Effect of Metformin and Rosiglitazone Combination Therapy in Patients With Type 2 Diabetes Mellitus: A Randomized Controlled Trial

Vivian Fonseca, MD
Julio Rosenstock, MD
Rita Patwardhan, PhD
Alan Salzman, MD, PhD

Type 2 diabetes is characterized by decreased insulin secretion and insulin sensitivity in the liver, adipose tissue, and skeletal muscle. Together these abnormalities confound efforts to treat diabetes because most antidiabetic agents target only 1 underlying cause of the disease. Approximately 50% of patients treated with monotherapy require additional therapy to achieve target glycated hemoglobin (HbA1c) levels 3 years after diagnosis.3

Rosiglitazone maleate, a member of the thiazolidinedione class of antidiabetic agents that was recently approved by the US Food and Drug Administration, targets insulin resistance by binding to the transcription factor peroxisome proliferator-activated receptor-γ, promoting synthesis of glucose transporters and activating adipocyte differentiation.4-6 In contrast, metformin hydrochloride promotes glucose lowering by reducing hepatic glucose production and gluconeogenesis and by enhancing peripheral glucose uptake.7-10

Because metformin and rosiglitazone act through different mechanisms, their combined use may be indicated in patients whose disease is poorly controlled with a maintenance dose of metformin. This study evaluated the efficacy and safety of adding 4 mg/d and 8 mg/d of rosiglitazone maleate to maximal-dosage of metformin in patients with poorly controlled type 2 diabetes. Combined efficacy was assessed by comparing the level changes between baseline and week 26, by treatment group.

Context Most antidiabetic agents target only 1 of several underlying causes of diabetes. The complementary actions of the antidiabetic agents metformin hydrochloride and rosiglitazone maleate may maintain optimal glycemic control in patients with type 2 diabetes; therefore, their combined use may be indicated for patients whose diabetes is poorly controlled by metformin alone.

Objective To evaluate the efficacy of metformin-rosiglitazone therapy in patients whose type 2 diabetes is inadequately controlled with metformin alone.

Design Randomized, double-blind, placebo-controlled trial from April 1997 and March 1998.

Setting Thirty-six outpatient centers in the United States.

Patients Three hundred forty-eight patients aged 40 to 80 years with a mean fasting plasma glucose level of 12.0 mmol/L (216 mg/dL), a mean glycated hemoglobin level of 8.8%, and a mean body mass index of 30.1 kg/m2 were randomized.

Interventions Patients were assigned to receive 2.5 g/d of metformin plus placebo (n = 116); 2.5 g/d of metformin plus 4 mg/d of rosiglitazone (n = 119); or 2.5 g/d of metformin and 8 mg/d of rosiglitazone (n = 113) for 26 weeks.

Main Outcome Measures Glycated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and β-cell function, compared between baseline and week 26, by treatment group.

Results Glycated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and β-cell function improved significantly with metformin-rosiglitazone therapy in a dose-dependent manner. The mean levels of glycated hemoglobin decreased by 1.0% in the 4 mg/d metformin-rosiglitazone group and by 1.2% in the 8 mg/d metformin-rosiglitazone group and fasting plasma glucose levels by 2.2 mmol/L (39.8 mg/dL) and 2.9 mmol/L (52.9 mg/dL) compared with the metformin-placebo group (P < .001 for all). Of patients receiving 8 mg/d of metformin-rosiglitazone, 28.1% achieved a glycated hemoglobin level of 7% or less. Dose-dependent increases in body weight and total and low-density lipoprotein cholesterol levels were observed (P < .001 for both rosiglitazone groups vs placebo). The proportion of patients reporting adverse experiences was comparable across all groups.

Conclusions Our data suggest that combination treatment with once-daily metformin-rosiglitazone improves glycemic control, insulin sensitivity, and β-cell function more effectively than treatment with metformin alone.

JAMA. 2000;283:1695-1702

Authors Affiliations and Financial Disclosure are listed at the end of this article.
Corresponding Author and Reprints: Vivian Fonseca, MD, Department of Medicine, Endocrinology Section, Tulane University, 1430 Tulane Ave, PO Box SL53, New Orleans, LA 70112 (e-mail: vfonseca@mailhost.tcs.tulane.edu).
in \( \text{HbA}_1c \), fasting plasma glucose (FPG), fructosamine, serum insulin, free fatty acids (FFA), lipids, lactate, and estimates of insulin sensitivity and \( \beta \)-cell function (BCF) between combined metformin-rosiglitazone treatment and metformin-placebo alone.\(^{12}\)

### METHODS

#### Study Subjects

To detect a 0.75% absolute difference in \( \text{HbA}_1c \) between treatment groups, 65 evaluable patients per group would be required to achieve a power of 95%. Planned enrollment was 280 patients (approximately 93 per group). Persons between the ages of 40 and 80 years with type 2 diabetes as defined by the National Diabetes Data Group\(^\text{12}\) with FPG concentrations of between 7.8 and 16.7 mmol/L (140 and 300 mg/dL) at screening and during the placebo-maintenance period while taking 2.5 g/d of metformin were eligible. All patients demonstrated insulin secretory capacity as determined by a fasting C-peptide concentration of 0.27 nmol/L (0.8 ng/mL) or more at screening. Subjects were required to have a body mass index, calculated as weight in kilograms divided by the square of height in meters, of 22 to 38 and a weight change of no more than 10% between screening and baseline.

Patients were excluded if they had clinically significant renal or hepatic disease, angina, New York Heart Association Classification class III or IV cardiac insufficiency, symptomatic diabetic neuropathy, significant clinical abnormality on electrocardiogram, abnormal laboratory test results (blood chemistry, hematology, or urinalysis), use of chronic insulin therapy, participated in any rosiglitazone-related study, or used any investigational drug (excluding metformin) within 30 days of study (or 5 half-lives of the investigational drug, if longer than 30 days). Anorectic agents were discontinued at least 30 days before screening. Patients with hyperlipemia, elevated cholesterol or triglyceride levels, or lipid metabolism disorders were eligible; lipid-lowering agents were maintained at the same dosage level throughout the study.

#### Study Design

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 36 sites in the United States between April 1997 and March 1998. Before the study, patients discontinued all antihyperglycemic medications, with the exception of metformin. Metformin dose tolerability was determined during a 3-week period in which metformin was titrated to 2.5 g/d; afterward, patients entered a 4-week, single-blind metformin-placebo maintenance period with a weight-maintenance diet. During this maintenance period, only investigators were aware that patients were receiving the metformin-placebo treatment. Patients previously treated with metformin at 2.5 g/d proceeded directly to maintenance; thus, with the exception of metformin, patients refrained from medication for a minimum of 4 weeks and a maximum of 7 weeks.

At the end of the maintenance period, patients with inadequate glycemic control (FPG concentration range, 7.7-16.7 mmol/L [140-300 mg/dL]) were randomly assigned (1:1:1 ratio) to receive double-blind metformin treatment in 1 of 3 combinations: placebo (control), 4 mg of rosiglitazone, or 8 mg of rosiglitazone once daily for 26 weeks. Randomization was computer generated with a fixed block size. No patient, investigator, or sponsor was aware of treatment allocation until study completion (FIGURE 1).

This study was conducted in accordance with the Declaration of Helsinki (as amended, 1989), Title 21 of the US Code of Federal Regulations, and Good Clinical Practice guidelines. The institutional review board at each center approved the protocol, and subjects provided informed consent before enrollment.

#### Efficacy and Safety Measurements

Laboratory measurements for efficacy and safety were performed by SmithKline Beecham Clinical Laboratories (Van Nuys,
Safety monitoring included physical examination, vital sign assessment, weight measurement, electrocardiogram, adverse experience query, and laboratory tests.

### Statistical Methods

The primary population for efficacy analysis was the intention-to-treat population, those with at least 1 value while receiving therapy (last observation was carried forward in the case of missing data or early withdrawals). Efficacy and safety parameters were measured at baseline and after 26 weeks of treatment. Safety parameters were assessed based on week 26 data (without the last observation carried forward).

Treatment groups were compared using analysis of covariance with terms for baseline, treatment, and center. The assumptions of the statistical model were tested before application. The Levene test of heterogeneity across treatments was applied at a significance level of $\alpha = .01$. If significant, the Shapiro-Wilk test of nonnormality ($\alpha = .01$) was examined. Parametric analysis or nonparametric analysis was used, depending on results of test assumptions. If prospectively defined assumptions for parametric analysis were not met, the Wilcoxon rank sum test was used. Pairwise comparisons to placebo used Dunnett multiple comparison procedure to maintain a 2-sided .05 significance level within each parameter. The statistical significance of the within-group change from baseline was tested by a paired $t$ test or a signed rank test. Safety parameters, including clinical laboratory tests, vital signs, and body weight, were examined using 1-way analysis of variance. Statistical analyses were performed using statistical software (SAS/STAT Software, Release 6.12, SAS Institute Inc, Cary, NC).

### Results

Of 443 patients screened, 437 entered the titration and maintenance period and 348 were randomized to treatment (Figure 1). Most withdrawals were due to failing to meet inclusion criteria (69.7%). Baseline characteristics were similar among treatment groups (Table 1). Fifty-eight patients withdrew before completion of the double-blind phase: 22 from the placebo group and 18 from the 4-mg/d and 18 from the 8-mg/d rosiglitazone groups. Most participants withdrew because of adverse experiences or lack of efficacy (Figure 1).

### Table 1. Baseline Demographic and Metabolic Characteristics of Randomized Patients (Intention-to-Treat Population)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Metformin Hydrochloride and Placebo (n = 113)</th>
<th>Metformin Hydrochloride and Rosiglitazone Maleate 4 mg/d (n = 116)</th>
<th>Metformin Hydrochloride and Rosiglitazone Maleate 8 mg/d (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>58.8 (9.2)</td>
<td>57.5 (10.5)</td>
<td>58.3 (8.8)</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>74.3</td>
<td>62.1</td>
<td>68.2</td>
</tr>
<tr>
<td>Women</td>
<td>25.7</td>
<td>37.9</td>
<td>31.8</td>
</tr>
<tr>
<td>Duration of diabetes, mean (SD), y</td>
<td>7.3 (5.7)</td>
<td>7.5 (6.3)</td>
<td>8.3 (6.3)</td>
</tr>
<tr>
<td>Prior treatment, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet and exercise only</td>
<td>4.4</td>
<td>6.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Oral monotherapy</td>
<td>48.7</td>
<td>39.7</td>
<td>43.6</td>
</tr>
<tr>
<td>Oral combination therapy</td>
<td>46.9</td>
<td>54.3</td>
<td>51.8</td>
</tr>
<tr>
<td>Baseline HbA1c, mean (SD), %*</td>
<td>8.6 (1.3)</td>
<td>8.9 (1.3)</td>
<td>8.9 (1.5)</td>
</tr>
<tr>
<td>Baseline fasting plasma glucose, mean (SD), mmol/L†</td>
<td>11.87 (2.91)</td>
<td>11.90 (3.17)</td>
<td>12.19 (3.05)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>30.3 (4.4)</td>
<td>30.2 (4.2)</td>
<td>29.8 (3.9)</td>
</tr>
</tbody>
</table>

*HbA1c indicates glycosylated hemoglobin.
†To convert millimoles per liter to milligrams per deciliter divide by 0.0555.
Glycemic Control

The mean HbA1c levels decreased significantly from baseline in a dose-dependent fashion in both rosiglitazone groups by 0.56% in the 4-mg/d and by 0.78% in the 8-mg/d rosiglitazone groups. But the control group experienced a significant increase in HbA1c levels (0.45%) (Figure 2). Furthermore, both rosiglitazone groups had HbA1c levels lower than those in the control group by 1.0% in the 4-mg/d and 1.2% in the 8-mg/d rosiglitazone groups. In contrast to results observed in the control group, the mean HbA1c levels in the rosiglitazone groups decreased after week 4 and plateaued by week 18 (Figure 3). The percentage who achieved a 1.0% reduction in HbA1c concentrations was 32.8% in the 4-mg/d and 37.3% in the 8-mg/d rosiglitazone groups and 7.1% in the control group.

Twenty-five (28.1%) of 89 patients taking 8 mg/d of rosiglitazone achieved the target HbA1c control levels of 7.0%, and 51 patients (57.3%) in the same group achieved HbA1c levels of 8.0%, or below the American Diabetes Association action point. Yet only 7.6% of the patients in the control group achieved HbA1c levels of 7.0% and 35.9% achieved an HbA1c level of 8.0%.

The mean baseline fructosamine levels of 341.73 µmol/L in the control group increased by 12.3 µmol/L. But in the rosiglitazone groups the levels decreased by 27.9 µmol/L from 340.9 µmol/L in the 4-mg/d group and by 36.8 µmol/L from 351.8 µmol/L in the 8-mg/d group (reference range, 200–278 µmol/L).

Although the mean FPG concentrations did not change significantly in the control group, they significantly decreased in a dose-dependent order from baseline in both rosiglitazone groups (1.8 mmol/L [−33.0 mg/dL], 4-mg/d rosiglitazone; −2.7 mmol/L [−48.4 mg/dL], 8-mg/d rosiglitazone; P<.0001). The mean FPG concentrations in both rosiglitazone groups also had decreased compared with the control group (−2.2 mmol/L [−39.8 mg/dL], 4-mg/d rosiglitazone; −2.9 mmol/L [−52.9 mg/dL], 8-mg/d rosiglitazone; P<.0001) (Figure 4). Furthermore, FPG concentrations in both rosiglitazone groups decreased during the first 4 weeks, plateaued at 12 to 18 weeks, and remained stable thereafter (Figure 5). Nine patients (7.9%) in the control group, 25 (21.6%) in the 4-mg/d and 33 (30.0%) in the 8-mg/d rosiglitazone groups achieved FPG concentrations of less than7.8 mmol/L (140 mg/dL).

Effects on Insulin Sensitivity and BCF

Adding rosiglitazone to maximum doses of metformin significantly increased HOMA-S values. The median baseline HOMA-S values ranged from 46.6 to 49.0 units. The HOMA-S values increased dose-dependently by 1.7 units in the 4-mg/d and by 3.8 units in the 8-mg/d rosiglitazone groups compared with the control group.

The metformin-rosiglitazone combination increased HOMA-B in a dose-dependent fashion. The median baseline HOMA-B values ranged from 32.5 to 35.8 units and were significantly increased by 10.3 to 13.7 units in the rosiglitazone groups compared with the control group.

Other Metabolic Effects

In the control group, the insulin value decreased by 11.05 pmol/L from a baseline of 118.56 pmol/L after treatment (P=.03) and in the 4-mg/d and 8-mg/d rosiglitazone groups the insulin values respectively decreased by 12.98 pmol/L from 124.55 pmol/L (P=.01) and by 31.07 pmol/L from 136.73 pmol/L (P<.001). The C-peptide values respectively decreased by 0.10 nmol/L from 0.93 nmol/L (P<.001), by 0.07 nmol/L from 0.92 nmol/L (P=.01), and by 0.12 nmol/L from 0.93 nmol/L (P<.001).

Mean total cholesterol-HDL-C, and LDL-C levels from baseline in both rosiglitazone groups achieved statistically significant increases in all treatment groups compared with the control group (Table 2). Total cholesterol–HDL-C ratios in the rosiglitazone groups were not significantly different from those in the control group.

Figure 3. Mean Change in Glycosylated Hemoglobin (HbA1c) Levels Over Time in Patients Taking Metformin Hydrochloride Alone Compared With Patients Taking Metformin and Rosiglitazone Maleate Combined

Error bars indicate 95% confidence interval.
Changes in LDL-C levels were evaluated based on those at baseline. In that analysis, we identified 2 subgroups: those with levels lower than 3.37 mmol/L (<130 mg/dL) and those at that level or higher. We did not provide P values for any of the subgroups because the values were not large enough for statistical analyses and because the subgroups were not randomized, so significance could not be established. In the lower subgroup, the median baseline LDL-C value increased by 0.13 mmol/L (5 mg/dL) from 2.59 mmol/L (100 mg/dL) in 51 patients in the control group. In both rosiglitazone groups, the LDL-C values increased by 0.54 mmol/L (21 mg/dL) from a median baseline value of 2.69 mmol/L (104 mg/dL) in 57 patients taking 4-mg/d and from 2.64 mmol/L (102 mg/dL) in 60 patients taking 8-mg/d, resulting in medians that remained below 3.37 (<130 mg/dL) for all 3 treatment groups.

In the higher subgroup, the median baseline LDL-C value increased by 0.07 mmol/L (3 mg/dL) from 3.78 mmol/L (146 mg/dL) in 30 patients in the control group. In the rosiglitazone groups, the median baseline LDL-C value increased by 0.31 mmol/L (12 mg/dL) from 3.72 mmol/L (144 mg/dL) in 27 patients taking 4-mg/d and by 0.34 mmol/L (13 mg/dL) from 4.20 mmol/L (162 mg/dL) in 20 patients taking 8-mg/d.

Changes in triglyceride levels also were evaluated based on baseline values, using 2 subgroups: those with levels lower than 2.26 mmol/L (<200 mg/dL) and those with that level or higher. In the lower subgroup, the median baseline triglyceride values increased by 0.15 mmol/L (13 mg/dL) from 1.44 mmol/L (128 mg/dL) in 52 patients in the control group. In the rosiglitazone groups, the median baseline triglyceride value increased by 0.16 mmol/L (15 mg/dL) from 1.67 mmol/L (148 mg/dL) in 56 patients taking 4-mg/d and by 0.07 mmol/L (6 mg/dL) from 1.34 mmol/L (119 mg/dL) in 55 patients taking 8-mg/d. The treatment values in all groups remained less than 2.25 mmol/L (200 mg/dL).

In the higher subgroup, the median baseline triglyceride values decreased by 0.12 mmol/L (11 mg/dL) from 3.24 mmol/L (287 mg/dL) in 41 patients in the control group. In the rosiglitazone groups, the baseline median triglyceride value increased by 0.15 mmol/L (13 mg/dL) from 3.50 mmol/L (310 mg/dL) in 43 patients taking 4-mg/d and decreased by 0.72 mmol/L (64 mg/dL) from 3.16 mmol/L (280 mg/dL) in the 8-mg/d rosiglitazone group.

Mean fasting lactate levels decreased significantly in patients taking both dose levels of rosiglitazone compared with those in the control group (4-mg/d rosiglitazone, P = .012; 8-mg/d rosiglitazone, P = .002). Free fatty acids concentrations decreased significantly from baseline in both rosiglitazone groups. (TABLE 3).

### Safety

The percentage of patients with at least 1 adverse event were comparable among each group (75.2%, 4-mg/d rosiglitazone; 78.2%, 8-mg/d rosiglitazone; 76.7%, control). The most frequently reported adverse events were upper respiratory tract infection, diarrhea, and headache. One death due to acute myocardial infarction occurred in the 4-mg/d rosiglitazone group but was judged to be unrelated to study medication. Serious nonfatal adverse events occurred in 5 (4.3%) of 116 patients in the control group and in 5 (4.2%) of 119 patients in the 4-mg/d and 5 (4.4%) of 113 patients in the 8-mg/d rosiglitazone groups, none considered related to study medication.

Symptomatic mild or moderate hypoglycemia was reported by 2 patients in the control group and by 3 patients in the 4-mg/d and by 5 patients in the 8-mg/d rosiglitazone groups. No patient required third-party interven-

---

**Figure 4.** Change in Fasting Plasma Glucose (FPG) Concentrations at Week 26 in Patients Taking Metformin Hydrochloride Alone Compared With Patients Taking Metformin and Placebo

![Graph showing change in FPG concentrations over time](image)

To convert from milligrams per deciliter to millimoles per liter multiply by .0555. Error bars indicate 95% confidence interval.

---

**Figure 5.** Mean Fasting Plasma Glucose (FPG) Concentrations Over Time in Patients Taking Metformin Hydrochloride Alone Compared With Patients Taking Metformin and Rosiglitazone Maleate

![Graph showing mean FPG concentrations over time](image)

To convert from milligrams per deciliter to millimoles per liter multiply by .0555. Error bars indicate SE.
Both rosiglitazone groups experienced small but statistically significant decreases in hemoglobin and hematocrit levels, which occurred primarily during the first 12 to 18 weeks of treatment, after which values for both parameters increased slightly. The mean decreases in hemoglobin levels were –5.0 g/L in the 4-mg/d and –8.0 g/L in the 8-mg/d rosiglitazone groups (P<.0001 for both groups), and mean decreases in hematocrit were –1.8% in the 4-mg/d and –2.5% in the 8-mg/d rosiglitazone groups (P<.0001 for both groups). There were no significant changes in these parameters in the control group. One patient in each rosiglitazone group withdrew because of anemia, and 1 patient in the 4-mg/d rosiglitazone group with low hemoglobin and hematocrit levels was withdrawn from the study after week 8 because of evidence of gastrointestinal tract bleeding, considered by the investigator to be unrelated to the study medication.

There were no significant changes from baseline in vital signs or electrocardiogram parameters in the rosiglitazone groups compared with the control group. Although infrequent, edema was observed with greater frequency in the rosiglitazone groups (2.5%, 4-mg/d; 3.5%, 8-mg/d) than in the control group (0.9%). No one withdrew due to edema.

Those in the control group experienced a mean decrease in body mass of 1.2 kg from baseline, but those in the rosiglitazone groups experienced a mean body mass increase of 0.7 kg in the 4-mg/d and 1.9 kg in the 8-mg/d rosiglitazone groups (P = .0001 for both groups). There were no significant differences in waist-to-hip ratios among groups.

No one in the rosiglitazone groups experienced elevations of alanine aminotransferase (ALT) levels greater than 3 times the upper limit of the reference range. Mean changes in aspartate aminotransferase (AST), ALT, and total bilirubin levels were similar in all groups, with a slight decrease observed in mean ALT (−1.9 U/L, control; −1.9 U/L, 4-mg/d rosiglitazone; −3.4 U/L, 8-mg/d rosiglitazone). Mean alkaline phosphatase decreased in all groups (−3.5 U/L, 4-mg/d; −2.5% in the 8-mg/d rosiglitazone groups) (P = .0001). No one withdrew due to edema.

Two patients in the control group were
noted to have liver function tests for potential clinical concern (>3 times the upper limit of the reference range) while in treatment. Both completed the study with elevated transaminase values.

COMMENT

This is the first large, multicenter, clinical trial demonstrating the efficacy and safety of combined rosiglitazone and metformin treatment in patients with type 2 diabetes. The combination treatment of metformin and rosiglitazone significantly reduced HbA1c and FPG concentrations, in a dose-ordered fashion compared with baseline and with metformin alone. Conversely, treatment with metformin was associated with significant increases in HbA1c concentrations, indicating that these agents complement each other to achieve optimal glycemic control and confirming the clinical utility of metformin in combination with a thiazolidinedione drug.

Consistent with the mechanisms of action of metformin and rosiglitazone, the reductions in FPG concentrations were proportionately smaller than those observed in HbA1c concentrations. Maximum doses of metformin decrease hepatic gluconeogenesis, which principally affects FPG concentrations, whereas rosiglitazone enhances insulin sensitivity at the peripheral level and affects overall glucose disposal, including postprandial excursions. Because the relative contribution of postprandial glucose on glycemic control depends on the magnitude of FPG concentrations, rosiglitazone may have an effect on postprandial hyperglycemia, as demonstrated directly in a rosiglitazone trial that showed significant improvements in fasting and postprandial glucose concentrations and excursions.

The complementary actions of combined metformin and rosiglitazone is further supported by the effects of rosiglitazone on insulin sensitivity despite maximum doses of metformin. Rosiglitazone may provide added therapeutic value by reducing peripheral insulin resistance. While HOMA-S is an indirect method for determining insulin resistance, it is noted to have liver function tests for potential clinical concern (>3 times the upper limit of the reference range) while in treatment. Both completed the study with elevated transaminase values.

### Table 3. Change in Free Fatty Acid Levels at Week 26 (Compared With Baseline and Metformin Hydrochloride and Placebo)*

<table>
<thead>
<tr>
<th>Free Fatty Acids, mg/dL</th>
<th>Metformin and Placebo (n = 113)</th>
<th>Metformin and Rosiglitazone Maleate (n = 116)</th>
<th>Rosiglitazone Maleate (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, mean (SD)</td>
<td>18.26 (7.75)</td>
<td>18.39 (7.56)</td>
<td>18.44 (8.00)</td>
</tr>
<tr>
<td>Week 26, mean (SD)</td>
<td>18.17 (6.06)</td>
<td>15.78 (6.05)</td>
<td>14.15 (6.13)</td>
</tr>
<tr>
<td>Change from baseline, mean (SD)†</td>
<td>−0.09 (7.66)</td>
<td>−2.61 (6.69)</td>
<td>−4.30 (7.88)</td>
</tr>
<tr>
<td>P value‡</td>
<td>&lt;.05</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean difference from control</td>
<td>. . . . 2.62</td>
<td>. . . . 4.22</td>
<td>. . . . 6.22</td>
</tr>
<tr>
<td>P value§</td>
<td>.0003</td>
<td>&lt;.0001</td>
<td>.0259</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable
†Calculated only for patients with both a baseline and a week 26 value.
‡Significance level is .05.
§Significance level is .0259.
increased cardiovascular risk. The small decreases in hemoglobin and hematocrit levels associated with metformin-rosiglitazone therapy may relate to plasma volume expansion derived from fluid retention and hemodilution.

Metformin-rosiglitazone therapy may be a safe alternative therapy to attain optimal glycemic control where monotherapy has failed because the statistically significant decreases in lactate levels associated with metformin-rosiglitazone treatment indicate that rosiglitazone may correct metabolic abnormalities beyond reducing hyperglycemia, and further suggest differing and complementary actions of metformin and rosiglitazone; and ALT elevations greater than 3 times the upper limit of the reference range were not observed in either of the rosiglitazone groups.

In summary, combination metformin-rosiglitazone treatment is effective and safe in reducing hyperglycemia in patients with type 2 diabetes. In patients whose fundamental abnormality is insulin resistance, such a combination raises the exciting possibility of treating diabetes by targeting the underlying cause of the disease, rather than the traditional approach of stimulating insulin secretion. Nearly 30% of patients taking the combination therapy achieved HbA1c levels of 7% or less. This level of glycemic control is 3-fold greater than what was achieved among those taking metformin alone. Additional investigation is needed to determine whether this combination will alter the long-term risk of cardiovascular disease or delay disease progression.

REFERENCES

methylaltrexone levels. Mean (SD [range]) peak plasma level for the other 4 patients (1 from the 1.0 mg/kg group and 3 from the 3.0 mg/kg group) was 17.8 (6.6 [10-26]) ng/mL.

Comment. Tertiary opioid antagonists, such as naloxone, cross the blood-brain barrier and reverse both the pain-relieving benefits and the adverse effects of opiates. Although oral naloxone may relieve opioid-induced constipation, the therapeutic index is very narrow, and naloxone may induce opioid withdrawal symptoms. Many patients receiving opioid pain medications face a difficult choice between burdensome adverse effects or ineffective analgesia. Methylaltrexone may allow for more aggressive use of opioid analgesics with fewer adverse effects. The low methylaltrexone plasma levels observed in our study suggest that this charged compound acts directly in the gut. Oral methylaltrexone has potential clinical utility in managing opioid-induced constipation with minimal adverse effects.

Chun-Su Yuan, MD, PhD
Joseph F. Foss, MD
Departments of Anesthesia and Critical Care
University of Chicago
Chicago, Ill

Funding/Support: This work was supported in part by a grant from the International Anesthesia Research Society, National Institutes of Health grants R01 CA75042 and M01 RR00055. Methylaltrexone was originally formulated and subsequently modified by faculty at the University of Chicago. The University of Chicago and Drs Yuan and Foss stand to benefit financially from the further development of methylaltrexone.


CORRECTIONS

Incorrect Wording and Footnote Symbol: In The Rational Clinical Examination entitled “Does This Patient Have Carpal Tunnel Syndrome?” published in the June 21, 2000, issue of THE JOURNAL (2000;283:3110-3117), there was incorrect wording in the abstract. In the Conclusion paragraph on page 3110, the first sentence should have read, “Hand symptom diagrams, hypalgesia, and thumb abduction strength testing are helpful in establishing the electrodiagnosis of CTS.” Also, in Table 2 on pages 3114 and 3115, the “No. of Hands” columns should include dagger symbols (†) instead of asterisks (*) down the column to indicate which studies used subjects instead of individual hands.

Incorrect Wording and Data Presentation and Omitted Acknowledgment: In the Original Contribution entitled “Effect of Metformin and Rosiglitazone Combina
tion Therapy in Patients With Type 2 Diabetes Mellitus: A Randomized Controlled Trial” published in the April 5, 2000, issue of THE JOURNAL (2000;283:1695-1702), incorrect wording and incorrect data presentation were printed. On page 1695, in the “Results” section of the Abstract, the sentence that read “28.1% achieved a glycosylated hemoglobin of less than 7%” should have read “7% or less.” On page 1698, the last sentence in the “Glycemic Control” section should have read “Nine patients (7.9%) in the control group, 25 (21.6%) in the 4-mg/d, and 33 (30.0%) in the 8-mg/d rosiglitazone groups achieved FPG concentrations of less than 7.8 mmol/L (140 mg/dl).” On page 1699 in the “Other Metabolic Effects” section, in the penultimate paragraph, which reports triglyceride findings, the phrase that read “in the rosiglitazone groups, the median baseline triglyceride value increased . . . by 0.07 mmol/L (6 mg/dl)” from 1.34 mmol/L (119 mg/dL) in 55 patients taking 8-mg/d “should have read “decreased by 0.72 mmol/L (64 mg/dl)” from 9.16 mmol/L (280 mg/dl) in 37 patients taking 8 mg/d.” The last sentence of the penultimate paragraph of the “Other Metabolic Effects” section was repeated from the prior paragraph and should be deleted. In Table 2, the “Total cholesterol–HDL ratio” section should not have been converted to mmol/L. To calculate the proper ratio, divide the values in that section by 0.0259. In the footnote of Table 2, the cholesterol conversion factor should have read “0.0259.” On page 1701 in the “Comment” section in the third column, the line that read “Among patients in the 8-mg/d rosiglitazone group . . . there was a significant sta
tistical decrease observed (6.4-mg/dL)” should have read “(64 mg/dl).” In addition, Sylvia K. Chai, PhD, should have been included in the acknowledgment for her significant contributions to the preparation and review of the article.