Pioglitazone Hydrochloride Monotherapy Improves Glycemic Control in the Treatment of Patients With Type 2 Diabetes

A 6-month randomized placebo-controlled dose-response study

OBJECTIVE — To evaluate the efficacy and safety of four doses of pioglitazone monotherapy in the treatment of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — There were 408 patients randomized in this multicenter double-blind placebo-controlled clinical trial. Patients who had HbA₁c ≥7.0%, fasting plasma glucose (FPG) ≥140 mg/dl, and C-peptide >1 ng/ml were randomized to receive placebo or 7.5, 15, 30, or 45 mg pioglitazone administered once a day for 26 weeks.

RESULTS — Patients treated with 15, 30, or 45 mg pioglitazone had significant mean decreases in HbA₁c (range −1.00 to −1.60% difference from placebo) and FPG (−39.1 to −65.3 mg/dl difference from placebo). The decreases in FPG were observed as early as the second week of therapy; maximal decreases occurred after 10–14 weeks and were maintained until the end of therapy (week 26). In the 15-, 30-, or 45-mg pioglitazone groups, there were significant mean percent decreases in triglycerides, significant mean percent increases in HDL cholesterol, and only small percent changes in total cholesterol and LDL. The subset of patients naive to therapy had greater improvements in HbA₁c and FPG (difference from placebo of 2.55% and 65.3 mg/dl for the 45-mg group) compared with previously treated patients. The overall adverse event profile of pioglitazone was similar to that of placebo. There was no evidence of drug-induced hepatotoxicity or drug-induced elevations of alanine aminotransferase in levels in this study.

CONCLUSIONS — Pioglitazone monotherapy significantly improves HbA₁c and FPG while producing beneficial effects on serum lipids in patients with type 2 diabetes with no evidence of drug-induced hepatotoxicity.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; LOCF, last-observation-carried-forward; ULN, upper limit of normal.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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nonacademic sites. Each patient gave informed consent, and each participating center's investigational review board approved the study protocol before any patients entered the trial.

Patients had to have an HbA1c ≥7.0%, FPG ≥140 mg/dl, and fasting C-peptide >1 ng/ml to be enrolled in the study. Patients who used insulin chronically, had a history of ketoacidosis, or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded, as were patients with impaired liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, or alkaline phosphatase >2.5 × upper limit of normal [ULN]), impaired kidney function (serum creatinine >1.8 mg/dl), or anemia. Patients with a myocardial infarction, a coronary angioplasty or bypass graft, unstable angina, transient ischemic attacks, or a documented cerebrovascular accident within 6 months of the study were also excluded.

The double-blind treatment period of 26 weeks was preceded by a 6- to 8-week single-blind washout period, including 2 weeks for baseline measurements. At the end of the washout period, patients were to have an HbA1c ≥7.0%. Patients were then randomized to one of five parallel treatment groups: pioglitazone 7.5, 15, 30, or 45 mg or placebo. During the double-blind period, patients were seen every 2 weeks for the first 6 weeks and every 4 weeks for the remaining 20 weeks.

To eliminate the effect of weight loss and isolate the observation of any effect of pioglitazone, there were no required modifications of current dietary regimens during the study. In this study, the duration of disease (time since diagnosis) was not recorded because of its limitation in providing accurate information about onset of disease.

Patients who were receiving prior antidiabetic medication were required to discontinue their antidiabetic medication(s) at the beginning of the washout period (i.e., 8 weeks before receiving double-blind treatment). Patients who had never received pharmacological antidiabetic therapy were enrolled in the study and entered a 6-week single-blind run-in period.

Efficacy parameters evaluated in this study included glycemic and lipid measurements. A safety profile included a complete laboratory panel (chemistry, hematology, and urinalysis) and assessment of adverse events.

Efficacy measurements

All laboratory specimens were collected at the participating sites and shipped to a central laboratory (Covance Central Laboratory Services, Indianapolis, IN). Single samples were used for the fasting glucose measurements and fasting plasma lipid concentrations.

HbA1c and FPG constituted the glycemic assessments. HbA1c was measured by automated ion-exchange high-performance liquid chromatography (Bio-Rad Variant Analyzer). Blood glucose was measured by the hexokinase enzymatic method (Hitachi 747-200 analyzer).

Serum lipid measurements taken were triglycerides and cholesterol (total, HDL, and LDL). LDL cholesterol was calculated based on the method by Friedewald et al. (9), which limits the calculation to triglyceride levels <400 mg/dl.

Statistical analysis

Descriptive statistics were used to summarize demographic and baseline characteristics. Comparability of the treatment groups was assessed using a two-way analysis of variance, with treatment and pooled study center as factors for continuous variables (e.g., age), or the Cochran-Mantel-Haenszel test (general association version), stratified by pooled study center, for discrete variables (e.g., sex).

An intent-to-treat approach was used for the primary analysis. Additionally, a completer analysis (i.e., those patients who received double-blind study medication and the investigator indicated had completed the study) was also performed.

The primary time point for the efficacy analyses was week 26 (last postbaseline measurement obtained during the study, excluding follow-up). A last-observation-carried-forward (LOCF) analysis was performed for the efficacy measurements. All efficacy variables were evaluated for the change from baseline. Within each treatment group, paired t tests were used to make comparisons to baseline at each time point for each of the efficacy parameters.

Comparisons between placebo and each pioglitazone treatment group, with respect to change from baseline, were carried out using Dunnett’s test with estimates of least-square means and variances obtained from a two-way analysis of covariance. The model included terms for treatment, pooled center, and treatment-by-pooled-study-center interaction and the baseline value as a covariate. P values ≤0.05 were considered statistically significant.

All patients who were randomized and who received double-blind study medication were evaluated for safety. The proportions of patients who reported adverse events (based on a modified WHOART dictionary) were summarized with frequency counts and percentages. For the standard panel of laboratory tests, mean changes from baseline and the number of patients who had laboratory values outside of the normal range or who had markedly abnormal values were summarized. Descriptive statistics were used to summarize changes in body weight.

RESULTS — There were 408 patients randomized to receive placebo (n = 79) or pioglitazone 7.5 mg (n = 81), 15 mg (n = 81), 30 mg (n = 87), or 45 mg (n = 80). Overall, the mean age was 53.7 years (range 29–75). Most (78%) patients were Caucasian; 12% were Hispanic, 8% were African-American, 2% were Asian, and 1% were other races. More than half (58%) of the patients were male. There were no significant differences in the baseline demographics or glycemic or lipid characteristics among the five treatment groups.

Of the 408 patients, 31% (127 of 408) were naive to prior antidiabetic therapy. The most common antidiabetic medications taken before the study were sulfonylureas (glyburide and glipizide). A small percentage (13%) of patients had received two or more antidiabetic medications.

The percentage of patients who completed the study was 33% in the placebo group and ranged from 44 to 58% in the pioglitazone groups. The most common reason for study withdrawal was because of lack of glycemic control, defined as insufficient therapeutic effect (an investigator opinion of an increase or no significant improvement in HbA1c values that indicated insufficient diabetic management and posed a risk to the patient), adverse event of symptomatic or asymptomatic hyperglycemia, and patients withdrawing consent because of perceived lack of glucose control. More patients in the placebo group were withdrawn from the study because of poor glycemic control compared with patients in any of the pioglitazone groups (49% for the placebo group vs. 35% for the 7.5-mg group, 33% for the 15-mg group, 33% for the 30-mg group, and 29% for the 45-mg group). These withdrawals generally occurred within the first 12 weeks of the double-blind treatment period. A similar number of patients in all five treatment groups withdrew from the study because of adverse events (3% for the
Glycemic control: all patients

During all weeks when HbA1c was measured, the placebo group showed mean increases from baseline in HbA1c (Table 1). The differences between the placebo group and the 15-, 30-, and 45-mg groups were statistically significant ($P \leq 0.05$) in favor of the pioglitazone groups beginning at week 14 (week 10 for the 15- and 45-mg groups) until the end of therapy (Fig. 1A).

During all weeks when FPG was measured, the placebo group showed significant ($P < 0.05$) mean increases in FPG from baseline (Table 1). All pioglitazone groups had statistically significant mean decreases from baseline at each visit throughout the study (Fig. 1B). For the 15-, 30-, and 45-mg groups, there was a statistically significant difference from placebo at all weeks of therapy. For the 7.5-mg group, there was a statistically significant difference from placebo at week 2 and at weeks 14 through the end of the study.

The baseline HbA1c and FPG in this trial were relatively high at initiation of double-blind therapy. However, in a subset analysis of randomized patients who had a baseline FPG $\leq 280$ mg/dl ($n = 217$), with mean baseline HbA1c of 9.02% and a mean FPG level of 211.1 mg/dl, pioglitazone showed similar efficacy to the data from all patients. Specifically, differences in HbA1c when compared with placebo were $-2.00\%$ with 45 mg, $-2.00\%$ with 30 mg, $-1.69\%$ with 15 mg, and $-0.94\%$ with 7.5 mg and were statistically significant ($P \leq 0.05$) in favor of all pioglitazone groups. The differences in FPG when compared with placebo were $-2.35\%$ with 45 mg, $-1.29\%$ with 30 mg, $-1.69\%$ with 15 mg, and $-0.94\%$ with 7.5 mg and were statistically significant ($P \leq 0.05$) in favor of the 15-, 30-, and 45-mg groups.

### Glycemic control: subset of patients naive to therapy

The placebo group showed mean increases from baseline in HbA1c throughout the study (Table 1). The 15-, 30-, and 45-mg groups...
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had mean decreases from baseline at weeks 6–26. The differences between the placebo group and the 15-, 30-, and 45-mg groups were statistically significant (P ≤ 0.05) at weeks 10–26 (Fig. 1C).

Glycemic control: subset of patients previously treated
The placebo group showed mean increases from baseline in HbA1c throughout the study (Table 1). The 15-, 30-, and 45-mg groups had mean decreases from baseline at weeks 18–26. The differences between the placebo group and the 15-, 30-, and 45-mg groups were statistically significant (P ≤ 0.05) at weeks 14–26 (Fig. 1D).

Insulin and C-peptide
All treatment groups had mean decreases from baseline in fasting insulin over the course of the study. However, the small mean decreases from baseline in the placebo group never achieved statistical significance. In contrast, the 30- and 45-mg pioglitazone groups had statistically significant (P > 0.05) mean decreases from baseline at weeks 2–26 (except week 26 for the 45-mg group). In addition, the magnitude of the changes from baseline in fasting insulin for the 30- and 45-mg groups were consistently two to three times greater than placebo throughout the study, ranging (i.e., minimum to maximum change) from −2.38 to −4.43 µU/ml for 30 mg, −1.55 to −5.32 µU/ml for 45 mg, and 0.08 to −1.42 µU/ml for placebo. Mean fasting C-peptide was only slightly changed for any treatment by end point (week 26).

Lipids
Patients receiving 15, 30, and 45 mg pioglitazone had decreases in mean percent change from baseline in triglycerides compared with an increase for the placebo-treated patients (Table 2). Conversely, mean percent change from baseline in HDL cholesterol increased to a greater extent in the 15, 30, and 45 mg pioglitazone-treated patients than in the placebo-treated patients at the end of the study (Table 2).

There were no statistically significant differences between any of the pioglitazone treatment groups and placebo group for total cholesterol or LDL cholesterol at any time point during the study. For both total cholesterol and LDL cholesterol, the pioglitazone and placebo groups showed small increases in mean percent change from baseline at all visits during double-blind therapy; the mean percent differences from baseline for LDL cholesterol were significant for the 15- and 45-mg groups and for total cholesterol for the placebo, 15-mg, and 45-mg groups.

Safety evaluations
The overall adverse event rate of pioglitazone was similar to that of placebo (76 vs. 85%, respectively). Relatively few of these

Figure 1—The least-squares mean change from baseline by visit (LOCF analysis) for all randomized patients in HbA1c (A) and FPG (B), for patients naïve to prior antidiabetic therapy in HbA1c (C), and for patients previously treated with antidiabetic therapy in HbA1c (D) during the course of the study. ▲, Placebo; ○, 7.5 mg pioglitazone; ●, 15 mg pioglitazone; □, 30 mg pioglitazone; ■, 45 mg pioglitazone. Data are means ± SEM. *P ≤ 0.05 vs. placebo at the end of the study.

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whereas no patients in the placebo group experienced edema or peripheral edema. No patient discontinued as a result of edema or peripheral edema. The incidence of edema or peripheral edema was 12 of 329 (3.6%) in the pioglitazone group, whereas no patients in the placebo group experienced edema or peripheral edema. No patient discontinued as a result of edema or peripheral edema.

Hypoglycemia was reported by 4 of the 329 patients who received pioglitazone, whereas no patients in the placebo group experienced hypoglycemia (P > 0.05). All of the events occurred while the patients were at home, so blood glucose levels could not be confirmed. The incidence did not appear to increase with dose. Two of the patients received 7.5 mg pioglitazone, one received 30 mg pioglitazone, and one received 45 mg pioglitazone. For all four patients, the occurrence of hypoglycemia was isolated and transient, resolving within a few hours or less. All of the events were considered mild or moderate in intensity and none resulted in discontinuation.

Mean ALT values at baseline ranged from 24.7 U/l in the 45-mg group to 28.1 U/l in the 7.5-mg group. The incidence of ALT values elevated from baseline to 2 × ULN were noted for the 45-mg group. The related increases observed for the 15-, 30-, and 45-mg groups. At the end of the study, the mean change from baseline in body weight compared with mean dose-related increases observed for the 15-, 30-, and 45-mg groups had mean decreases in body weight compared with mean dose-related increases observed for the 15-, 30-, and 45-mg groups. The mean change from baseline in body weight was -0.59 kg in the 7.5-mg group, 1.30 kg in the 15-mg group, 1.29 kg in the 30-mg group, 2.82 kg in the 45-mg group, and -1.28 kg in the placebo group. Linear regression analysis demonstrated that weight gain was associated with decreases in HbA1c (R² = 0.1942).

**CONCLUSIONS** — The present study demonstrates that in patients with type 2 diabetes, pioglitazone is effective in decreasing HbA1c and FPG. Decreases in FPG began relatively quickly after receiving study med-
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This result is most likely related to the study design. As mentioned earlier, previously treated patients discontinued their antidiabetic medications and during the washout period, when patients received single-blind placebo, experienced deteriorating glycemic control to such an extent that the ability to quickly respond (i.e., within 12 weeks) to any oral agent could be severely impaired. Previously reported studies have indicated that significant improvements with thiazolidinediones are not observed across the first 8–12 weeks of therapy (12).

The results of the completers analysis showed improved glycemic control (as measured by HbA1c and FPG), as did the LOCF analysis, although the magnitude of the response was greater in the completers analysis.

Although recent data show that modest increases in LDL correlate with increased cardiovascular risk, additional information suggests that the diminution of the rate of cardiovascular disease can be enhanced by increasing HDL cholesterol and, thus, the LDL-to-HDL ratio may be a strong predictor of cardiovascular outcome (13–16). In this study, patients treated with 15, 30, and 45 mg pioglitazone showed significant mean percent decreases from baseline in triglycerides and significant mean percent increases from baseline in HDL. No untoward effects when compared with placebo were observed for LDL cholesterol. The mean percent LDL-to-HDL ratio in this study decreased from baseline, with the largest reductions in the 45-mg group, although the full impact of the serum lipid changes will ultimately need to be assessed by changes, if any, of cardiovascular events.

Pioglitazone was found to be generally well tolerated. The frequency of cardiac adverse events in the pioglitazone group was not greater than that observed in the placebo group. Importantly, there were no cases of jaundice and no evidence of drug-induced hepatotoxicity or drug-induced elevations of ALT levels observed in this study. The results of this study are consistent with all placebo-controlled clinical studies of pioglitazone, in which the incidence of patients with ALT ≥3 × ULN was low and was comparable between patients who received pioglitazone (+ of 1,526 [0.26%]) and patients who received placebo (2 of 793 [0.25%]) (17). Pioglitazone patients did experience edema and small decreases in hemoglobin, hematocrit, and erythrocyte counts; however, no patients discontinued because of edema or anemia. A dose-related increase in mean weight for patients treated with pioglitazone was observed during the study; however, the increase generally was proportional to improved glycemic control (i.e., decreases in HbA1c). It should be noted that the occurrence of edema, decreases in hemoglobin and hematocrit, and increases in weight have been observed with all of the thiazolidinediones (18–20). A few patients (4 of 329) reported hypoglycemic episodes (blood glucose values not documented); however, none were severe or prompted discontinuation of study medication.

In summary, the results of this study show that pioglitazone is a well-tolerated and efficacious treatment for patients with type 2 diabetes. The ability of pioglitazone to ameliorate some degree of dyslipidemia may provide an additional benefit in this patient population with known cardiovascular complications.

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APPENDIX

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