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EFFICACY OF SULFONYLUREA IN COMBINATION WITH METFORMIN OR TROGLITAZONE IN AGED PATIENTS WITH NON − INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)

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Efficacy of sulfonylurea in combination with either metformin or troglitazone was investigated in 34 patients with non-insulin dependent diabetes mellitus (NIDDM) without serious diabetic complications. The patients were aged from 48 to 78 yr (mean±SD: 63.9 ±8.1) with a diabetic history of 5 to 9 yr, in which glycemic control by sulfonylurea alone was unsatisfactory with elevated HbA1c levels (8.0 ± 1.0%). They were assigned to the combination therapy with sulfonylurea and either metformin (750mg/day) (group 1, n=19) or troglitazone (400mg/day) (group 2, n=15) for three months. The baseline characteristics did not differ between groups 1 and 2 before the therapy. In group 1, fasting plasma glucose (FPG) decreased from 147.5 ± 29.4mg/dl to 119.7 ± 24.2 ng/ml (P<0.001) and hemoglobin A1c (HbA1c) decreased from 7.9 ± 1.2% to 6.5 ±0.7% after the combination therapy for three months. In group 2, FPG and HbA1c were also decreased from 161.8 ± 25.4mg/dl to 134.7± 20.0mg/dl (P<0.05) and from 8.0± 0.7% to 7.2± 0.7% (P<0.001), respectively. HbA1c levels were more reduced in group 1 than in group 2 (P<0.02). Fasting plasma C-peptide (CPR) levels were more reduced (P<0.02) in group 2 (from 2.6 ± 0.5 to 1.1± 0.5ng /ml, P<0.001) than in group 1 (from 2.7 ± 1.0 ng/ml to 1.4 ± 0.5ng/ml, P<0.001). Body mass index (BMI) was decreased in group1 (from 26.1 ± 3.6 to 25.7 ± 3.3, P<0.05) whereas it was not changed in group 2 after the treatment for three months. These findings suggest that sulfonylurea in combination with either metformin or troglitazone is effective for better glycemic control in patients with NIDDM which are not well controlled by sulfonylurea alone, and that metformin is more effective to reduce BMI whereas troglitazone is more effective to reduce plasma CPR without changing BMI in these patients.

Key words: metformin / troglitazone / sulfonylurea / combination therapy / NIDDM

INTRODUCTION

Non-insulin dependent diabetes mellitus (NIDDM) is a metabolic disorder characterized by insufficient insulin secretion and increased insulin resistence (1,2). Sulfonylurea (SU) is a representative hypoglycemic drug which stimulates insulin secretion by acting at the SU receptor which is a subunit of the adenosine triphosphate-sensitive pottasium (K_{ATP}) channel in the plasma membrane of pancreatic beta cells (3). Metformin and troglitazone increase peripheral glucose disposal and decrease hepatic glucose output without causing hypoglycemia (4,5). These pharmacological agents, either alone or in combination, can improve plasma glucose regulation in patients with non-insulin-dependent diabetes mellitus (NIDDM) (6,7). However, the efficacy of the combination therapy remains to be more elucidated in aged patients with NIDDM.

In the present study, we investigated the effect of either metformin or troglitazone administration in combination with sulfonylurea on control of plasma glucose in aged patients with NIDDM who were not well controlled by sulfonylurea alone.

PATIENTS AND METHODS

We investigated 34 patients with NIDDM, 23 females and 11 males, with the mean (±SD) age of 63.9 ± 8.1 yr. These patients had been treated with sulfonylurea agents using either gliclazide (more than 40mg/day) or glibenclamide (more than 5mg/day) for more than six months before the present study. Although they were kept on the diet and exercise instructed, plasma glucose levels were not well controlled so that HbA1c levels remained over 7% (8.0±1.0%). Patients with severe diabetic complicatons or liver and renal dysfunction were not included in the present study.

At the end of the observation period of three months when the sulfonylurea treatment remained without any modification, 34 patients were randomly divided into two groups and followed by the combination therapy. The first group of 19 patients (6 males and 13 females) were then treated with sulfonylurea and metformin (250 mg t.i.d) for three months. The second group of 15 patients (5 males and 10 females) were treated with sulfonylurea in combination with troglitazone (200 mg b.i.d.) for three months. The protocol for sulfonylurea treatment was not modified after the start of the combination therapy with either troglitazone or metformin until the end of the present study.

Their clinical courses were carefully followed up every two weeks in three different out-patient clinics under an identified protocol. Fasting plasma glucose

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(FPG), fasting plasma C-peptide (CPR) and hemoglobin A1c (HbA1c) levels were measured immediately before, and one month and three months after the start of the combination therapy. FPG was measured by glucose oxidase method and plasma CPR was measured by specific radioimmunoassay. HbA1c was measured by a HPLC method in which stable HbA1c was selectively detected. Hematological and biochemical parameteres were also carefully monitored every month during and after the study. All results were collected and shown as mean ± SD.

Statistical differences between the two groups, and before and three months after the combination therapy in each group were evaluated by one-way analysis of varience, and Student's unpaired t-test or paired t-test, apropriately. $P<0.05$ was considered significant.

RESULTS

There was no statistical difference in such base-line parameters as age, Body Mass Index (BMI), FPG, HbA1c and plasma CPR levels between the groups 1 and 2. As shown in Fig. 1, mean (±SD) FPG levels decreased from 147.1±29.4 to 126.5±21.6mg/dl after one month and to 119.7±24.2mg/dl after three months in group 1. HbA1c also decreased from 7.9 ± 1.2% to 6.5 ± 0.8% ($P<0.001$) after three months although HbA1c levels were not changed after one month 7.5± 1.4mg/dl ($P=0.08$) in group 1. In group 2, FPG levels also decreased from 161.8±25.4mg/dl to 141.8±17.1 mg/dl after one month and 134.7±20.0mg/dl after three months, respectively, as shown in Fig. 2. HbA1c levels decreased from 8.0 ± 0.7% to 7.7 ± 0.9% after one month and to 7.2 ± 0.7% after three months in group 2. HbA1c levels were more decreased in group 1 than in group 2 after three months ($P<0.02$) whereas FPG levels were not different between both groups.

Fasting plasma CPR levels decreased from 2.7±1.0 ng/ml to 1.4 ± 0.8ng/ml ($P<0.001$) after one month and to 1.4±0.5ng/ml ($P<0.001$) three months after the start of the combination theraoy in group 1 (Fig. 2). Fasting plasma CPR levels also decreased from 2.6 ± 0.5ng/ml to 1.2 ± 0.4ng/ml ($P<0.001$) after one month and to 1.1 ± 0.5ng/ml ($P<0.001$) three months after in group 2.

As shown in Fig. 2, BMI decreased from 26.1±3.6 to 25.8±3.5 ($P<0.02$) after one month and to 25.7± 3.3 ($P<0.05$) after three months in group 1 whereas there was no change in BMI in group 2 (before, 26.1 ± 2.7: after one month, 25.9 ± 2.8; after three months, 26.1±2.8).

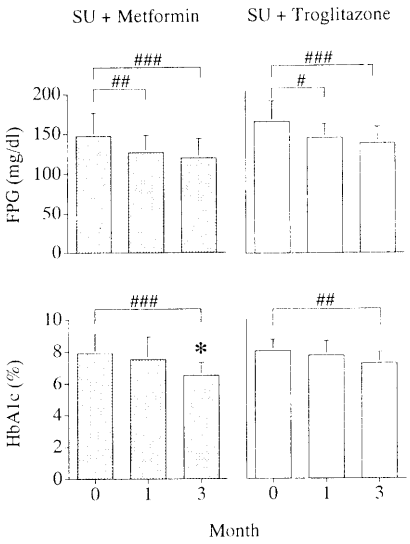

Fig. 1. Mean(±SD) fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels in patients with NIDDM before, and one month and three months after the start of combination therapy of sulfonylurea and either metformin (group 1) or troglitazone (group 2). # : $p < 0.05$, ## : $p < 0.01$, ### : $p < 0.001$ vs. before treatment (0 month) * : $P<0.02$ vs. sulfonylurea + troglitazone.

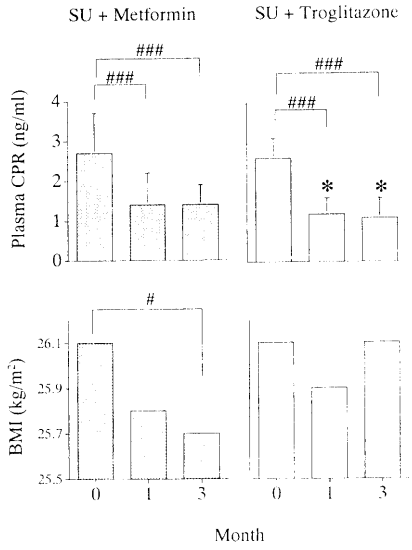

Fig. 2. Mean(±SD) plasma C-Peptide (CPR) and BMI values in patients with NIDDM before, and one month and three months after the start of combination therapy of sulfonylurea and either metformin (group 1) or troglitazone (group 2). # : $p < 0.05$, ## : $p < 0.01$, ### : $p < 0.001$ vs. before treatment (0 month).

DISCUSSION

NIDDM is a common metabolic disease characterized by insufficient insulin secretion and increased insulin resistance (1,2). Patients with NIDDM are usually treated according to a stepped progression, starting with a regimen of diet and exercise, followed by the therapy with oral hypoglycemic agent (OHA). Sulfonylurea, a representative OHA, augments insulin secretion, but has no direct action on insulin sensitivity. Metformin, a classic biguanide agent, is useful in diabetic patients with insulin resistence (4). The beneficial effect of metformin is primarily to lower endogenous glucose production, presumably acting at the liver (8). Clinical experience has proved metformin, either alone or in combination with sulfonylurea, to be safe and effective for reducing plasma glucose concentrations in patients with NIDDM (6). Troglitazone, a newly established anti-diabetic agent, enhances insulin sensitivity by acting through peroxisome proliferative-activated receptor gamma (PPARgamma) (5,8,9). Troglitazone increases insulin-mediated peripheral glucose disposal which occurs predominantly in the skeletal muscle (10).

It was previously reported that the combination therapy of sulfonylurea with either troglitazone or metformin was more effective than that of sulfonylurea alone in patients with NIDDM (6,7). However, the effect of the combination therapy in aged patients with NIDDM remains to be fully elucidated. In the present study, we demonstrated that FPG, HbA1c and plasma CPR levels decreased after the combined treatment of sulfonylurea with either metformin or troglitazone in aged patients with NIDDM who were not well controlled by sulfonylurea alone. These observations are on the same line with Inzucchi SE et al. (9). They suggested that sulfonylurea and metformin therapy may have similar efficacy in patients with NIDDM as sulfonylurea with troglitazone.

Metformin is known to have an inhibiting effect on food intake in both the ZDF rat and in human although the exact mechanism remains to be elucidated (11). Diminished food intake is related to an improvement in insulin action. We also found in the present study that BMI was remarkably reduced in group 1 which was treated with sulfonylurea and metformin, suggesting that the combination therapy with sulfonylurea and metformin might be useful to avoid an increase in body weight in NIDDM.

In contrast, BMI was not changed in group 2 treated with sulfonylurea and troglitazone. Recently it has been pointed out that the troglitazone-treated patients often have small dose-related increases in body weight (5). In our findings, plasma CPR levels were more reduced in patients treated with sulfonylurea and troglitazone, suggesting a benefit of troglitazide to reduce insulin resistance independently of BMI. However, weight gain could decrease the effect of troglitazone therapy for a long period.

In summary, we have demonstrated that sulfonylurea administration in combination with either metformin or troglitazone was effective for improving glycemic control in aged patients with NIDDM who were not well controlled by sulfonylurea alone. It was also suggested that sulfonylurea with metformin is effective to reduce BMI and plasma CPR levels whereas sulfonylurea with troglitazone is more effective to reduce plasma CPR levels without affecting BMI in aged patients with NIDDM. However, further studies are required to elucidate differences in prolonged effects of these drugs in NIDDM.

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REFERENCES

1) Reaven GM (1984) Insulin secretion and insulin action in non-insulin dependent diabetes mellitus. *Diabetes Care* 7 (suppl 1) : 17-24.
2) Olefsky JM (1985) Pathogenesis of insulin resistence and hyperglycemia in non-insulin dependent diabetes mellitus. *Am J Med* 79 (suppl 3B) : 1-7.
3) Babenko AP, Aguilar-Bryan L and Bryan J (1998) A view of sur/KIR 6.X, KATP channels. *Ann Rev Physiol* 60: 667-687.
4) DeFronzo RA, Goodman AM and Multicenter Metformin Study Group (1995) Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333: 541-549.
5) Schwartz S, Raskin P, Fonseca V and Graveline JF (1998) Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med* 338: 861-866.
6) Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V and Shulman GI (1998) Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 338: 867-872.
7) Iwamoto I, Kosaka K, Kuzuya T, Akanuma Y, Shigeta Y and Kaneko T (1996) Effect of combination therapy of troglitazone and sulphonylureas in patients with type II diabetes who were poorly controlled by sulphonylurea therapy alone. *Diabet Med* 13: 365-370.
8) Iijima K, Yoshizumi M, Ako J, Eto M, Kim S, Hashimoto M, Sugimoto N, Liang YQ, Sudoh N, Toba K and Ouchi Y (1998) Expression of perxisome proliferator-activated receptor gamma (PPAR-gamma) in rat aortic smooth muscle cells. *Biochem Biophs Res Commun* 247: 353-356.
9) Stumvoll M, Nurjhan N, Perriello G, Dailey G and Gerich JE (1995) Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* 333: 550-554.
10) Lee M-K, Miles PD, Khoursheed M, Gao K-M, Moossa AR and Olefsky JM (1995) Metabolic effects of troglitazone on fructose-induced insulin resistence in the rat. *Diabetes* 43: 1435-1439.
11) Sreenan S, Sturis J, Pugh W, Burant CF and Polonsky KS (1996) Prevention of hyperglycemia in the zucker diabetic fatty rat by treatment with metformin or troglitazone. *Am J Physiol* 271 (Endocrinol Metab 34) : E742-747.
12) Schwartz S, Raskin P, Fonseca V and Graveline JF (1998) Effect of troglitazone in insulintreated patients with type II diabetes mellitus. *N Engl J Med* 338: 861-866.