Academic Sciences Asian Journal of Pharmaceutical and Clinical Research
Vol 5, Suppl 1, 2012 ISSN - 0974-2441

Research Article

ADVERSE EFFECTS OF METFORMIN IN COMBINATION WITH GLIMEPIRIDE AND GLIBENCLAMIDE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Received: 22 October 2011, Revised and Accepted: 15 December 2011

ABSTRACT

In type 2 diabetes mellitus, it is considered that the lowered insulin secretion and the lowered insulin sensitivity cause hyperglycaemia. Sulfonylureas have strong blood-glucose lowering effect by stimulating insulin secretion and have been widely used in the treatment of type 2 diabetes. However, the use of sulfonylureas has several issues (weight gain, hypoglycaemia, secondary failure etc.), some of which may be due to stimulation of strong insulin secretion. Sulfonylurea's, which have evolved through two generations since their introduction nearly many years ago, remain the most frequently prescribed oral agents for treatment of patients with type 2 diabetes mellitus.Sulfonylureas also represent the most cost effective therapeutic option alone or in combination with drugs like metformin.There is an enormous amount of data concerning their efficacy and safety in humans. Despite their wide acceptance, however certain critical issues remain. It is increasingly obvious that to achieve this on a global perspective we will need to identify the better and safer treatment strategies to maintain tight glycemic control as well as lower adverse effects in type 2 diabetic patients. This study was suggesting that combination therapy with metformin plus glimepiride was more effective in improving glycemic control, exhibiting weight neutralizing/reducing effects, and having minimum adverse effect than metformin plus glibenclamide combination treatment in patients with type 2 diabetes mellitus.

Key words: Type 2 diabetes, adverse drug reaction, metformin, glimepiride, glibenclamide.

INTRODUCTION

Type 2 diabetes mellitus emerges as a result of multiple pathophysiologic changes. If the pharmacotherapy of type 2 diabetes should be tailored to the underlying pathophysiology, it would be necessary to use a combination of agents with complementary mechanisms of action. The two principal defects in type 2 diabetes are insulin deficiency and insulin resistance. Therefore, combining an insulin-providing agent with an insulin sensitizing agent will augment the efficacy of current antihyperglycemic agents. This is the rational for combining the sulfonylurea/metformin agents.

The ultimate or primary goal of therapy for type 2 diabetes is to prevent the mortality and morbidity related to the microvascular and macrovascular complications. Since these diseases are lifelong disorders, reduction in the number of tablets and daily doses is a very important consideration from the patient's point of view. It is increasingly obvious that to achieve this on a global perspective we will need to identify better and more effective treatment strategies to maintain tight glycemic control.

The current practice of starting therapy with one agent and increasing to maximum dosage before adding a second agent, rather than starting with combination therapy, also needs to be addressed. There is much evidence to suggest that initiating therapy with lower doses of two agents that have complementary effects can increase the overall efficacy and decreases the incidence of adverse effects[1-5].

MATERIALS & METHODS

A total of 270 Indian type 2 diabetic patients were enrolled in the study, on the basis of inclusion & exclusion criteria after getting approval from Institutional Human Ethics Committee. Men and women were eligible to participate in the study if they had uncontrolled type 2 diabetes mellitus, obese/overweight, fasting plasma glucose > 140 mg/dl and glycosylated hemoglobin > 7.0 % from inpatient and outpatient departments of the hospital. All patients were enrolled in the study after signing the informed consent form. Each patient was interviewed, for their past medication history for diabetes before participation in the study. Patients were included in the study if their diabetes was not adequately controlled by diet, physical activity, and weight reduction alone, or by treatment with single oral hypoglycemic agents (OHA's). Patients those taking glibenclamide, metformin, or glimepiride alone; one of two varied combinations wassubstituted. Additional exclusion criteria included were type 1 diabetes, a clinically relevant, medical or psychological condition, history of drug or alcohol abuse, pregnancy, breast feeding, renal insufficiency, hepatic insufficiency, respiratory insufficiency, hypoxic conditions, acute myocardial infarction, congestive cardiac failure, acute hepatitis, ketoacidosis, disseminated tuberculosis (severe infections), history of adverse reaction to sulfonylurea or metformin. Baseline data of all patients (n = 270) **(Table 1).** Data collected were patient name, inpatient number, address, age, gender, height (cm), body weight (kg), body mass index (BMI, kg/m^2), date of visit, review on, social status, family history, associated disease/disorder, HbA1c levels. Patients were not given renewed advice about dietary measures and weight loss at the start of this study. All the parameters such as HbA1c, BMI (kg/m^2), fasting plasma glucose, postprandial plasma glucose, were evaluated at the baseline and at the end of 6 months; along with possible adverse effects of drugs.

RESULTS

Demographic and Baseline Characteristic of Patients:

A total of 270 patients were monitor for possible adverse effect, and data were available for all the patients at baseline **(Table 1).** The two varied combination therapy included 154 men and 116 women. Follow up of all 270 patients were taken up to 6 months.

Table 1: Demographic and Clinical Characteristics of Patients at Baseline (n = 270).

N = 270	
Sex[a]	
Male	154 (57.04%)
Female	116 (42.96%)
Age (years)[b]	49 (range 32-68)
Body height (cm)[c]	169 ± 8.1
Body weight (kg)[c]	67.4 ± 10.2
BMI (kg/m^2)[c]	25.7 ± 4.1
Duration of diabetes (years)[c]	6.2 ± 3.2

Data are [a]number (%), [b]median (range) and [c]mean (± SD)

Adverse Effects of Metformin plus Glimepiride Vs Metformin plus Glibenclamide Combination Therapy in Type 2 Diabetics

A total 270 patients were taking metformin plus glimepiride Vs metformin plus glibenclamidecombination therapy up to 6 months. All possible adverse effects were measure in diabetic patients **(Table 2).**Adverse effects were measures in two phases as 0 to 15 week & 16 to 30 week's time period. In this study, we monitor the possible adverse effects of two varied combination treatment. Hypoglycemic attack was observed more in metformin plus glibenclamide than metformin plus glimepiride treatment **(Table 2).**

Table 2: Adverse Effects of Two Varied Combination Therapy in Type 2 Diabetics.

Over 6 Months (n = 270) [Data are number (%)].

Types of Adverse Effect	Metformin plus Glimepiride (n=135)		Metformin plus Glibenclamide (n=135)	
	0-15 Week	16-30 Week	0-15 Week	16-30 Week
Nausea	21 (15.55)	11 (8.15)	30 (22.22)	19 (14.07)
Vomiting	15 (11.11)	09 (6.66)	19 (14.07)	09 (6.66)
Diarrhoea	07 (5.19)	04 (2.96)	10 (7.41)	05 (3.70)
Hypoglycemia	20 (14.81)	09 (6.66)	39 (28.88)	19 (14.07)
Weight Gain	10 (7.41)	07 (5.19)	15 (11.11)	09 (6.66)
Abdominal Pain	21 (15.55)	10 (7.41))	25 (18.52)	19 (14.07)
Metallic Taste	17 (12.59)	09 (6.66)	24 (17.77)	14 (10.37)

DISCUSSION

Diabetes is a chronic progressive disorder. The progression of diabetes results from a vicious cycle of insulin resistance and β-cell failure. Excess circulating glucose in turn itself is damaging to the β-cell (Commonly referred to as glucotoxicity) and may further accelerate the progression of the disease. Thus, loss of β-cell function is inevitable in patients with diabetes regardless of the treatment modality[1, 6-9].

Sulfonylurea and metformin have different mechanisms of action. Sulfonylurea mainly decrease blood glucose levels by stimulating insulin release from the pancreatic β-cells whereas metformin reduces blood glucose levels predominantly by improving hepatic and peripheral tissue sensitivity to insulin i.e. decreases hepatic and peripheral insulin resistance by decreasing affinity of insulin receptors towards insulin and by increasing the number of insulin receptors. Thus, decreases hyperinsulinemia. It also decreases hepatic gluconeogenesis thereby decreasing high glucose output, reduces intestinal absorption of glucose and reduces blood glucose levels (fasting and post-prandial). Decreases weight thereby improves insulin resistance. Metformin also has beneficial effects on serum lipid levels and fibrinolytic activity, thereby decreasing the cardiovascular risk. Because of their complementary mechanisms of action, combination therapy with sulfonylurea and metformin is rational and is associated with additive beneficial effect on the glycemic control. Combination therapy with a sulfonylurea and metformin is potentially effective in maintaining glycemic control and avoiding of insulin for a mean duration of 7.9 years. Sulfonylurea like glibenclamide and glimepiride are approved by USFDA in combination with metformin[10-12].

There is much evidence to suggest that initiating therapy with lower doses of two agents that have complementary effects can increase the overall efficacy and decreases the incidence of adverse effects. Therefore, combining an insulin-providing agent with an insulin sensitizing agent will augment the efficacy of current antihyperglycemic agents. This is the rational for the development and marketing of sulfonylurea/metformin combination tablets. Glimepiride is generally safe and well tolerated. In earlier comparative trials, adverse events occurred in a similar proportionsin glimepiride and glipizide patients and were less frequent with glimepiride than glibenclamide.

One of the most important side effects of sulfonylurea treatment is hypoglycaemia, which in rare cases can be fatal. A comparative study in 1044 patients showed 14% and 11% hypoglycaemic episodes with glibenclamide and glimepiride patients respectively. In this present study, Metformin plus Glibenclamide combination having more risk of hypoglycemic attack than the Metformin plus Glimepiride treatment.

In another double blind, glibenclamide-controlled study in NIDDM patients; significantly less hypoglycaemia occurred with glimepiride patients (1.7%) and glibenclamide (5.6%) during the first month of treatment even though fasting blood glucose reduction was similar (glimepiride and glibenclamide: 48 mg/dL)[13]. In this study, most of the patients having adverse effects in their first phase i.e. 0 to 15 week time period.

Weight increase is another critical issue of sulfonylurea treatment. In UK Prospective Diabetes Study (UKPDS), the average weight gain during treatment with glyburide was 4.5 kg at 10 years [14]. In the present study, we have got the more number of people having weight gain as adverse effect in Metformin plus Glibenclamide combination.

CONCLUSION

The present study reveals that, Metformin plus Glimepiride was effective in improving glycemic control over Metformin plus Glibenclamide combination treatment. This combination exhibits weight neutralizing/reducing effects in patients with type 2 diabetes mellitus with minimal adverse effects, has a lower risk of hypoglycaemia, thus supporting its first - line use in type 2 diabetes mellitus.

Source(s) of support:Nil

Conflicts of Interest: None declared

ACKNOWLEDGEMENT

The authors are appreciating the cooperation of Dr. P. N. Dighore (M.D.), General Physician, Indira Gandhi Memorial Hospital, Shirpur-425405, Dhule, Maharashtra, India.

We are grateful to the patients who participated in this study; and to the kind assistance of the staff members of the Indira Gandhi Memorial Hospital, Shirpur and all people who kindly helped us in conducting this research, especially in acquisition of the data.

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