Comparison of a generic and a brand metformin products in type II diabetes: A double blind randomized clinical trial study

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ABSTRACT

Metformin is often prescribed for glycemic control in type II diabetes mellitus. This drug is the first line treatment for obese without renal or liver failure. Different pharmaceutical types of Metformin are available. As a clinical trial, therapeutic effects of a generic (Aria Pharmaceutical Company, Iran) with a brand metformin (Glucophage, product of Merck pharmaceutical company, France) in diabetic patients were compared. This double blind randomized clinical trial study was performed in 60 non-pregnant diabetic patients in order to compare therapeutic effects of combination therapy (Glibenclamide - Metformin "Generic or Brand" a 12-week period). Patients were evaluated for FBS, BS2hpp, HbA1C, lipid profile, liver function tests, weight, BMI, and side effects.

Both pharmaceutical types of Metformin had the same therapeutic effects for controlling of glycemia, and lipid profile and weight, between two groups statistically were not significantly different. GI discomfort (distention) was the most common side effects of both drugs (33%). There were no significant statistical differences between these two products regarding their side effects and 70% of patients were satisfied by taking each kind of product.

On the basis of results, while both products had comparable efficacy, the generic product which is a domestic product and easier for patients to have access to it showed fewer side effects.

Keywords: Type 2 diabetes mellitus, Metformin, Clinical trial, Therapeutic effects.

INTRODUCTION

Diabetes mellitus (DM) is one of the major international health problems. The annual increase of DM prevalence is 6% in the world (1) which shows that the worldwide prevalence of diabetes mellitus and its complications are increasing constantly. This increase is due to population growth, aging, urbanization, increase in obesity and insufficient physical activity. Currently, it is estimated that 150 million people in the world are suffering from diabetes. This number is expected to increase to 333 million by the year of 2025 (2). In this trend 97% of patients will have type 2 which is similar to the present prevalence (3). The goal of treatment is to decrease the symptoms, to increase the quality of life and to prevent its complications.

Metformin is not only one of the choice drugs for controlling glycemia, but it is also suggested as the first choice of drug therapy for obese patients (4). Metformin has the lowest possibility for hypoglycemic effect (5-7) and compared to other antidiabetic agents has similar effects on FBS and HbA1C (8).The specific effects of Metformin is to decrease and to stabilize weight and lipids of the serum, which in turn decreases cerebral stroke (41%) and MI (39%) (9). In Iran, Generic types of Metformin (Parsminoo & Aria) or its brand types (Merck, Cipla, and Apo-Canada) are available. In a double blind randomized clinical trial study, therapeutic effects of a generic (Aria pharmaceutical company, Iran) with a brand Metformin (Glucophage, product of Merck pharmaceutical company, France) in diabetic patients were compared.

MATERIALS AND METHODS

This double blind randomized clinical trial study was performed in 60 non-pregnant diabetic patients in order to compare the therapeutic effects of combination therapy (Glibenclamide + Metformin "Aria or Merck ") during 12-week. Study was done by diabetes clinic of Dr. Shariati Hospital and Aboozar Clinic. These patients were candidate for regimen of metformin + gliben-clamide.

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Inclusion criteria

Diabetes type 2, patients were 30-80 years old, with FBS = 125-250mg/dl, BS2hpp < 200 mg /dl, serum ceratinin < 1.4 mg/dl, TG< 400 mg/dl, LDL< 130 mg/dl or HDL > 35 mg/dl. Candidates with abnormal lipid profiles which were under treatment of anti-hyperlipidemic agents had to receive stable dosage of anti lipid agents during the study.

Exclusion criteria

Chronic or acute alcoholic patients, addiction to any kind of medicine, any past history of vascular and heart disease, class III or IV CHF, acute or current MI, hepatic impairment test (more than 3 times of normal level), serum ceratinin ≥1.5 mg /dl in men or ≥1.4 mg /dl in women, pregnancy, progressive lung disorders, candidate for doing radiography with media contrast.

After obtaining written informed consent, patients were evaluated for the following Para clinic tests including: HbA1C, FBS, BS2hpp, lipid profiles, AST, ALT, Cr, SGPT, SGOT, and weight by means of the standard measure. Dosage of glibenclamide was constant during the study. According to the method of study and randomized number chart, patients were given 500 mg of Aria or Merck metformin of a similar shape and package with codes which were unknown for both patients and examiners. Initial dose was 500mg / BD.

After 2 weeks, patients were reevaluated for FBS and adverse effects. This evaluation was reported each 2 weeks. The dosage of metformin increased every 2 weeks to maximum of 2500mg, until the blood sugar decreased to less than 120mg/dl by metformin with the starting code. In the case that FBS reached to 120mg/dl or less, patients were monitored every month during the study for FBS, BSh2pp, HbA1C, lipid profiles, AST, ALT, SGPT, SGOT, weight, BMI, adverse effects, and satisfaction of medicine.

Laboratory Methods

All tests were done in Hormone laboratory of Endocrinology and Metabolism Research Center of Shariati Hospital. HbA1C was measured by Drew-DS5. Evaluation of biochemical tests were performed by auto analyzer (Parsazmoon Co, Iran, kit), and enzymatic method.

The study protocol was approved by the medical ethics committee of Tehran University of Medical Sciences.

Statistical Methods

Statistical tests were Fisher's Exact Test, Independent t-test, Paired t-test and Chi Square. P value ≤ 0.05 was considered as significant.

RESULTS

Following randomization of the samples via double blind method, 29 patients received generic and others received brand metformin (500mg/BD).

The results are as follows:

After randomization of the samples, demographic characteristics of patients had equal distribution in age, sex, occupation, level of education, family history of diabetes, daily glibenclamid intake and smoking.

Mean age of patients in group which received generic metformin was 55 ± 10 (mean ± SD) and in group which received band product was 52 ± 6 years old and both with a normal distribution (p=0.140).

Sex frequency distribution in both groups was similar; (p=0.427).

Diabetes had been diagnosed in since 7 ± 6 years in the group which received generic product and group which received brand product since 7±4 years with equal distribution (p=0.769).

Lab results after blood sugar control, anthropometrics and biochemical tests are illustrated in Tables 1 and 2.

There was no significant difference in blood sugar, serum lipids and BMI in both groups (Table-3).

Among 60 patients , 15 (25%) developed GI discomfort (8 in generic and 7 in brand group), 11 patients (18.3%) had hypoglycemia (4 in generic and 7 in brand group) , 27 patients (45%) had both adverse effects (14 in generic and 13 in brand group) and finally 7 patients (11.7%) did not show any side effects (3 in generic and 4 in brand group) (Table 4).

Patients satisfaction for the generic and brand Metformin were good (79%) or excellent (90%), respectively (p=0.469).

DISCUSSION

Combination therapy of Glibenclamid and Metformin (in both groups) led to normal FBS and BSh2pp, HbA1C and lipid profile, without significant statistical differences.

The number of diabetes type 2 patients was estimated about 2 millions in Iran in 2000 (10). Hyperglycemia, insulin resistance, hypertension, increased LDL, decreased HDL, and in turn increase of susceptibility to cardiovascular diseases have a higher incidence in diabetes type 2 (11). Therefore intensive therapy can decrease both complications and the cost (12).

According to UKPDS studies; each 1% increase in HbA1C (more than 7%) leads to 10% increase in the cost of diabetes. Tight glycemic control has been recommended for prevention of the diabetes complications (13).

Table 1. Results of status of the blood sugar and anthropometric tests before and end of the study in generic and brand groups

Variable	Generic metformin (mean ± SD)			Brand metformin(mean ± SD)		
	before study	end of study	P value	before study	end of study	P value
FBS (mg/dl)	199±66	138±72	0.000	199±54	128±33	0.000
BS2hpp (mg/dl)	216±69	148±49	0.000	212±66	127±37	0.000
HbA1C (%)	7.7±2	7.7±2.2	0.972	7.7±1.7	7.1±1.8	0.022
Weight (Kg)	74±11	73±10	0.501	71±9	70±9	0.189
BMI (Kg/m^2)	28±4	28±4	0.530	27±4	27±4	0.203

Table 2. Results of biochemical tests before and end of study in generic and brand group

Variable	Generic metformin (mean ± SD)			Brand metformin (mean ± SD)		
	before tudy	end of tudy	P value	before tudy	end of tudy	P value
TG (mg/dl)	211±110	198±125	0.505	213±96	173±96	0.023
Chol(mg/dl)	225±40	199±46	0.002	235±40	201±28	0.000
LDL(mg/dl)	109±25	113±31	0.367	117±23	114±20	0.315
HDL(mg/dl)	72±22	83±37	0.092	73±24	81±19	0.029
Cr(mg/dl)	0.9±0.2	0.9±0.2	0.909	0.8±0.2	0.8±0.1	0.169
SGOT(Iu/I)	28±10	30±8	0.235	31±15	28±9	0.165
SGPT(Iu/I)	32±18	28±12	0.314	34±14	24±10	0.000

Table 3. Comparison of differences in results of before and end of study in generic and brand group

Variable	Difference before –after study in generic metformin (mean ± SD)	Difference before –after study in brand metformin (mean ± SD)	P value
FBS (mg/dl)	-62 ± 73	-64±41	0.766
BS2hpp(mg/dl)	-68±61	-79±51	0.440
HbA1C (%)	0.01±2	-0.6±1.5	0.160
Cr(mg/dl)	0.003±0.2	-0.04±0.2	0.247
TG(mg/dl)	-13±104	- 34±94	0.456
Chol(mg/dl)	-26±40	- 32±33	0.477
LDL(mg/dl)	4±25	-2±16	0.236
HDL(mg/dl)	11±33	9±20	0.792
SGOT(Iu/I)	2±9	-4±11	0.044
SGPT(Iu/I)	-4±22	-11±14	0.227
Weight(Kg)	-0.3±2	-0.3±2	0.928
BMI(Kg/m^2)	-0.1±0.9	-0.1±0.7	0.898

Table 4. Comparison of adverse effects in generic and brand group (%, Number)

Adverse effects	Sub adverse effect	(%, Number) generic	(%, Number) brand	P value
GI symptoms	nausea	20.7% (6)	6.5% (2)	0.140
	vomiting	10.3% (3)	3.2% (1)	0.346
	diarrhea	3.4% (1)	6.5% (2)	1.000
	distention	31% (9)	35.5% (11)	0.788
	constipation	24.1% (7)	9.7% (3)	0.178
	indigestion	31% (9)	22.6% (7)	0.563
	metal taste	20.7% (6)	25.5% (8)	0.763
Hypoglycemic symptoms	headache	3.4% (1)	9.7% (3)	0.613
	vertigo	10.3% (3)	9.7% (3)	1.000
	palpitation	3.4% (1)	6.5% (2)	1.000
	flashing	17.2% (5)	16.1% (5)	1.000
	dizziness	10.3% (3)	6.7% (3)	1.000
	sweating	24.1% (7)	19.4% (6)	0.758
	tremor	10.3% (3)	12.9% (4)	1.000
Both of them	---	48.3% (14)	41.9% (13)	0.837
None of them	---	10.3% (3)	12.5% (4)	0.837

Metformin has pharmacological effect on obese and non obese patients (14-16). Recently, prescription of metformin by itself or in combination with other oral antidiabetic agents such as sulfonylurea has increased (17). Metformin similar to sulfonylurea group decreases FBS to about 60mg/dl and HbA1C about 1.5-2% (5). In this study, combination therapy of glibenclamide and generic or brand metformin could decrease FBS about 60-66 mg/dl. HbA1C was increased to about 0.01% in generic group but decreased to 0.6% in the brand group, without significant statistical differences. However, further long term studies with larger samples are required for better results.

In contrast to the group which received sulfonylurea, metformin decreased serum lipid which results in prevention of cardiovascular diseases (7, 8, 18).In this study both kind of metformins (generic and brand) had similar effects on modification of blood lipids, and reduction of weight and BMI.

Metformin has side effects such as GI disturbances (nausea, vomiting 25.5%, diarrhea 53.2%, distention 12.1%, indigestion 7.1%, and abdominal discomfort 6.4% compared to placebo), headache, and dermatological complications (4). Initial titration and administration with meal is advised to decrease side effects (19). Metformin dose not increases insulin secretion, and at therapeutic dosage will not causes hypoglycemia and therefore it can be prescribed safely in elderly patients (7-9). In this study the most common side effect was GI disturbances in the form of bloating (distention; 31% for by generic and 35.5% by the brand product). Hypoglycemia was 7% in the generic group and 12% in brand group. Incidence of GI disturbances and hypoglycemia adverse effects in both groups were similar (without significant statistical differences). Most of patients (more than 70%) were satisfied of both of agents.

CONCLUSION

According to these results while, the efficacy of the generic metformin is similar to that of the brand, it has fewer side effects. In addition the generic metformin is a domestic product and it is easy for patients to have access to it.

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