

Safety and Efficacy of Metformin in a Restricted Formulary

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Abstract

Objective: To assess the efficacy and safety of metformin (MET) in the Veterans' Administration Northern California Health Care System during the period from June 1995 through April 1996 when its use required approval by Endocrinology.

Study Design: A retrospective review of patient charts and computerized pharmacy and laboratory records. Patients served as their own historical controls.

Patients and Methods: Patients receiving MET (n = 251) were identified from the pharmacy database. On-line laboratory data, including the intermediate outcome variable HbA_{1c}, were retrieved by computer for the interval 4 months prior to the initial prescription to May 1996. Clinical data including weight and blood pressure were obtained from chart review.

Results: Of 228 patients whose charts were available for review, 29 reported side effects, and 12 discontinued use due to these side effects. No patients were identified with lactic acidosis. Both baseline and treatment data on HbA_{1c} were available on 164 patients. Mean HbA_{1c} (%) data (unpaired), expressed as mean ± SE, were as follows: between 4 months pretreatment and 1 month pretreatment, 9.41 ± 0.19 (n=103 tests); between 1 month pretreatment and baseline, 9.41 ± 0.19 (n=110 tests); 3 months of treatment, 8.79 ± 0.16 (n=157 tests, P < 0.05); 6 months of

treatment, 8.30 ± 0.17 (n=79 tests, P < 0.0001); 9 months of treatment, 8.72 ± 0.24 (n=70 tests, P < 0.05), compared to pretreatment values. Similar analysis of unpaired weight and blood pressure data in 152 patients did not reveal any reduction in these clinical parameters over this treatment period. Serum lipids were unchanged on treatment (by paired analysis), but the number of tests was limited.

Conclusion: In this setting, MET provided sustained beneficial effects on glycemic control and was well tolerated. Any effects on weight, blood pressure, and serum lipids were not demonstrable in this analysis. We conclude that MET can substantially improve outcome of diabetes care.

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Metformin, a biguanide derivative, has been used throughout the world as an oral agent for managing blood glucose levels in patients with type 2 (noninsulin-dependent) diabetes mellitus for almost two decades. It was not released in the United States until 1995¹⁻⁵ because of safety concerns about a related medication, phenformin, which was withdrawn from the market in 1977 due to reports of fatal lactic acidosis.

Metformin became available to the Department of Veterans Affairs Northern California Health Care System (VANCHCS) shortly after June 1995. Until April 1996, its use required Endocrinology approval due to concerns about its safety in patients with compromised renal function, either at baseline or during treatment, for example after radiological studies using contrast media.

We retrospectively evaluated metformin safety and efficacy during this "closed formulary" period using computer-based analysis. In keeping with observations

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of the Diabetes Control and Complications Trial,⁶ HbA_{1C} was used as the marker of diabetes control.

... PATIENTS AND METHODS ...

We identified patients who received metformin prescriptions between June 1995 and April 1996 using computerized pharmacy records from the VA Decentralized Hospital Computer Program (DHCP). We previously reported our experience using DHCP to identify and monitor pharmacologically-treated diabetic patients.⁷ HbA_{1C} and cholesterol data were retrieved for the study period and were normalized for the period of treatment (ie, we calculated and compared days rather than months of treatment to eliminate calendar differences between patients). Thus, 3 months of treatment represents 45 to 134 days, 6 months represents 135 to 224 days, and 9 months represents 225 to 314 days of treatment. We chose these intervals to correspond to the frequency of HbA_{1C} monitoring recommended by the American Diabetes Association (ADA).⁸ To assess stability, we divided the baseline data into -120 to -31 days (-4 months), and -30 to 0 days (-1 month). Weight and blood pressure data were also normalized for days of treatment.

HbA_{1C} was measured by the Bio-Rad Diamat high-performance liquid chromatography (HPLC) Fully-Automated Glycosylated Hemoglobin Analyzer System (Bio-Rad Laboratories, Diagnostics Group, Hercules, CA). Serum lipids were measured following an overnight fast by routine enzymatic methodology (Paramax by Baxter Diagnostics, Los Angeles, CA). Weight, blood pressure, and HbA_{1C} were compared between baseline and 3, 6, and 9 months of treatment by using all available data for each time interval (unpaired *t* tests) and by using only paired data for each comparison (paired *t* tests). The former assesses the global impact of metformin use; the latter takes into account the decreasing sample size with time. For the unpaired analyses involving HbA_{1C} data, "n" refers to the number of determinations obtained in the interval, not the number of patients tested; in a limited number of cases, patients had two values in an interval. For blood pressure and weight data, "n" refers to the number of patients studied since a single value was taken by the clinic nurse for each interval. For the paired data analyses, the mean of repeat values in any interval was used. Baseline and treatment lipid data from the 48 patients who also had baseline and treatment HbA_{1C} data were analyzed in the same way as HbA_{1C} data, with one exception: only paired analysis was done because of the smaller number, and data

from all three treatment periods were pooled. *P* < 0.05 was considered significant.⁹ Data are shown as mean ± standard error, unless otherwise indicated.

Table 1. Baseline Characteristics of the Study Population (n = 152 patients, unless otherwise noted)

Age (y)	62.4±0.86	
Sex	147 male, 5 female	
Duration of Diabetes (y)	8.5±0.7 (n=113)	
Systolic Blood Pressure (mm Hg)	140.8±1.62	
Diastolic Blood Pressure (mm Hg)	77.5±0.85	
Weight (lbs)	218.9±4.41	
Body Mass Index (kg/m ²)	31.5±0.71 (n=104)	
HbA _{1C} (%)	9.41±0.16 (n=164)	
Creatinine (mg/dL)	1.01±0.016	
Ethnicity (n=164)	no	(%)
White, not of Hispanic origin	100	(61%)
Hispanic white	3	(2%)
Black, not of Hispanic origin	33	(20%)
Asian or Pacific Islander	4	(2%)
American Indian/Alaskan native	2	(1%)
Unknown	22	(13%)

Table 2. Treatment Strategies in the Study Population (n = 152)

Strategy	No
M only	13
M+SU	103
M+INS	12
M+SU+INS	11
M+SU+INS, -INS	10
M+SU+INS, -SU	2
M+INS, -INS	1

M = metformin; SU = sulfonylurea (68 glyburide, 30 glipizide, 11 tolazamide, 11 chlorpropamide, and 1 tolbutamide); INS = insulin; M+SU = metformin + sulfonylurea, M+INS = metformin + insulin, M+SU+INS = metformin+sulfonylurea+insulin; M+SU+INS, -INS = metformin added to sulfonylurea + insulin, insulin discontinued subsequently; M+SU+INS, -SU = metformin added to sulfonylurea + insulin, sulfonylurea discontinued subsequently; and M+INS, -INS = metformin added to insulin, with subsequent discontinuation of insulin.

... RESULTS ...

During the study period, 251 patients received metformin from our pharmacy. This is about 8% of all the pharmacologically-treated diabetic patients in the VANCHCS during this period. Charts were obtained for 228 (91%) of these patients and were reviewed for historical information and weight and blood pressure data. Patients were excluded from the outcome analysis if their charts could not be obtained ($n = 23$), they were noncompliant as assessed by refill irregularity ($n = 4$), or they were already on metformin ($n = 5$). A subgroup of 164 patients had both baseline and on-treatment HbA_{1C} values, and these values were used to assess the effects of metformin therapy on glycemic control. Of these 164 patients, 152 also had baseline and on-treatment weight and blood pressure data. This subgroup ($n = 152$) is the focus of the remaining analysis unless otherwise indicated.

The baseline clinical and demographic characteristics of our study population are shown in Table 1. This was a largely male, older, middle-aged group. Although we were unable to determine the exact duration of diabetes, there was a wide range of disease

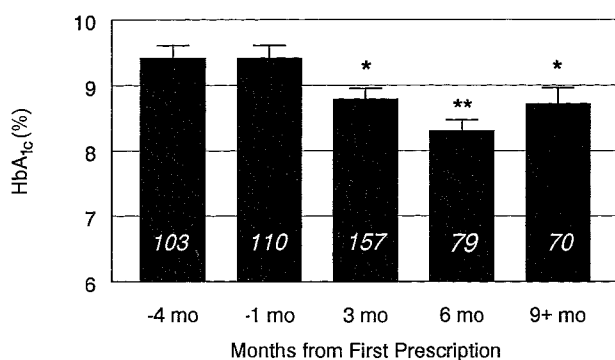
duration. On average, there was a slight elevation of systolic blood pressure, although some patients were clearly hypertensive. Diastolic blood pressure was generally < 90 mm Hg. Obesity was common, as demonstrated by the substantial weight and body mass index (BMI) expressed as weight in kg/(height in meters)². Average baseline HbA_{1C} was 9.41 ± 0.16 ; the average clinic value for all diabetic patients during the period of the study was 8.37 ± 0.04 ,⁷ indicating that patients were selected for treatment due to poor glycemic control. Kidney function, as assessed by serum creatinine, was adequate in keeping with the strict prescribing guidelines. Only one patient had creatinine >1.5 mg/dL at baseline.

Comorbid medical conditions were substantial, reflecting both age and underlying metabolic abnormalities (eg, syndrome X, which links type 2 diabetes mellitus, hypertension, and cardiovascular disease by the common feature of insulin resistance). The chart review showed that 87 of 152 patients were diagnosed with hypertension, 34 had coronary artery disease, 29 had degenerative arthritis, 16 were labeled as "smokers," 12 were diagnosed with chronic obstructive pulmonary disease, and 11 had peripheral vascular disease. The following conditions were also noted in one patient each: cerebrovascular disease, prostatic hypertrophy, bladder cancer, schizophrenia, human immunodeficiency virus infection, gastroesophageal reflux, thyroid cancer, and testicular cancer.

Dosing data are shown in Table 2. Metformin is supplied as 500-mg and 850-mg tablets. The typical starting dose is 500 mg daily or twice daily; the maximum dose is 850 mg tid. Most of our patients were started on 500 mg twice daily and the dosage was titrated up at the provider's discretion. The mean dose in our population was 1.37 ± 0.55 g; the large SD confirms a broad range of dosing.

Providers administered metformin as part of a number of hypoglycemic strategies. Predominantly, metformin was added to ongoing sulfonylurea therapy. The next most common strategy involved metformin as monotherapy (both as initial therapy and after discontinuation of sulfonylurea or insulin monotherapy). In some cases, metformin was administered concomitantly with sulfonylurea-insulin combinations and, in other cases, it replaced either the sulfonylurea or insulin in patients who previously received this combination therapy. The predominant sulfonylurea was glyburide, followed by glipizide, tolazamide, chlorpropamide, and tolbutamide. Most sulfonylureas were prescribed in maximum doses. Insulin was predominantly prescribed as mixtures of NPH/regular, usually in multiple injections.

Figure 1. The Response of HbA_{1C} to Metformin Therapy



Data are shown as mean HbA_{1C} at each time interval. Numbers in bars refer to number of determinations of HbA_{1C} in that time interval.
 * $P < 0.05$ (for 3 and 9+ months of therapy).
 ** $P < 0.001$ (for 6 months).

Figure 1 shows the response of HbA_{1C} to metformin therapy (unpaired data). There were significant drops in HbA_{1C} between baseline and 3 months ($P < 0.05$), between baseline and 6 months ($P < 0.001$), and between baseline and 9 months ($P < 0.05$). The apparent increase in HbA_{1C} between 6 and 9 months was not statistically significant. HbA_{1C} readings taken 4 months and 1 month prior to baseline were not statistically different from those taken 1 month prior to baseline and at baseline, respectively (data not shown). When these data are analyzed by paired *t* test, the results are similar: baseline vs 3 months, 9.52 ± 0.18 vs 8.84 ± 0.17 ($P < 0.0001$, $n = 132$); baseline vs 6 months, 9.23 ± 0.23 vs 8.23 ± 0.18 ($P < 0.0001$, $n = 76$); baseline vs 9 months, 9.75 ± 0.30 vs 8.80 ± 0.31 ($P < 0.001$, $n = 53$). Because of the relatively small number of patients who had readings at all four intervals ($n = 22$), ANOVA analysis was not needed to evaluate the HbA_{1C} response during 9 months of treatment.

Paired analysis of limited data available for patients with baseline and on-treatment HbA_{1C} ($n = 164$) showed that metformin did not significantly affect the plasma lipid profile. The respective baseline and pooled treatment lipid values for these patients follow: total cholesterol, 196.75 ± 4.9 vs 193.45 ± 4.7 ($P = \text{NS}$, $n = 48$); triglycerides, 246.3 ± 23.5 vs 234.2 ± 18.8 ($P = \text{NS}$, $n = 47$); high-density lipoprotein (HDL)-cholesterol, 34.5 ± 1.3 vs 34.9 ± 1.2 ($P = \text{NS}$, $n = 44$); low-density lipoprotein (LDL)-cholesterol, 122.2 ± 4.8 vs 120.3 ± 4.2 ($P = \text{NS}$, $n = 39$).

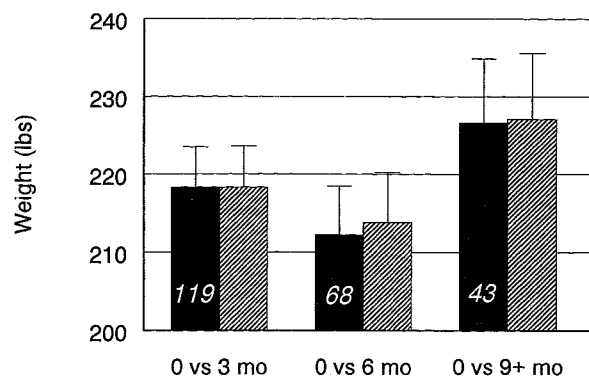
The effect of metformin on weight is shown in Figure 2. There were no statistically significant differences in mean weight when baseline weight was compared with weight at 3, 6, or 9 months. Similarly, there were no apparent effects of metformin on systolic (Figure 3) or diastolic (Figure 4) blood pressure.

Side effects were recorded for 29 of 228 patients (12.7%) and were predominantly gastrointestinal (flatulence, diarrhea, bloating). Seven patients dropped out, mostly because of gastrointestinal side effects, after obtaining at least one treatment of HbA_{1C}. There were no episodes of lactic acidosis. There was one death from an unrelated condition (lung cancer), and there were six recorded cases of hypoglycemia, none requiring hospitalization. Serum creatinine was measured within the time interval in 226 patients; only 3 had values >1.5 mg/dL (maximum: 2.2 mg/dL).

... DISCUSSION ...

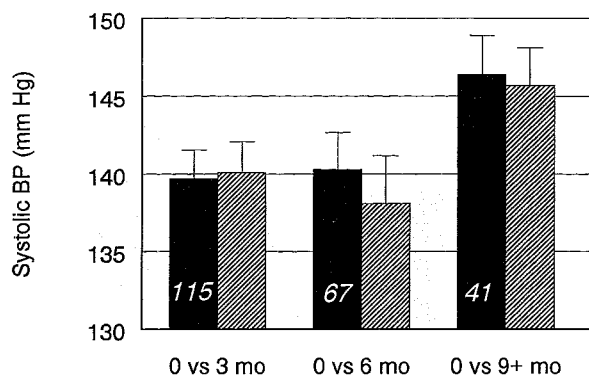
In these selected type 2 diabetic patients, metformin resulted in significant reductions in HbA_{1C} without any apparent effect on weight or blood pres-

Figure 2. The Effect of Metformin on Weight



Data are shown as weight (lb.) at each treatment interval, compared with baseline. Numbers in bars refer to number of patients with weight documented at both baseline and the specific treatment interval. Solid bars = baseline, while hatched bars = values at the treatment interval. There was no significant difference between baseline and treatment weights at any treatment interval.

Figure 3. Effect of Metformin on Systolic Blood Pressure



Data are shown as systolic blood pressure (mm Hg) at each treatment interval, compared with baseline. Numbers in bars refer to number of patients with systolic blood pressure documented at both baseline and the specific treatment interval. Solid bars = baseline, while hatched bars = values at the treatment interval. There was no significant difference between baseline and treatment systolic blood pressure for any treatment interval.

sure. Metformin was used alone and in combination with other agents, primarily sulfonylureas, but also with insulin and insulin and sulfonylureas together. In general, it was well tolerated, and the tolerability profile is in keeping with previous reports.¹⁻⁵

Our failure to achieve good glycemic control despite a substantial improvement in HbA_{1C} probably reflects the types of patients who received metformin. These individuals tended to be older diabetics who had the condition for a substantial time and were not responding well to sulfonylureas or, having failed sulfonylureas, insulin. In addition, comorbid conditions were frequent and severe. While researchers have been unable to correlate health status with glycemic control or the response to metformin, it is likely that a younger, healthier population would have achieved better glycemic control. Kaplan and Feinstein¹⁰ were the first to classify comorbid conditions as cogent and noncogent, with cogent comorbidities defined as those shown to impact survival—including hypertension, chronic lung disease, and peripheral vascular disease. Such diag-

noses were well represented in our population. Ahroni et al¹¹ reported that diabetics with advancing age and symptoms of neuropathy and claudication, as well as other diabetic complications, had a worsened health status than did “healthier” diabetics, although this did not correlate with glycemic control. Ferrannini and colleagues¹² also reported that glycemic control was not associated with obesity, hypertension, or hyperlipidemia.

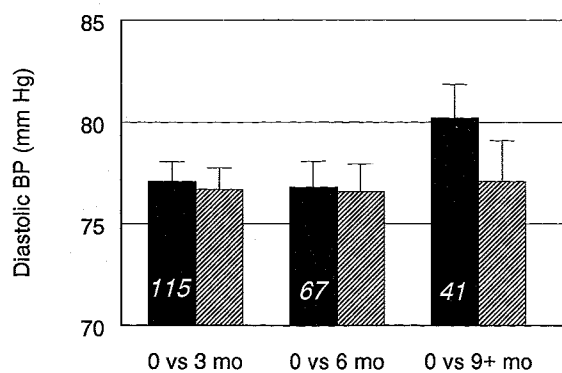
Further, during the study, only about half the maximum dose of metformin was achieved on average. In other parts of the world, metformin is used as first-line therapy; perhaps it may be more suited for addressing the basic insulin-resistant pathophysiology of the type 2 diabetic rather than being used in poorly-controlled sulfonylurea-treated patients in an attempt to avoid initiation of insulin therapy, as it seemed in our population.

In this study, improved glycemic control occurred without weight loss, although metformin has been reported in other studies to aid weight loss. The reason for this is unclear, although the fact that there was no weight reduction during the baseline period suggests that the patients could have been noncompliant with dietary regimens, particularly when beginning a “new” diabetes drug. It is also possible that the study was too short to reveal any statistically significant changes in weight, or that the metformin helped prevent weight gain in patients who also received “traditional” agents typically associated with weight gain—including sulfonylurea and/or insulin.

The effect of metformin appeared to be time-dependent, with the lowest HbA_{1C} occurring at 6 months of therapy. While this appeared to suggest a gradual loss of effectiveness with time beyond 6 months, the paired analysis showed a higher baseline in the group treated for 9 months and a very similar net effect at 6 and 9 months. Although it is possible that tolerance occurred, this has not been described to our knowledge, particularly over such a short period of time.

In other studies, metformin has been associated with an improved plasma lipid profile,¹³⁻¹⁷ even in nondiabetics.¹³ Metformin is reported to exert its major hypolipidemic effect on triglycerides, and to some degree, LDL-cholesterol. This may be particularly evident in postprandial lipemia,¹⁸ and may be more pronounced in nonobese patients.¹³ Our failure to demonstrate an improved lipid profile could be related to any number of factors, including overall poor glycemic control, obesity and dietary noncompliance significant enough to override any improvement, and/or the concomitant use and adjustment of lipid-lowering medications. Further, the relatively

Figure 4. Effect of Metformin on Diastolic Blood Pressure



Data are shown as diastolic blood pressure (mm Hg) at each treatment interval, compared with baseline. Numbers in bars refer to number of patients with diastolic blood pressure documented at both baseline and the specific treatment interval. Solid bars = baseline, while hatched bars = values at the treatment interval. There was no significant difference between baseline and treatment diastolic blood pressure for any of the treatment intervals.

small number of patients tested may have been insufficient to detect a small effect on lipid profiles.

We were unable to demonstrate an improvement in blood pressure in a clinic setting, despite improved HbA_{1C}. Grant¹⁶ also reported that metformin did not affect blood pressure or BMI, while lipids fell only in patients receiving doses of metformin of 3000 mg/dL—roughly 20% in excess of the recommended maximum dose. In other studies, however, metformin has been associated with improved blood pressure,^{14,17,19} possibly due in part to a direct effect on vascular tone.²⁰ The lack of a hypotensive effect of metformin in our patients could reflect the fact that some patients were normotensive at baseline, and that others, while hypertensive, were already receiving antihypertensive medications.

It is possible that our failure to demonstrate significant effects on weight, blood pressure, and lipids reflects patient noncompliance with multiple daily dosing regimens. Metformin has an atypical dose-response curve, in that higher doses do not proportionately increase plasma concentrations; there is a decrease in the amount absorbed with high doses.²¹ As a result, divided doses seem to be more effective at lowering plasma glucose than single doses. While our patients were instructed to take divided doses and the computerized pharmacy records documented that patients took the correct number of tablets per month, there is no guarantee that doses were properly timed. Many of these patients were also taking other medications, which could increase the risk of drug administration errors.

This study is limited in several ways. Because the historical data from the chart review were poorly documented, we were limited in our analysis of these data, particularly height, weight, duration of diabetes, and blood pressure. Similarly, side effects and dietary compliance were variably recorded. BMI, a marker of obesity, was frequently unavailable. In addition, our population was overwhelmingly male, which does not match the demographics of this age group in the private sector. As such, it may be difficult to extrapolate these data to a population that includes a more representative proportion of women. There is no evidence to suggest that metformin affects women differently, but the possibility exists.

We believe that limiting this type of study to computer-accessible data would minimize many of these variables. We urge health administrators to upgrade clinical databases to include weight, height, blood pressure, adverse drug reactions, and other pertinent information, and to provide a reliable means of entering these data.

... CONCLUSION ...

In conclusion, we believe that metformin is an effective adjunct for diabetes management in properly selected patients, including those with relatively poor control. We focused on HbA_{1C} as an outcome measure as validated in the Diabetes Control and Complications Trial⁶ but we did not address the impact on fasting or random sugars. In contrast to some reports from other investigators, there were no demonstrable effects on blood pressure, weight, and lipids. Thus, evidence of an objective benefit was limited. However, there is strong evidence that microvascular complications of diabetes are attenuated by improved glycemic control in both type 1 and type 2 diabetes. Therefore, we believe that even a modest improvement in glycemic control can have significant long-term benefit.

We were not able to ascertain any financial impact of the use of metformin. Metformin is substantially more expensive than sulfonylureas but roughly comparable to insulin on a daily basis when the cost of syringes and other supplies is included. Savings could result from prevention and reduction of hospitalization. On the other hand, these rewards will have to be balanced with the care needed for patients who live longer.

While there are published, randomized, placebo-controlled studies demonstrating the benefit of metformin, our study is the first in a "real world" setting. Adverse events were relatively infrequent.

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