

USE OF METFORMIN IN SELECTED CASES OF NIDDM A CLINICAL TRIAL

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SUMMARY:

The usefulness of metformin in the management of diabetes was assessed in 55 NIDDM patients who did not have any contraindications for the use of the drugs. None had evidence of vascular complications or hepatic derangement. Diabetes was under good control in all (PPBS < 160 mgs/dl and HbA1 < 9%), with diet and a combination of glibenclamide and metformin. Metformin was withdrawn in all of them and 34 out of 55 patients continued to have good control of glycaemia. In the remaining 21 patients, plasma glucose increased significantly and metformin had to be reintroduced after a mean period of 4 weeks. In 14 of these patients plasma glucose decreased to normal in 2 weeks and in the other 7 the dose had to be increased to higher than the initial one to achieve good control.

Thus the study shows that addition of metformin proves useful in selected patients when sulphonylurea alone proves ineffective in control of diabetes.

INTRODUCTION

The use of biguanides in the treatment of diabetes has declined due to the fear of hyperlactatemia^{1,2}. Earlier studies have shown that biguanides are useful in carefully selected patients especially in combination with sulphonylureas^{3,4}. It has been shown that a combination therapy with biguanide and sulphonylurea is more effective than either drug used alone both in clinical⁵ as well as in pharmacological experiments in dogs⁶.

This study was taken up to evaluate whether metformin really contributes to effective control of diabetes in patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM).

MATERIAL AND METHODS

The study was taken up in two phases. In the first phase, metformin was withdrawn in non-insulin dependent diabetic patients (NIDDM) who were regulated with a combination of glibenclamide and metformin. The effect of withdrawal was monitored when pa-

tients were continued on glibenclamide and placebo. In the second phase of the trial, metformin was reintroduced in those in whom there was increase in blood sugar and the subsequent effect was recorded.

Fifty five NIDDM patients (32 men and 23 women) were taken up for the study. The duration of diabetes varied from 1 to 22 years and the mean age was 45 ± 7.0 years. The mean body mass index was 24 ± 3.2 . All patients received glibenclamide (5 mg/day in two divided doses) plus metformin (500 mg/day) and high carbohydrate high fibre diet (HCHF diet) containing 68% carbohydrate, 12% fat and 20% proteins, the total diet allowance of which ranged from 1600-2000 calories.

None of the patients had retinopathy or nephropathy nor any hepatic or heart disease. All were under good glycemic control at the start of the study (PP BG < 160 mg/dl). The PP plasma glucose remained below 160 mg/dl on three consecutive visits in a period of 3 months, and HbA₁ was $8.5 \pm 1.1\%$. Metformin was withdrawn at this stage (Phase I) and the patients were continued on same dose of glibenclamide plus a placebo. They were reviewed at the centre fortnightly. At every visit

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the patients were reviewed by the dietitian in order to obtain continued satisfactory dietary adherence during the study period. If the PP Plasma glucose was found to be <160 mg and HbA_1 remained $<9\%$ they were advised to continue the same treatment. If the glucose concentration was above 180 mg% or the $HbA_1 > 9.0\%$ metformin was reintroduced in the same dose at the time of withdrawal (Stage II). These patients were reviewed every week and glycaemic regulation assessed for a further period of 4-8 weeks.

Plasma glucose was estimated by the O-toluidine method and HbA_1 by the colorimetric procedure of Eross *et al*⁷.

Statistical analysis were done using the Mann-Whitney-U test.

RESULTS:

Table 1 gives the results of the study.

Despite metformin withdrawal 34 of the 55 patients continued to have good regulation of glycaemia. In the remaining 21 patients, the plasma glucose increased significantly and metformin had to be reintroduced after a mean period of 4 weeks. In 14 of these patients the plasma glucose decreased to normal in 2 weeks. In the remaining 7 the dose had to be increased to higher than the initial dose to achieve good glycaemic control.

DISCUSSION:

Metformin is still widely used in the treatment of NIDDM patients. This compound has survived the severe restrictions laid on the use of biguanides, due to its minimum risk of side reactions⁸ and the use of metformin is approved in several European countries. In a large number of patients, we have shown that the blood lactate levels do not increase with biguanides provided these patients have no contraindications for its use^{3,4}. Hence we have not estimated blood lactate levels in the patients in this study.

Earlier studies^{5,6} have reported on the synergistic effect of biguanides when used in combination with sulphonylureas. They help in rapid control of hyperglycemia and also help to reduce the dose of individual drugs. The beneficial effect of the combination may be due to enhanced action of the endogenous insulin. The present study demonstrates that metformin is helpful in maintaining sustained metabolic control in several NIDDM patients. Withdrawal of drug leads to deterioration and reintroduction to improvement of diabetes control in a considerable proportion of the patients in this study.

In many patients with NIDDM a well balanced diet, weight reduction and physical ex-

Table 1
EFFECT OF WITHDRAWAL OF METFORMIN AND ITS
REINTRODUCTION ON PP PLASMA GLUCOSE AND HbA_1 VALUES
(n = 21)

PP Glucose \pm SD mg/dl			HbA_1 % \pm SD		
I	II	III	I	II	III
151 \pm 11	253 \pm 47	176 \pm 50	8.5 \pm 0.88	9.9 \pm 1.2	8.9 \pm 1.0
	X	XX		X	
	P < 0.001	P < 0.001		P < 0.01	
I. At withdrawal	II. At the time of Reintroduction (4 weeks)		III. Subsequent to Reintroduction (4 weeks)		

x In comparison with I

xx In comparison with II

ercise are adequate for amelioration of the diabetic state. In others sulphonylurea compounds are indicated. We reserve the use of metformin to patients in whom sulphonylureas alone prove ineffective to control diabetes. Addition of metformin helps to control diabetes in such cases where the alternative would be insulin injection. However it is essential to ensure that patients have normal liver and kidney functions and that anoxic states are absent. If used in carefully selected cases, metformin still appears to have a role in the treatment of NIDDM.

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