant diseases in the different populations are presented in Table 1. The data for metformin are derived from the metformin monotherapy and metformin add-on to sulfonylurea groups and the data for gliclazide are derived from the gliclazide monotherapy and gliclazide add-on to metformin groups. Almost all patients were Caucasian (>95%). Although the patients were well matched, those receiving gliclazide were slightly younger and had a slightly shorter duration of diabetes than those receiving pioglitazone or metformin, and this was reflected in slightly less cardiac and vascular (mainly hypertension) concomitant disease in this group. In the add-on to sulfonylurea study, the main sulfonylureas used as background medication were glibenclamide (41%), gliclazide (31%), and glimepiride (18%).

3.2. Changes in glycemic control

Changes from baseline to week 52 in glycated hemoglobin A_{1C} (HbA_{1C}) and fasting glucose were similar between study treatments in the various trials (Table 2) [7–10].

3.3. Adverse events

Table 3 gives an overview of tolerability and adverse events in the different treatment groups. More patients with pioglitazone than metformin or gliclazide achieved the maximum dose prescribed in the protocol, although the numbers of patients actually withdrawing from treatment because of adverse events were similar with all treatments. At the end of the titration period in the monotherapy studies, the mean doses were: 43 mg/day pioglitazone, 2124 mg/day

Table 2
Changes from baseline to week 52 in glycated hemoglobin A_{1c} (HbA_{1C}) and fasting glucose

	Monotherapy				Combination therapy			
	Study 1		Study 2		+Sulfonylurea		+Metformin	
	Pio[a] ($n = 597$)	Met ($n = 597$)	Pio ($n = 624$)	Glic ($n = 626$)	Pio ($n = 319$)	Met ($n = 320$)	Pio ($n = 317$)	Glic ($n = 313$)
Change from baseline in mean HbA_{1c} (%)	−1.41	−1.50	−1.43	−1.35	−1.20	−1.36	−0.99	−1.01
Change from baseline in mean fasting glucose (mmol/L)	−2.5	−2.2	−2.4	−2.0	−2.2	−2.3	−1.9	−1.7

[a] Pio: pioglitazone; Met: metformin; Glic: gliclazide.

Table 3
Overview of tolerability and adverse events

Patients	Pioglitazone (n = 1857)	Metformin (n = 917)	Gliclazide (n = 939)
Percent titrated to maximum dose	77%	59%	30%
With adverse event	61.7%	59.7%	66.2%
With adverse event leading to withdrawal	5.9%	6.2%	5.6%
With serious adverse event	5.9%	7.4%	5.5%
With fatal adverse event	0.4%	0.4%	0.6%

metformin, and 198 mg/day gliclazide. In the combination studies, the mean doses were 38 mg/day pioglitazone, 2074 mg/day metformin, and 212 mg/day gliclazide. Patients treated with gliclazide had a slightly higher reporting rate of adverse events, whilst patients receiving metformin reported slightly more serious adverse events. The individually reported adverse events varied in the different trials (Table 4). The most commonly reported adverse events were symptoms consistent with hypoglycemia (as assessed by the investigator), most often reported with sulfonylurea treatments. Diarrhea was reported more often with metformin. Edema was reported more often with pioglitazone at incidence rates of two to three times those reported with metformin or gliclazide. Despite the occurrence of edema with pioglitazone, reports of congestive cardiac failure were rare and occurred in 0.6% of pioglitazone-treated patients and 0.5% of metformin- and gliclazide-treated patients. There was no clear difference in reporting rates of other commonly reported adverse events, although nausea appeared to be reported slightly more often with metformin than with pioglitazone or gliclazide. Hypertension was reported more often with the metformin/sulfonylurea combinations than with pioglitazone/metformin or pioglitazone/sulfonylurea combinations.

Combining data from monotherapy and combination trials, there were no major differences in the reporting rates and the nature of serious adverse events (mainly hospitalizations) between pioglitazone, metformin, and gliclazide. For all treatments, cardiovascular events were the most common reason for hospitalization (pioglitazone 1.2%, metformin 1.4%, and gliclazide 1.0%). Infections were the reason for hospitalization in 0.7% of pioglitazone-, 0.8% of metformin-, and 1.5% of gliclazide-treated patients. Neoplasms were reported as serious adverse events in 0.5% of pioglitazone and 0.4% of metformin and gliclazide patients. Hypoglycemia caused hospitalization in only one patient treated with a combination of metformin and gliclazide.

None of the adverse events leading to death was considered to be related to study medication by investigators. The seven deaths in the pioglitazone

Table 4
Most commonly reported adverse events (% patients) in the different trials

	Monotherapy				Combination therapy			
	Study 1		Study 2		+Sulfonylurea		+Metformin	
	Pio[a] (n = 597)	Met (n = 597)	Pio (n = 624)	Glic (n = 626)	Pio (n = 319)	Met (n = 320)	Pio (n = 317)	Glic (n = 313)
Hypoglycemia	1.5	1.3	3.5	10.1	10.7	14.1	1.3	11.2
Diarrhea	3.2	11.1	2.9	3.4	2.5	12.5	1.3	3.8
Headache	4.4	2.3	8.7	8.9	3.8	3.4	4.1	3.8
Edema	6.7	1.8	8.1	4.2	6.9	1.6	6.3	2.2
Nasopharyngitis	4.2	3.2	6.6	5.3	2.2	2.2	2.2	3.5
Arthralgia	1.5	2.0	7.1	6.2	4.1	2.8	1.6	3.8
Back pain	2.3	2.8	6.4	5.0	1.6	3.8	3.2	2.9
Nausea	2.3	4.2	4.3	5.1	2.5	3.1	2.2	2.2
Dizziness	2.3	1.8	4.0	6.5	1.3	2.8	2.8	1.3
Hypertension	2.5	2.8	3.4	3.8	0.9	3.8	1.9	4.5

[a] Pio: pioglitazone; Met: metformin; Glic: gliclazide.

groups (monotherapy or add-on therapy) were: one due to cardiac failure, two due to a cerebrovascular accident, one due to myocardial infarction, one due to a ruptured aortic aneurysm, one sudden death, and one from metastases to the liver from an unknown primary. In the metformin groups (monotherapy or add-on therapy), causes of the four deaths were: one patient suicide, one cardiac failure, one meningioma, and one pancreatic carcinoma. In the gliclazide groups (monotherapy and add-on therapy), there were six deaths: two reported as sudden deaths and a further two sudden deaths reported as cause unknown and probable myocardial infarction, one death from a suspected pulmonary embolism, and one death from a combination of emphysema, coronary artery atherosclerosis, and coronary artery thrombosis.

3.4. Laboratory values

Effects of treatment on hematological variables are shown in Table 5. Pioglitazone and metformin treatments resulted in similar small reductions in hemoglobin and hematocrit, whereas effects of gliclazide were less pronounced. Both metformin and gliclazide treatments were associated with increases in white cells, whereas pioglitazone had virtually no effect. Platelet counts showed increases with all treatments, the least with pioglitazone.

Liver testing results (Table 5) showed mean decreases in all enzymes with pioglitazone, whilst gliclazide treatment was associated with small mean increases. In general, metformin was associated with similar, but less marked, changes to pioglitazone. The numbers of patients with a large increase in a liver test (>3 ULN) were similar with all treatments.

Effects of treatment on blood pressure were minimal with small decreases in mean diastolic pressures with all treatments (pioglitazone: -1.4 ± 9.2 mmHg; metformin: -1.2 ± 8.8 mmHg; gliclazide: -0.6 ± 9.4 mmHg). With gliclazide treatment, there were slightly more patients with newly diagnosed hypertension or worsening of hypertension (7.6%) compared with pioglitazone (5.3%) or metformin treatments (4.7%).

3.5. Body weight

Mean weight increased with both pioglitazone and gliclazide treatment, but decreased with metformin (Table 6). The greatest increase in mean weight was 2.8 kg seen with use of pioglitazone as monotherapy and in combination with a sulfonylurea. Despite weight increases, improvements in glycemic control

Table 5
Effects of pioglitazone, metformin, and gliclazide on hematological variables and liver function tests, and numbers of patients with large increases in liver tests

	Pioglitazone ($n = 1857$)	Metformin ($n = 917$)	Gliclazide ($n = 939$)
Hemoglobin (S.D.)[a] (g/dL)	−0.59 (0.86)	−0.48 (0.84)	−0.23 (0.88)
Hematocrit (S.D.)[a] (%)	−1.9 (2.9)	−1.7 (2.8)	−0.6 (2.9)
White cells (S.D.)[a] ($\times 10^9$ L^{-1})	−0.25 (1.7)	0.49 (1.8)	0.31 (1.7)
Platelets (S.D.)[a] ($\times 10^9$ L^{-1})	3 (40)	17 (44)	7 (38)
ALT			
Mean % change (S.D.)[b]	−16.6 (59.6)	−1.2 (45.5)	9.3 (44.1)
% Patients >3 ULN	0.9	1.9	1.1
AST			
Mean % change (S.D.)[b]	−3.1 (39.1)	1.2 (35.8)	3.3 (35.5)
% Patients >3 ULN	0.5	0.7	0.3
GGT			
Mean % change (S.D.)[a]	−17.6 (112.1)	−8.7 (62.8)	7.5 (53.4)
% Patients >3 ULN	3.5	4.7	3.9
Alkaline phosphatase			
Mean % change (S.D.)[a]	−9.9 (20.2)	−12.0 (18.2)	3.1 (19.5)
% Patients >3 ULN	0	0	0

[a] Data are change (±S.D.) from baseline.
[b] Data are % relative change from baseline.

Table 6
Changes in weight in the different trials

	Monotherapy				Combination therapy			
	Study 1		Study 2		+ sulfonylurea		+ metformin	
	Pioglitazone ($n = 597$)	Metformin ($n = 597$)	Pioglitazone ($n = 646$)	Gliclazide ($n = 626$)	Pioglitazone ($n = 319$)	Metformin ($n = 320$)	Pioglitazone ($n = 317$)	Gliclazide ($n = 313$)
Mean weight change (S.D.) (kg)	1.9 (4.6)	−2.5 (4.3)	2.8 (5.2)	1.9 (4.5)	2.8 (4.2)	−1.0 (3.5)	1.5 (4.6)	1.3 (4.1)
Patients gaining weight	65.2%	23.3%	71.8%	67.4%	69.0%	31.1%	60.0%	61.0%

were maintained over the year of the trials with pioglitazone treatment, whereas with gliclazide there was a gradual increase in HbA_{1c} levels over time. The percentages of patients with weight gain were similar with pioglitazone and gliclazide, whereas this was considerably lower with metformin. With pioglitazone, weight gain was greatest in patients with the highest baseline weights, whereas with metformin weight loss was greatest in the heaviest patients.

4. Discussion

The results from these four large studies provide the first comparison of safety and tolerability of drugs representing the three most important classes of oral glucose-lowering therapies. The results confirm the safety of all treatments and no unexpected organ toxicities were reported from the studies. This is a particularly important finding with pioglitazone as, for the combination studies, the dose of 45 mg is higher than that previously prescribed in reports of earlier studies [11,12]. This dose appeared well tolerated both as monotherapy and combination therapy, as judged by the large percentage of patients reaching and maintaining treatment on this higher dose. The highest recommended doses of metformin and gliclazide were achieved by a lesser proportion of patients than with pioglitazone, mainly due to tolerability issues of gastrointestinal side effects and hypoglycemia, respectively. However, despite this, all treatments produced similar improvements in glycaemic control.

The side-effect profiles of the three drugs confirm those previously reported [6,13,14]. Hypoglycemia was relatively common with gliclazide treatment, although there was only one case requiring hospitalization, and most reports were only mild or moderate in intensity, thus allowing patients to continue treatment with dose-adjustment. Gastrointestinal side-effects, particularly diarrhea, were common with metformin, but the relatively slow dose escalation with dose adjustment used in these trials, demonstrated that this well-known side-effect need not lead to an excess of withdrawals from treatment with this drug. Pioglitazone treatment resulted in reports of edema in less than 10% of patients, but this was generally mild or moderate and only very rarely resulted in withdrawal of treatment. There have been reports of massive edema and very rapid weight gain with other thiazolidinediones [15], but this was not seen in the cohort of patients treated with pioglitazone in this analysis. Equally, any fluid retention associated with edema did not manifest in any excess of reports of CHF with pioglitazone compared with a sulfonylurea or metformin over 1 year's treatment. This is supported by the recent joint consensus statement developed by the American Heart Association and the American Diabetes Association [16]. The use of thiazolidinediones in patients with pre-existing heart failure and in those who developed edema or unexpected weight gain during thiazolidinedione therapy was evaluated and the statement gives safety guidelines on the use of thiazolidinediones in patients with cardiac failure, but explains that the cardiac heart failure risk is low given the large number of patients managed with thiazolidinediones.

The effects of treatments on hematological variables were surprising. Both pioglitazone and metformin had effects to cause small and similar decreases within the normal range in hemoglobin and hematocrit. This effect with pioglitazone has been ascribed to hemodilution [17,18], which in itself has been proposed to be secondary to the vasodilation [6] that occurs with thiazolidinediones [19]. The effect of metformin has not been widely reported previously. Whilst indivi-

dual cases of megaloblastic anemia due to reduction of B_{12} and folate are known to occur with metformin [20], this cannot be the mechanism of the overall population effect seen in these trials. It is possible that metformin may also produce its effects secondary to vasodilation, which has been demonstrated in animals [21]. However, in addition, at least part of the effects of pioglitazone and metformin may simply be due to improvements in glycemic control as a smaller, but demonstrable effect was also seen with gliclazide treatment and hyperglycemia is considered a state of relative hemoconcentration. Small reductions in hemoglobin may reduce a hypercoagulable state and may be beneficial in terms of occlusive vascular disease. Metformin has been reported to have cardiovascular disease reductions greater than is explicable by its glucose-lowering effects alone [22].

Effects of pioglitazone on liver tests may represent an improvement in sub-clinical steatohepatitis, possibly secondary to reduced insulin resistance [23]. Such effects could potentially reduce the incidence of more severe liver disease seen in some patients with type 2 diabetes as has been suggested in pilot trials with other thiazolidinediones [24,25], although longer term trials, specifically, would be required to confirm this. Metformin had a similar, but smaller effect to pioglitazone, whereas with gliclazide treatment liver tests showed increases over time.

Blood pressure showed only minor decreases with treatment, although gliclazide treatment had the smallest effect and more patients treated with gliclazide required additional anti-hypertensive therapy during the trial than patients treated with pioglitazone or metformin. This may be as a result of vasodilatory action of the latter two drugs not seen with gliclazide.

Weight increase is a well-known consequence of both thiazolidinedione and sulfonylurea treatment, although the mechanisms involved are different. Thiazolidinedione treatment affects adipocyte differentiation directly, resulting in increases in subcutaneous fat in particular [26], although some effect to increase insulin-sensitive sodium retention with secondary fluid retention may also occur. Sulfonylureas increase weight at least partly by increasing glucose-independent plasma insulin levels, with a possible secondary effect on appetite and peripheral glucose metabolism. The mean weight changes seen in the current trials with pioglitazone therapy are somewhat less than those reported in other trials [6]. This may be the result of the stricter dietary advice that was given. Overall mean weight increase with pioglitazone was similar to that seen with gliclazide, but with both drugs weight gain was not a necessary concomitant of improved glycemic control, as about one quarter of patients lost weight during treatment with these drugs. With pioglitazone, weight gain was generally greatest in patients with the highest weight at baseline. The opposite was true of metformin, where weight loss was greatest in the heaviest patients.

Overall, the results of these analyses demonstrate that the three classes of oral glucose-lowering agents are safe in the treatment of type 2 diabetes. However, the tolerability profiles and specific organ effects of the different drugs do vary as would be expected from their differing mechanisms of action. The sulfonylurea chosen for these studies was gliclazide which represents only one of a relatively large number available for prescription. It is not clear that exactly the same profile would have been seen with others, although, in comparative trials of a number of sulfonylureas, gliclazde had better efficacy and tolerability than others and therefore may well represent the best in its class [27].

The choice of treatment in type 2 diabetes requires consideration, not only of the overall safety and tolerability of a drug, but in addition, the specific pathophysiological and risk profile of an individual patient and the likely effects of an individual drug on such profiles. The results from the present analysis suggest that pioglitazone, metformin, and gliclazide can all be considered as alternative safe approaches. The effects of these different approaches on long-term outcome in patients with type 2 diabetes will, however, require even larger, longer-term studies than those described in this paper. Such studies are currently underway [28].

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