

# Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-controlled, Dose-Response Trial

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**PURPOSE:** To study the efficacy and safety of various dosages of metformin as compared with placebo in patients with type II diabetes mellitus.

**PATIENTS AND METHODS:** A 14-week, multicenter, double-blind, dose-response study was conducted. After a 3-week, single-blind, placebo-controlled washout, 451 patients with fasting plasma glucose levels of at least 180 mg/dL were randomized to receive an 11-week course of placebo or metformin given at 500, 1000, 1500, 2000, or 2500 mg daily.

**RESULTS:** Metformin improved glucose variables as compared with placebo. The adjusted mean changes in fasting plasma glucose from baseline associated with each metformin group at week 7, 11, or at endpoint exceeded those associated with placebo by 19 to 84 mg/dL at dosages of 500 to 2000 mg daily, respectively. The corresponding between-group differences in glycated hemoglobin (HbA<sub>1c</sub>) ranged from 0.6% to 2.0% at dosages of 500 to 2000 mg daily, respectively. All between-group differences were significant ( $P < 0.05$ ) for both fasting plasma glucose and HbA<sub>1c</sub> at week 7, week 11, and endpoint, except for the difference between placebo and metformin 500 mg in fasting plasma glucose at endpoint ( $P = 0.054$ ). Treatment-related adverse events occurred in 15% of patients in the placebo group and in 28% in the metformin group ( $P = 0.02$ ); these were primarily manifested as digestive disturbances, such as diarrhea.

**CONCLUSIONS:** Metformin lowered fasting plasma glucose and HbA<sub>1c</sub> generally in a dose-related manner. Benefits were observed with as little as

500 mg of metformin; maximal benefits were observed at the upper limits of the recommended daily dosage. All dosages were well tolerated. Metformin appears to be a useful therapeutic option for physicians who wish to titrate drug therapy to achieve target glucose concentrations. *Am J Med.* 1997;102;491-497. © 1997 by Excerpta Medica, Inc.

The primary goal of treatment in patients with type II diabetes mellitus is to prevent chronic complications. The results of the Diabetes Control and Complications Trial<sup>1</sup> indicate that intensive glycemic control prevents the development and delays the progression of chronic complications in patients with type I diabetes. The results of a similar, but smaller, study from Japan<sup>2</sup> indicate that virtually identical benefits of glycemic control result from intensive management in patients with type II diabetes. Until 1995, the only therapeutic agents for glycemic control were diet, sulfonylureas, and insulin.<sup>3</sup> Now three more therapeutic classes are available: a biguanide, an  $\alpha$ -glucosidase inhibitor, and a thiazolidinedione; there is also a new sulfonylurea.

Metformin is an oral biguanide that has been available in Europe for more than 30 years and in the United States since 1995. Metformin, which is classified as an antihyperglycemic agent, lowers glucose variables by increasing insulin sensitivity in peripheral tissues<sup>4-8</sup> and inhibiting hepatic glucose production.<sup>4,5,9,10</sup> Unlike sulfonylureas, metformin does not stimulate insulin secretion and, consequently, does not produce hypoglycemia.<sup>11-13</sup> In fact, the plasma insulin response to glucose is unchanged or may be decreased in patients with hyperinsulinemia.<sup>11,14</sup> In view of these complementary mechanisms of action for biguanides as compared with sulfonylureas, it is understandable that metformin has synergistic action with sulfonylureas.<sup>13</sup> Metformin alone also has beneficial effects on plasma lipid concentrations and in dyslipidemias, which are independent of glycemic control.<sup>9,13,15</sup> Finally, metformin promotes stabilization of weight and may even cause weight loss.<sup>11</sup>

Despite this extensive clinical research and clinical experience worldwide, no formal dose-ranging study has been conducted because, when the drug was originally developed, such studies were not rou-

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tinely performed in patients. The initial daily dosage selected for clinical studies,<sup>16-18</sup> approximately 3000 mg, was based on animal data.<sup>19-21</sup> Because this dosage was often associated with digestive disturbances, the initial dose was lowered and the drug was titrated at weekly intervals to the final maintenance dosage. Consequently, the current dosing strategy of metformin was determined empirically, rather than by an understanding of the minimal effective dose or of its dose-response relationship in patients with type II diabetes.

The purpose of the current trial was to study the pharmacodynamic effect of various dosages of metformin as compared with placebo in patients with type II diabetes as measured by changes in fasting plasma glucose. Additionally, glycated hemoglobin (HbA<sub>1c</sub>) was evaluated. A secondary objective was to determine the minimal effective dose of metformin.

## PATIENTS AND METHODS

### Study Design

This was a 14-week multicenter, double-blind, dose-response study of 451 patients in 6 parallel treatment groups. All patients were instructed to maintain their recommended dietary and exercise programs. After a 3-week, single-blind, placebo-controlled washout phase, patients were randomized to receive placebo or 1 of 5 dosages of metformin for 11 weeks. The final daily metformin dosages were 500, 1000, 1500, 2000, and 2500 mg. Metformin was supplied as 500-mg tablets. To maintain blinding, matching placebo tablets were used as needed, so that each patient received five tablets daily. The tablets were given 3 times daily (TID) with meals according to the following dose escalation schedule: 1 tablet TID, which was increased over 3 weeks to 2 tablets with breakfast, 1 with lunch, and 2 with dinner. The final regimens, which were given for a minimum of 8 weeks, were metformin 500 mg once daily; 500 mg twice daily (BID); 500 mg TID; 1000 mg BID; and 1000 mg with breakfast, 500 mg with lunch, and 1000 mg with dinner. Compliance was assessed by tablet count at each visit.

### Patients

Eligible patients were men and women at least 30 years old who had type II diabetes, which was suboptimally controlled on diet alone or which was previously treated with an oral sulfonylurea. Three weeks after discontinuing previous drug therapy, they had to have a fasting plasma glucose of at least 180 mg/dL without symptoms.

Patients were excluded if any of the following was present: significant disease or conditions likely to affect their diabetes or ability to complete the study,

markedly symptomatic diabetes, biguanide hypersensitivity, previous insulin therapy, or concomitant treatment with nephrotoxic drugs or other investigational drugs. Women who were pregnant, nursing, or not using adequate methods of contraception were also excluded.

The study protocol was approved by each institution's review board or by the central review board. All patients gave written informed consent before enrollment.

### Evaluation of Safety and Efficacy

Patients visited the local study site weekly during washout and during the first 3 weeks of double-blind treatment; thereafter, patients visited the center after 7 and 11 weeks of double-blind treatment. Physical examination was performed at enrollment and at study completion. Vital signs, adverse events, and concomitant medications were assessed at each visit. Fasting plasma glucose was measured at each visit. Other laboratory evaluations, including HbA<sub>1c</sub>, hematology profile, chemistry profile, and urinalysis, were performed at the beginning and end of washout, and after 7 and 11 weeks of double-blind treatment. Laboratory evaluations were performed by a central laboratory (MAYO Medical Laboratories, Rochester, Minnesota).

The primary efficacy endpoint was defined as the last valid double-blind evaluation for each patient. To be eligible for the efficacy analysis, the patient had to have received at least 4 weeks of treatment and to have data from either week 7 or 11. The primary efficacy variable was fasting plasma glucose at endpoint; data from double-blind treatment weeks 7 and 11 were also analyzed. The other efficacy variable was HbA<sub>1c</sub> from corresponding evaluation periods.

### Statistical Analysis

Baseline demographic characteristics were compared for homogeneity across treatment groups using a Cochran-Mantel-Haenszel test for categorical data and analysis of variance (ANOVA) for continuous variables.

Efficacy analyses were based on intent-to-treat data, without regard to study withdrawal, compliance, or concomitant medications, and on change from baseline in fasting plasma glucose and HbA<sub>1c</sub>. ANOVA was performed using a two-way model with terms for treatment and center; treatment-by-center interactions were found to be insignificant. The dose response was evaluated by pairwise comparisons using a general linear model. William's *t*-bar test<sup>22</sup> was used to determine the minimum effective dose.

All patients were included in the safety analysis. Adverse experience data were analyzed by chi-

square or Fisher's exact test. Laboratory variables were categorized as low, normal, or high. The Stuart-Maxwell statistic, McNemar's test, or the sign test was performed to assess the change in distribution of laboratory variables across the 3 categories from baseline and at double-blind treatment weeks 7 and 11. All tests were two-tailed with levels of significance of 0.05 for efficacy analyses, and 0.10 for treatment-by-center interaction and safety analyses.

## RESULTS

### Patients

Six hundred ninety-three patients were entered into the single-blind, placebo-controlled washout in 1995. Two-hundred forty-two patients (35%) were not randomized because of the presence of exclusion criteria (22%), patient withdrawal (6%), protocol violation (3%), loss to follow-up (2%), physician preference (1%), or an adverse event (1%) during the washout. The remaining 451 patients were evenly distributed across treatment groups based on demographic characteristics, except for age (**Table I**). Mean glucose variables were similar across treatment groups at baseline.

One hundred-ten patients did not complete the entire double-blind treatment but were included in the intent-to-treat analysis. Reasons for stopping treatment were evenly distributed across treatment groups (**Table I**), except for adverse events, which are addressed in the safety analysis.

### Efficacy Analysis

In the placebo group, adjusted mean fasting plasma glucose increased by 0.4 mg/dL between baseline and 7 weeks, and decreased by 8 mg/dL at 11 weeks and at endpoint (**Table II**). In contrast, metformin reduced adjusted mean fasting plasma glucose (FPG) by 24 to 88 mg/dL from baseline, depending on the dose and time of evaluation. The adjusted mean differences between the change from baseline in the placebo group versus the corresponding changes in each metformin group were significant at all evaluation times, except for the difference associated with metformin 500 mg at endpoint ( $P = 0.054$ ). At endpoint, these between-group differences ranged from 19 mg/dL at the lowest dosage to 78 mg/dL at the 2000 mg dosage (**Figure 1**).

Analogous findings were observed for HbA<sub>1c</sub>. In the placebo group, adjusted mean HbA<sub>1c</sub> increased by 1.1%, 1.2%, and 1.2% between baseline and 7 weeks, 11 weeks, and endpoint, respectively (**Table II**). In contrast, metformin reduced adjusted mean HbA<sub>1c</sub> by up to 0.9% from baseline. The adjusted mean between-group differences were significant at all evaluation times ( $P \leq 0.01$ ), ranging at endpoint

from 0.9% at the lowest metformin dosage to 2.0% at the 2000 mg dosage (**Figure 1**).

The results of the William's t-bar test for the minimum effective daily dosage (test statistic and two-sided critical values not shown) were consistent with the ANOVA results ( $P$  values shown in **Table II**). At the 500 mg dosage, the change in FPG from baseline to endpoint was marginally insignificant in the intent-to-treat population ( $P = 0.054$ ) and significant when 13 patients who received concomitant antidiabetic therapy were excluded ( $P = 0.03$ ). At the 500 mg dosage, the corresponding change in HbA<sub>1c</sub> was significant in both patient populations ( $P < 0.001$  and  $P < 0.001$ ).

Pairwise comparisons of adjusted mean changes in FPG from baseline between adjacent metformin dosages confirmed that the maximal response occurred at 2000 mg. All differences between 2000 and  $\leq 1500$  mg were significant ( $P < 0.001$ ). The difference between 2000 and 2500 mg was not significant ( $P = 0.1$ ), suggesting a plateau effect.

### Safety Analysis

The incidence of adverse events, which were considered by the investigator to be related to treatment, was higher in the collective metformin groups than in the placebo group (28% versus 15%;  $P = 0.02$ ) (**Table III**). This resulted primarily from digestive disturbances (24% versus 13%,  $P = 0.025$ ), which were usually manifested as diarrhea (15% versus 5%;  $P = 0.02$ ), nausea (9% versus 5%;  $P = 0.4$ ), or dyspepsia (4% versus 1%;  $P = 0.5$ ). The only other adverse events that occurred in at least 2% of patients within a treatment group were anorexia (2% versus 1%), abdominal pain (2% versus 0%), and hyperglycemia as defined by clinical judgment (1% versus 3%).

When all adverse events were considered, including those considered to be unrelated to treatment, placebo was associated with a twofold higher incidence of hyperglycemia than metformin (16% versus 8%;  $P = 0.02$ ). The only other between-group differences in all adverse events, digestive disturbances and diarrhea, were also reflected in the subset of treatment-related adverse events.

Most treatment-related adverse events were mild or moderate. During treatment with metformin or placebo, only 11 patients experienced serious adverse events, including 1 who was hospitalized because of shortness of breath and chest pain and who was ultimately diagnosed with dyspepsia, which was of moderate severity and possibly related to receiving metformin 1500 mg daily. The other 10 cases were attributed to their underlying diseases.

Metformin was stopped in 17 patients (5%) because of treatment-related adverse events, usually digestive disturbances. All adverse events that led to

TABLE I

## Baseline Demographic Characteristics, Baseline Glucose Variables, and Study Completion Status

Variable	Placebo (n = 79)	Metformin Dose (mg)				
		500 (n = 73)	1000 (n = 73)	1500 (n = 76)	2000 (n = 73)	2500 (n = 77)
Mean age ± SD (y)*	55 ± 11	57 ± 10	55 ± 10	59 ± 10	60 ± 11	59 ± 11
Mean weight ± SD (kg)	90.9 ± 20.1	90.0 ± 20.3	90.0 ± 18.9	89.6 ± 16.2	89.1 ± 20.3	94.5 ± 23.4
Mean height ± SD (cm)	168 ± 10	168 ± 10	168 ± 10	168 ± 13	170 ± 10	168 ± 13
Male (%)	56	62	55	63	53	65
Caucasian (%)	66	74	77	71 <sup>†</sup>	70	79
Black (%)	22	11	12	12 <sup>†</sup>	14	10
Hispanic (%)	11	14	10	15 <sup>†</sup>	12	10
Other (%)	1	1	1	2 <sup>†</sup>	4	0
FPG <sup>‡</sup> ± SD (mg/dL)	279 ± 59.1 <sup>†</sup>	282 ± 59.5	281 ± 60.3	262 ± 51.7	288 ± 61.1	287 ± 59.9
HbA <sub>1c</sub> ± SD (%)	9.9 ± 1.9 <sup>†</sup>	10.1 ± 1.7 <sup>†</sup>	10.0 ± 2.0 <sup>†</sup>	9.7 ± 1.5 <sup>†</sup>	10.1 ± 2.1	10.0 ± 1.8
Study status (%)						
Completed	70	74	75	82	82	71
Incomplete	30	26	25	18	18	29
Adverse event related	6 (0)	4 (0)	5 (5)	7 (3)	7 (4)	14 (10)
Treatment failure	9	10	5	3	1	6
Lost to follow-up	1	3	3	3	0	1
Personal preference	6	4	7	3	3	3
Protocol violation	3	4	3	4	4	3
Other	5	1	1	0	3	1

\* P = 0.03 across all treatment groups.

<sup>†</sup> Data missing for one patient.<sup>‡</sup> FPG = fasting plasma glucose.

TABLE II

## Adjusted Mean Changes from Baseline in Glucose Variables During Double-Blind Treatment

Variable	Placebo (n = 79)	Metformin Dose (mg)				
		500 (n = 73)	1000 (n = 73)	1500 (n = 76)	2000 (n = 73)	2500 (n = 77)
Fasting plasma glucose (mg/dL)						
Week 7	+0.4	-24**	-41***	-49***	-84***	-62***
Week 11	-8	-29*	-43**	-52***	-88***	-73***
Endpoint	-8	-27 <sup>†</sup>	-39**	-49***	-86***	-70***
HbA <sub>1c</sub> (%)						
Week 7	+1.1	+0.4**	-0.01***	-0.3***	-0.5***	-0.1***
Week 11	+1.2	+0.2***	-0.1***	-0.6***	-0.9***	-0.5***
Endpoint	+1.2	+0.3**	+0.01***	-0.5***	-0.8***	-0.4***

\* P &lt; 0.05; \*\* P &lt; 0.01; \*\*\* P &lt; 0.001 for mean difference from placebo, adjusting for center effect in linear model.

<sup>†</sup> P = 0.054 for mean difference from placebo, adjusting for center effect in linear model.

discontinuation of metformin were mild or moderate, except for one case of severe diarrhea and one case of severe abdominal pain, diarrhea, nausea, and vomiting. All of these adverse events resolved after stopping metformin.

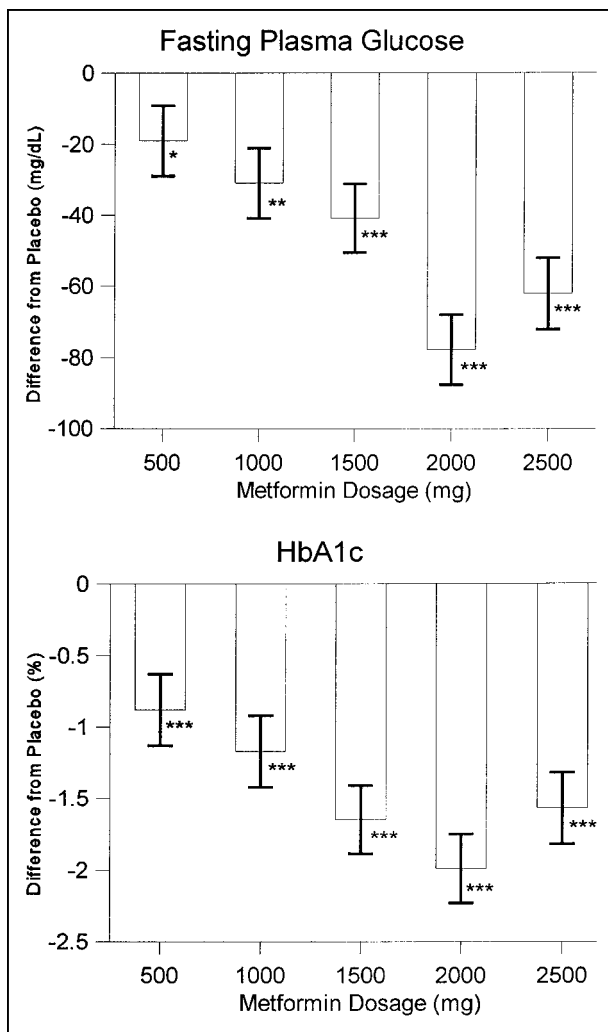
There were no clinically relevant changes in vital signs. Mean weight changes were generally evenly distributed across treatment groups; there was a nonsignificant tendency toward weight loss in all treatment groups. There were no clinically relevant shifts in laboratory variables as measured by the proportions of patients who experienced changes relative to normal values. There were only 3 episodes of

hypoglycemia as defined by clinical judgment, 1 each at daily dosages of 1500, 2000, and 2500 mg; 2 were mild and 1 was moderate; none required discontinuation of treatment.

## COMMENTS

The results of this double-blind, placebo-controlled, multicenter trial in 451 patients with type II diabetes indicate that metformin lowered glucose variables in a generally dose-related manner. Metformin improved glucose variables by more than did placebo. Metformin, at dosages of 500 to 2000 mg daily, reduced adjusted mean FPG from baseline by





**Figure 1.** Estimated difference from placebo ( $\pm$ SE) as measured by changes from respective baseline glucose variables at endpoint. \* $P = 0.054$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$  for estimated difference from placebo.

19 to 84 mg/dL and adjusted mean HbA<sub>1c</sub> by 0.6% to 2.0% more than did placebo. This disproportionate effect on glucose variables is not surprising; FPG rapidly reflects the full effect of treatment whereas the time required for HbA<sub>1c</sub> to reflect the full effect of treatment may have exceeded the 11-week study period. Importantly, these findings indicate that the minimal effective daily dosage of metformin is 500 mg, not 1500 mg as previously reported.<sup>23,24</sup>

Only one previous double-blind study<sup>24</sup> provides direct evidence of a dose relationship. When 75 patients with type II diabetes were randomized to receive placebo or metformin 1500 or 3000 mg daily for 6 months, the between-group differences from their respective baseline FPG values were approximately 27 mg/dL for the lower dosage (NS) and 82 mg/dL for the higher dosage ( $P = 0.001$ ). The authors<sup>24</sup> attributed the lack of benefit at the lower dosage to good initial glycemic control; small sample

size may also have been a confounding factor. In any event, the corresponding between-group differences for HbA<sub>1c</sub> were 1.5% ( $P < 0.001$ ) and 1.8% ( $P < 0.001$ ) for the lower and higher dosages, respectively.

In the current study, the maximal efficacy of metformin was observed at 2000 mg, not at 2500 mg. The explanation for this finding is elusive. It is conceivable that the slightly higher discontinuation rate at the highest dosage may have diluted the effect on glucose variables at the highest dosage in this intent-to-treat analysis. Unfortunately, the current study was not designed to evaluate the clinical practice of titrating the dosage according to individual response because each patient was randomly assigned to a predetermined dosage. Although previous studies were not designed to evaluate dose relationships, their titration phases provide indirect evidence of a within-patient dose relationship up to daily dosages of 2500 mg. For example, the incremental reductions in mean FPG were 22, 23, and 15 mg/dL when the daily dosage was escalated from 850 mg to 1700 mg, then to 2550 mg, respectively.<sup>25</sup> Similarly, the incremental reductions in FPG were 14, 28, 13, 11, and 23 mg/dL when the daily dosage of metformin (in the presence of glyburide) was escalated from 500 mg to 2500 mg at 500-mg intervals.<sup>25</sup>

The reductions in glucose variables observed in the current study are consistent with the findings of a previous study. A 29-week course of metformin 2550 mg reduced mean FPG by 58 mg/dL and mean HbA<sub>1c</sub> by 1.8% more than did placebo in a double-blind study of 289 moderately obese patients with type II diabetes.<sup>25</sup>

The improvements in glycemic control have also been reported for other newly available antidiabetic agents in similar studies of patients with type II diabetes. Three daily dosages of the new sulfonylurea, glimepiride, were evaluated in a dose-response study.<sup>26</sup> Glimepiride reduced median FPG by 43 to 73 mg/dL and median HbA<sub>1c</sub> by 1.2% to 1.9% more than did placebo; however, the median within-treatment change from baseline was relatively slight for HbA<sub>1c</sub>, ranging from +0.2% to -0.3%.<sup>26</sup> Three daily dosages of the new  $\alpha$ -glucosidase inhibitor, acarbose, significantly improved glucose variables compared with placebo, with between-group differences of 27 to 39 mg/dL for mean FPG and 0.8% to 1.0% for mean HbA<sub>1c</sub>.<sup>27</sup> The new thiazolidinedione, troglitazone, reduced mean FPG by 20 mg/dL and mean HbA<sub>1c</sub> by 0.6% more than did placebo.<sup>28</sup> Of course, differences in study design and patient populations may have contributed to the between-study differences in glucose-lowering activity. For example, mean baseline FPG values ranged from 180 mg/dL in the troglitazone study<sup>28</sup> up to approximately 230 mg/dL in the other two studies<sup>26,27</sup>; mean baseline HbA<sub>1c</sub>

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