The Effects of Metformin on Glycemic Control and Serum Lipids in Insulin-Treated NIDDM Patients With Suboptimal Metabolic Control

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OBJECTIVE — To test the hypothesis that metformin therapy, given as an adjunct to insulin therapy, improves metabolic control in insulin-treated NIDDM patients with suboptimal glycemic control.

RESEARCH DESIGN AND METHODS — A total of 33 subjects with insulin-treated NIDDM were investigated; all had commenced insulin after secondary failure of antihyperglycemic agents. Two randomized double-blind placebo-controlled crossover studies were run. In study 1 (n = 19), insulin-treated subjects with suboptimal glycemic control received 12 weeks of metformin 1 g b.i.d. and 12 weeks of placebo. In study 2 (n = 14), subjects already established on adjunctive metformin/insulin therapy stopped the metformin component and received 12 weeks of metformin at their baseline dosage (range 1–2.5 g) and 12 weeks of equivalent placebo. Fasting plasma glucose, HbA_{1c}, and serum lipids were measured at baseline and midway through and at the end of each treatment phase. The effect of 12 weeks of metformin treatment was compared with the effect of 12 weeks of placebo in each study and in both studies combined.

RESULTS — In study 1, metformin treatment was associated with significant improvements in fasting plasma glucose (mean 12-week difference from placebo [95% CI]: 5.8 mmol/l [3.5–8.1], $P < 0.001$) and HbA_{1c} (1.6% [0.9–2.4], $P < 0.001$). In study 2, metformin treatment was associated with significantly lower fasting plasma glucose (5.3 mmol/l [0.6–9.9], $P = 0.029$) and lower HbA_{1c} (2.4% [1.0–3.8], $P = 0.003$) compared with those for placebo. Study 2 also showed metformin treatment to be associated with significantly lower total cholesterol than that for placebo (1.0 mmol/l [0.1–1.9], $P = 0.032$) and lower LDL cholesterol (1.0 mmol/l [0.1–1.9], $P = 0.028$). This significant difference in serum lipids seen in study 2 was not seen in study 1, but was present when both sets of data were combined (n = 33, mean total cholesterol difference at 12 weeks [95% CI]: 0.6 mmol/l [0.1–1.1], $P = 0.015$). Metformin had no significant effect on triglyceride, HDL cholesterol, weight, or blood pressure. Two subjects on metformin withdrew because of side effects.

CONCLUSIONS — Metformin, when given as adjunctive therapy, was well tolerated and improved glycemic control and lipid concentrations in patients with insulin-treated NIDDM whose diabetes was poorly controlled. These improvements could be maintained over the long term.

Metformin has been used in the U.K. since 1957, particularly for overweight patients with NIDDM, and has recently been approved for use in the U.S. (1). It has a significant antihyperglycemic action and a beneficial effect on serum lipids (2,3). It has been shown to lower both total and LDL cholesterol and serum triglycerides in NIDDM (4,5). Many studies have shown a significant association of metformin treatment with weight loss (6). The underlying mechanisms for the drug's antidiabetic effects are not fully understood, but it is accepted that they are not mediated through increased insulin secretion. Identified mechanisms include suppression of hepatic glucose output and an increase in peripheral glucose uptake and intestinal glucose use (7). Thus, we hypothesized that metformin was a suitable drug for combination with insulin in the treatment of poorly controlled insulin-treated NIDDM. We aimed to study the effects of giving metformin to insulin-treated NIDDM subjects with suboptimal metabolic control in two randomized placebo-controlled crossover studies.

RESEARCH DESIGN AND METHODS

Study 1

The study was approved by the local research ethics committee of the Kensington, Chelsea, and Westminster Health Authority. Patients with NIDDM were selected from a teaching hospital outpatient diabetic clinic. The diagnosis of NIDDM was based on clinical history and the finding of a fasting plasma glucose concentration >7.8 mmol/l on two occasions. In all cases, insulin had been started after secondary failure of maximum-dose oral antihyperglycemic agents and had been their sole diabetic treatment for at least 1 year. Female subjects of childbearing age, those unable to give fully informed consent, and those already taking any oral antihyperglycemic agent in addition to their insulin were excluded. There was no upper age limit. All patients entered a 6-week run-in phase with two baseline assessments (on days 1 and 28) to determine eligibility for the randomized treatment phase. At enrollment, demographic details and a diabetic history were obtained with a fasting blood sample for laboratory measurements of glucose, creatinine, HbA_{1c}, total cholesterol,

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Received for publication 13 October 1997 and accepted in revised form 22 January 1998.

Table 1—*Baseline characteristics of the patients*

	Study 1	Study 2
n	19	14
Age (years)	61.3 ± 7.1	56.1 ± 8.9
Sex (M/F)	7/12	3/11
Weight (kg)	80.9 ± 6.9	83.2 ± 12.7
BMI (kg/m²)	29.5 ± 3.5	30.9 ± 3.8
Duration of diabetes (years)	15 ± 7	14 ± 6
Retinopathy (yes/no)*	9/10	9/5
Neuropathy (yes/no)*	6/13	3/11
Proteinuria (yes/no)†	1/18	4/10
Systolic blood pressure (mmHg)	137 ± 16	144 ± 23
Diastolic blood pressure (mmHg)	79 ± 10	87 ± 11
Metformin dose (g/24 h)	—	2.0 ± 0.5
Insulin requirement (U/day)	71 ± 47	41 ± 16

Data are *n* or means ± SD. *Information from review of clinical notes. †On dipstick testing.

triglycerides, and HDL cholesterol. On the second baseline visit, a fasting blood sample was taken for glucose and HbA_{1c} measurement, and any change in insulin requirement was noted. Inclusion criteria necessary to proceed to the treatment phase were as follows: suboptimal glycemic control (HbA_{1c} ≥7.5%), stable glycemic control and insulin dosage (baseline values to differ by ≤15%), normal renal function (creatinine ≤125 μmol/l), and BMI ≥23 kg/m².

There were 20 qualifying subjects randomized to receive either metformin 500 mg b.i.d. (increasing to 1 g b.i.d. after 7 days) or placebo for 12 weeks, at which point crossover took place, the treatment phases lasting a total of 24 weeks.

Assessments were performed at 6-week intervals. Each subject attended the metabolic investigation unit at St. Mary's Hospital between 8:00 A.M. and 10:00 A.M. after a 12-h fast. Adverse effects were detected by direct questioning. After examination of the patient's general condition, weight and height were recorded in light clothing and without shoes; resting blood pressure was recorded in the right arm with diastolic pressure recorded at phase V Korotkoff sounds. Venous blood was analyzed for glucose, HbA_{1c}, total cholesterol, triglycerides, and HDL cholesterol. At the conclusion of each visit, subjects were given metformin or matching placebo (Lipha Pharmaceuticals, West Drayton, U.K.), and returned tablets were counted. We aimed to keep insulin dosage constant for the duration of the treatment phase with adjustments made only in the presence of hypoglycemia or significant hyperglycemic symptoms.

Study 2

The study was approved by the local research ethics committee of the Barnet Health Authority. Subjects with NIDDM (diagnostic criteria as for study 1) were selected from a district general hospital outpatient diabetic clinic. As in study 1, all patients were insulin-treated after secondary failure of maximum-dose oral antihyperglycemic agents. In contrast to those entering study 1, however, these subjects were already taking metformin as the sole oral antihyperglycemic agent in addition to their insulin therapy (1,000–2,550 mg/day) and had been doing so for at least 1 year (range 2–11 years). Metformin had been combined with insulin because of suboptimal glycemic control when using insulin alone, despite steady increases in daily insulin dosage. Other inclusion and exclusion criteria were the same as for those of study 1, and all entered an identical run-in phase. The entry criteria for the treatment phase were as follows: stable glycemic control and insulin dosage (baseline values to differ by ≤15%), normal renal function (creatinine ≤125 μmol/l), and BMI ≥23 kg/m².

There were 15 qualifying subjects randomized to receive either metformin (500- or 850-mg tablets) or matching placebo in a regimen equivalent to their normal metformin prescription, which was stopped. At 12 weeks, crossover took place, the treatment phase lasting a total of 24 weeks.

Assessments were performed at 6-week intervals, following the same protocol as in study 1. At the conclusion of each visit, metformin or matching placebo was dispensed, and returned tablets were counted. Again, we aimed to keep insulin dosage constant for the duration of the treatment phases with adjustments made only in the presence of hypoglycemia or significant hyperglycemic symptoms.

Analytic methods

Plasma glucose, triglycerides, total cholesterol, and HDL cholesterol were quantified by enzymatic techniques using an Olympus AU5200 analyzer (Olympus). HbA_{1c} was quantified after separation by low-pressure cation exchange chromatography in conjunction with gradient elusion using a 765 Glycomat analyzer. LDL cholesterol was calculated using Friedewald's formula (8).

Statistical analysis

Data are expressed as means ± SD. To assess the differences between the two treatments, we compared the change in variables over the 12 weeks of each of the two treatment phases: the metformin phase or the placebo phase. Changes in variables have been calculated as values at the end of a 12-week phase minus values at the beginning of that 12-week phase. For triglycerides, changes in values refer to ratios: end of period to start of period. Differences between the changes in variables after metformin and placebo treatment were analyzed using the method for a two-way crossover clinical trial described by Hills and Armitage (9), which takes into account any differences due to order of treatment (first or second phase) and also any carryover effects from one treatment phase to the next. Means and 95% CIs for the differences between treatments are given.

RESULTS

Study 1

We recruited 20 subjects, and 19 completed the study. One subject withdrew after the onset of diarrhea early in the metformin phase. Baseline characteristics of the remaining 19 subjects are shown in Table 1. One subject suffered mild abdominal bloating and completed the study on a reduced dose of metformin (500 mg b.i.d.). One subject suffered from a VIth nerve palsy during the placebo phase; investigation concluded that this was a complication of his diabetes. All exhibited poor but stable glycemic control (mean of baseline HbA_{1c} 9.1 ± 1.2% [normal range <6.5%]; mean difference between first and second baseline HbA_{1c} 5.4 ± 4.5% of first value). Insulin dosage was also stable during the

Table 2—*Results from study 1: effects of 12-week metformin versus placebo on clinical and metabolic parameters*

Parameter	Baseline	Change after 12 weeks placebo	Change after 12 weeks metformin	Difference	*P* value
Body weight (kg)	81.1 ± 16.9	0.0 ± 1.8	−0.5 ± 3.1	0.5 (−1.0 to 2.1)	0.465
Fasting plasma glucose (mmol/l)	11.8 ± 3.7	1.9 ± 3.8	−3.8 ± 3.2	5.8 (3.5 to 8.1)	<0.001
HbA_{1c} (%)	8.9 ± 1.0	0.5 ± 0.9	−1.1 ± 1.3	1.6 (0.9 to 2.4)	<0.001
Total cholesterol (mmol/l)	6.0 ± 1.1	0.0 ± 0.8	−0.3 ± 0.7	0.3 (−0.2 to 0.8)	0.248
HDL cholesterol (mmol/l)	1.1 ± 0.3	0.1 ± 0.2	0.0 ± 0.1	0.1 (−0.1 to 0.2)	0.284
Triglycerides (mmol/l)	2.2 ± 1.3	1.0 ± 0.4	0.9 ± 0.2	0.1 (−0.2 to 0.3)	0.543
LDL cholesterol (mmol/l)	3.9 ± 1.2	0.0 ± 0.8	−0.2 ± 0.6	0.3 (−0.2 to 0.7)	0.244
Systolic blood pressure (mmHg)	138 ± 16	2 ± 23	−4.0 ± 13	6 (−11 to 23)	0.452
Diastolic blood pressure (mmHg)	78 ± 9	4 ± 11	−3 ± 9	7 (0 to 15)	0.053

Data are means ± SD or means (95% CI). Change was calculated as the value at the start of each 12-week treatment period (metformin or placebo) minus the value at the end of that 12-week treatment period; a negative value implies a lowering of that value. The difference was calculated by subtracting change after metformin from change after placebo (weighted according to the number of patients receiving metformin first and the number receiving placebo first). For triglycerides, changes refer to ratios (end of period to start of period). *P* values were assessed using methods described by Hills and Armitage.

run-in phase, with only one subject altering his or her total daily dose (4-U increase). The results of study 1 are shown in Table 2. There was no evidence of a treatment-order or carryover effect. Daily insulin dosage was relatively constant throughout the treatment phase: mean change during the placebo phase was +0.6 U and during the metformin phase −1.9 U. Metformin treatment was associated with significant improvement in fasting plasma glucose at the 12-week assessment (mean difference from placebo 5.8 mmol/l, $P < 0.001$). Similarly, metformin treatment was associated with significant improvement in HbA_{1c} at 12 weeks (mean difference from placebo 1.6%, $P < 0.001$). Insignificant numerical improvements in both HbA_{1c} and fasting plasma glucose were seen after 6 weeks of metformin treatment. There were no significant changes in weight, total cholesterol, triglycerides, HDL cholesterol, or diastolic and systolic blood pressure. There were no significant correlations between change in BMI and change in fasting plasma glucose or HbA_{1c}. No serious hypoglycemic episodes were reported, and compliance was satisfactory as assessed by tablet counting.

Study 2

We recruited 15 subjects, and 14 satisfactorily completed the study. One subject withdrew complaining of abdominal pain and gastric upset. She recovered, and her symptoms were judged to be related to a past history of diverticular disease. Baseline characteristics of the subjects who completed the treatment phase are shown in Table 1. All exhibited stable glycemic control (mean difference between first and second baseline HbA_{1c} 5.8 ± 4.7% of first value). Insulin dosage was also stable during the run-in phase, with only three subjects altering their daily total, and each by just 2 U. The results of study 2 are shown in Table 3. There was no evidence of a treatment-order or carryover effect. While total daily insulin dosage remained relatively constant during the metformin phase (mean change −0.2 U), it tended to be increased during the placebo phase to combat symptomatic hyperglycemia (mean increase 9.0 U). Despite this, metformin treatment, as compared with placebo, was associated with significantly lower fasting plasma glucose values at the 12-week assessments (mean difference 5.3 mmol/l, $P = 0.029$) and with significantly lower HbA_{1c} (mean difference 2.4%, $P = 0.003$). Metformin treatment was also associated with lower total cholesterol values at 12 weeks (mean difference from placebo 1.0 mmol/l, $P = 0.032$) and also

Table 3—*Results from study 2: effects of 12-week metformin versus placebo on clinical and metabolic parameters*

Parameter	Baseline	Change after 12 weeks placebo	Change after 12 weeks metformin	Difference	*P* value
Body weight (kg)	83.2 ± 12.7	−0.8 ± 1.6	0.3 ± 2.2	−1.0 (−2.2 to 0.3)	0.116
Fasting plasma glucose (mmol/l)	10.6 ± 4.2	2.5 ± 3.0	−3.0 ± 6.1	5.3 (0.6 to 9.9)	0.029*
HbA_{1c} (%)	9.5 ± 1.2	1.4 ± 1.5	−1.1 ± 1.3	2.4 (1.0 to 3.8)	0.003†
Total cholesterol (mmol/l)	6.4 ± 1.2	0.5 ± 0.6	−0.6 ± 1.1	1.0 (0.1 to 1.9)	0.032†
HDL cholesterol (mmol/l)	1.2 ± 0.4	0.0 ± 0.3	0.1 ± 0.2	−0.1 (−0.4 to 0.2)	0.439
Triglycerides (mmol/l)	2.5 ± 2.4	1.1 ± 0.3	1.1 ± 0.2	0.1 (−0 2 to 0.3)	0.665
LDL cholesterol (mmol/l)	4.1 ± 1.5	0.4 ± 0.6	−0.7 ± 1.0	1.0 (0.1 to 1.9)	0.028†
Systolic blood pressure (mmHg)	144 ± 23	3 ± 24	1 ±18	0 (−21 to 21)	0.985
Diastolic blood pressure (mmHg)	87 ± 11	−1 ± 9	3 ± 9	−6 (−14 to 2)	0.135

Data are means ± SD or means (95% CI). Change was calculated as the value at the start of each 12-week treatment period (metformin or placebo) minus the value at the end of that 12-week treatment period; a negative value implies a lowering of that value. The difference was calculated by subtracting change after metformin from change after placebo (weighted according to the number of patients receiving metformin first and the number receiving placebo first). For triglycerides, changes refer to ratios (end of period to start of period). *P* values were assessed using methods described by Hills and Armitage. *$P < 0.05$; †$P < 0.01$.

with lower LDL cholesterol values (mean difference from placebo 1.0 mmol/l, $P = 0.028$). Insignificant numerical improvements in both HbA_{1c}, fasting plasma glucose, and total and LDL cholesterol were seen after 6 weeks of metformin treatment. There were no significant changes in weight, triglycerides, HDL cholesterol, and diastolic or systolic blood pressure. There were no significant correlations between change in BMI and change in fasting plasma glucose, HbA_{1c}, and LDL or total cholesterol. No serious hypoglycemic episodes were reported and compliance was considered satisfactory.

Studies 1 and 2 combined

When both sets of data were analyzed together, metformin-associated improvements in fasting plasma glucose, HbA_{1c}, and total and LDL cholesterol remained significant (mean differences: fasting plasma glucose 5.6 mmol/l, $P < 0.001$; HbA_{1c} 2.0%, $P < 0.001$; total cholesterol 0.6 mmol/l, $P = 0.015$; LDL cholesterol 0.6 mmol/l, $P = 0.015$).

CONCLUSIONS — Lifestyle modifications are first-line treatment for NIDDM patients. However, only a minority achieve satisfactory metabolic control after 1 year. Second-line treatment is with oral antihyperglycemic agents, usually a sulfonylurea, with metformin reserved for the obese. Upon failure of oral antihyperglycemic agents, conversion to insulin therapy is the usual next treatment step. Many insulin-treated NIDDM patients still achieve only poor glycemic control and suffer high complication rates (10–13). Despite progressive increases in dosage, insulin may not improve diabetic control and often causes weight gain. NIDDM patients who are insulin-treated subsequent to oral antihyperglycemic agent failure, who also exhibit weight gain and poor metabolic control despite increasing insulin dosage, can usefully be described as having insulin treatment failure.

There is no consensus on how best to treat poorly controlled insulin-treated NIDDM patients. Options include intensifying the insulin regimen or combining insulin with an oral antihyperglycemic agent. The Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes showed how a four-step intensive therapy regimen could substantially improve glycemic control, as compared with a single morning insulin injection regimen (14). However, most of the decrease in HbA_{1c} occurred with a single dose of intermediate insulin at bedtime; the addition of glipizide and multiple daily insulin injections led to only small additional decreases in HbA_{1c}. Some studies have shown significant improvements in glycemic control and serum lipids when sulfonylureas are given in addition to insulin (15) but have failed to show a fall in serum insulin levels (16), despite reductions in exogenous insulin dosage, or a reduction in weight, and none have investigated long-term effectiveness.

There are few data on the adjunctive use of metformin. Metformin has been shown to be safe and effective in improving glycemic control in NIDDM patients when diet or sulfonylureas alone have been inadequate (1,17,18) and, in just one study, in obese insulin-treated NIDDM subjects (19). In addition, reductions in weight, triglyceride, LDL cholesterol, insulin resistance, and plasminogen activator inhibitor and an increase in HDL cholesterol (2–5,20–23) have been recorded. The current studies found that adjunctive metformin therapy significantly improves glycemic control in NIDDM patients who have insulin treatment failure, reducing fasting plasma glucose by 40% and HbA_{1c} by 20%. LDL cholesterol was lowered by 15%. There was no apparent change in HDL cholesterol, in contrast to some previous studies where an increase has been associated with metformin therapy (3,24). Long-term benefit from metformin is suggested by our study 2 data, where cessation of additional metformin therapy in insulin-treated NIDDM resulted in a deterioration of glycemic control and LDL cholesterol despite increases in total daily insulin dosage. The reduction in LDL cholesterol associated with metformin therapy in our studies is of interest because of the strong association between LDL cholesterol concentration and the development of ischemic heart disease and the demonstration that a reduction in LDL cholesterol is associated with a reduction of coronary mortality in nondiabetic men (25). Metformin had no effect on weight in either study 1 or 2, in contrast with several previous sulfonylurea and insulin combination studies (26,27).

In conclusion, adjunctive metformin therapy may improve metabolic control in insulin-treated NIDDM patients.

Acknowledgments — This study was supported by a grant from Lipha Pharmaceuticals.

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