COMBINATION THERAPY OF GLIBENCLAMIDE AND INSULIN IN NIDDM PATIENTS WITH SECONDARY FAILURE TO ORAL DRUGS

V Mohan*, C Snehalatha**, A Ramachandran*, M. Viswanathan***

SUMMARY

A trial of combination therapy with glibenclamide + insulin was conducted in 26 patients with non insulin dependent diabetes mellitus (NIDDM) who had secondary failure to oral hypoglycaemic agents (OHA). Patients were included in the study if they failed to respond to a dose of 15 mg of glibenclamide under strict dietary regulations. Small doses of insulin were added until satisfactory glucoregulation was achieved. On withdrawal of the OHA, in 20 patients, the post-prandial plasma glucose values (PPBS) increased again by ≥25%; they were considered as "responders". Responders were divided into two equal groups of alternate patients; group I was treated with insulin + glibenclamide and group II with insulin + placebo. The patients were then followed up at monthly intervals for 6 months.

The dose of insulin required to maintain normal plasma glucose value was significantly lower ($P < 0.05$) in group I. Fewer patients in group I needed two injections of insulin per day; however this difference was not statistically significant. Normlisation of serum triglyceride and lowering of HbA1 occurred in both groups. This study shows that addition of glibenclamide to insulin treatment is advantageous in NIDDM patients showing secondary failure to OHA.

Key Words: Diabetes mellitus, hypoglycaemic drugs.

INTRODUCTION

The management of non-insulin dependent diabetes mellitus (NIDDM) consists of diet, exercise and oral hypoglycaemic agents (OHA). After periods of time ranging from a few months to several decades,[1] patients with NIDDM may develop secondary failure to OHA.[2] The annual rate of secondary drug failure ranges from 3% to 30%.[3] In patients who have become unresponsive to OHA alone, the question arises whether these agents should be completely stopped and insulin therapy alone instituted or whether a combination of insulin plus OHA should be given. Recent studies from Europe and USA[4-6] suggest that combined OHA – insulin therapy does have certain benefits.

NIDDM in Indians shows certain peculiarities from that seen in Europe, including younger age at diagnosis, reversal of sex ratio and relative infrequency of obesity.[7] We therefore undertook a trial of combined OHA – insulin therapy in Indian NIDDM patients.

MATERIAL AND METHODS

The protocol followed was similar to that adopted by the German multicentre study on combined insulin – glibenclamide therapy in Type 2 diabetes.[4]

*Deputy Director; **Head Department of Biochemistry; ***Director; Diabetes Research Centre and MV Hospital for Diabetes, Madras-13.

Received: 17.11.1989
Revised 16.5.1990
Accepted 18.6.1990

Inclusion criteria

1. Diabetes mellitus as defined by the WHO study group report.[8]
2. The patient should be treated for a minimum of 3 years with sulphonylureas (SU) and a minimum of 3 months on maximal doses of glibenclamide (15 mg/day).
3. With strict adherence to diet and the maximal dose of glibenclamide stated above, the fasting plasma glucose values at the time of study should be ≥ 220 mg/dl or post prandial plasma glucose ≥ 280 mg/dl, 90 minutes after breakfast.
4. Over 40 years of age.
5. Non-abese i.e. body mass index (kg/m^2) <25 for women and <27 for men.

Exclusion criteria

1. Any other antidiabetic drug treatment apart from glibenclamide.
2. Evidence of liver or kidney damage.
3. Neoplasms.
4. Patients with severe, long term complications of diabetes.
5. Severe chronic diseases.
6. Recurrent infections.
7. Corticosteroid therapy.
8. Pregnancy.

Thirty five patients with NIDDM who showed secondary failure to OHA after 4 to 18 years (mean 7 ± 6.5) of OHA treatment, were selected for the study. There were 22 men and 13 women in the age group 40 to 72 years (the mean age is 48 ± 7.8 years). They were

all of ideal body weight (mean BMI 21.6 ± 1.8 kg m). All patients were admitted as in-patients to the hospital and the response to glibenclamide was tested for one week under strict dietary regulations and treatment with maximum dose of 10 mg of glibenclamide in the morning and 5 mg in the evening. 3- minutes before food. At the end of one week ("SU phase"), if the fasting plasma glucose and or the 90' post-prandial glucose values were ≥ 220 or ≥ 280 mg dl. they were included in the study.

In the "combination phase" they were started on 10 u day of intermediate acting insulin (*Monotard MC*, Novo) in addition to glibenclamide. They were reviewed as out-patients at 3 day intervals. The doses of insulin were increased and, if necessary, regular insulin or an additional evening dose was introduced until satisfactory metabolic control was achieved. In the next stage or the "withdrawal phase", the sulphonylurea was withdrawn and insulin therapy alone was continued. At the end of another week, the post prandial plasma glucose was repeated. If the plasma glucose increased by ≥ 25% after stopping the sulphonylurea drug, the patients were considered as "responders" to the combination therapy.

The "responders" were divided into two equal groups (alternate patients). Group I was prescribed a combination of insulin + sulphonylurea and group II was given a placebo (3 tablets) in place of sulphonylurea. The placebo tablets were specially prepared by Boehringer Mannheim W Germany and were identical in appearance to glibenclamide. Patients were asked to bring the leftover tablets at the time of review to assess the regularity of the placebo intake. The patients were reviewed a week later and thereafter regularly followed up at two monthly intervals for a further period of 6 months. Necessary adjustments in the dose of insulin were prescribed to maintain good control of hyperglycaemia. Side effects of tablets if any were recorded. The number of tablets left over at each time was recorded.

The "non-responders" were continued on insulin alone for a period of 6 months.

Laboratory investigations

At each time point the patient was weighed. Blood samples were drawn in the fasting state between 8.0 and 8.30 AM and again 90 minutes after breakfast.

Fasting and post prandial (90') plasma glucose were estimated every day during the first week of admission and during the subsequent visits. A standard breakfast consisting of 1400 to 2000 K calories and 60% carbohydrate 20% protein, 20% fat was used throughout the study period. Plasma glucose was estimated by the glucose oxidase Method (*GOD-PAP*, Boehringer Mannheim). Glycosylated haemoglobin (HbA1),[9] serum ing DPC kit, USA) were estimated at two monthly intervals. The detection limit of the assay was 0.03 pmol/ml. The intra and inter assay coefficients of variation were 5% and 7.6% respectively.

Statistical analysis

All values are expressed as mean ± SD. Paired *t* test was used for comparison of follow-up values within groups and analysis of variance for significance between groups. Fischer's exact probability test was used where indicated.

RESULTS

Among the 35 patients selected, 9 dropped out at various time periods due to inability to report for follow-up at the required time. Of the remaining 26 patients, 20 patients were responders" and 6 were "non-responders". These two groups were not different with respect to mean age, duration of diabetes and body mass index (Table 1). They had similar values of PP

Table 1: Clinical and Biochemical Parameters at Entry

	Responders (n = 20)	Non-responders (n = 6)
Sex ratio (M:F)	13:7	3:3
Mean age (years)	48 ± 7	50 ± 8
Duration of Diabetes (years)	12 ± 4	11.0 ± 5
BMI (kg/m^2)	22.2 ± 2.3	21.0 ± 3.1
Fasting plasma glucose (mg/dl)	247 ± 43	220 ± 47
Post prandial plasma glucose (mg/dl)	326 ± 48	334 ± 44
HbA1 (%)	11.0 ± 0.47	12.0 ± 0.8
TG (mg/dl)	133 ± 30	110 ± 10
Fasting C-peptide (pmol/ml)	0.35 ± 0.13	0.30 ± 0.20
Post prandial C-peptide (pmol/ml)	0.53 ± 0.2	0.42 ± 0.33

plasma glucose, HbA1 and TG values. Fasting and post prandial values of C-peptide were slightly higher in the responders, althought he differences were not statistically significant. The initial fasting glucose value was higher in the responders ($p < 0.01$).

Results of follow-up treatment

There was no significant weight gain (>3 kg) in any of the patients during the follow-up. The initial weight of patients in group I was 60.1 ± 7.9 kg and at the 24th week, it was 61.2 ± 7.8 kg. In group II, the mean weight changed from 64.8 ± 5.7 kg to 65.6 ± 5.5 kg. There were 6 hypertensives in the study and their blood pressures were maintained under control with appropriate therapy.

Prior to the withdrawal of the SU (response-finding

...ar (Table 2). Substitution of the SU with the ...ebo in group II resulted in significant ($p < 0.001$) increase in the insulin requirement even in a week. Though the dose of insulin had to be increased in some patients in group I also, their mean insulin requirement at the 24th week remained significantly lower ($p < 0.05$) compared to group II. Only 2 patients in group I required 2 injections/day, whereas 6 patients in group II required 2 injections/day. This difference was not, however, statistically significant ($p < 0.08$).

Gradual and significant reduction in HbA1 values was observed in both groups (Table 3). TG values decreased significantly ($p < 0.001$) in the 8th week of treatment in both groups and the values continued to be normal thereafter.

The initial fasting and post-prandial C-peptide levels were similar in group I and group II (Table 4). The fasting levels were reduced in both the groups during the treatment. The reduction was more marked ($p < 0.01$) in group II and also occurred within eight weeks of insulin therapy.

Table 4: **Serum C-Peptide Values in the two Subgroups of Responders**

	At entry	8th week	16th week	24th week
Group I (Ins + SU)				
CP (pmol/ml)				
Fasting	0.38	0.38	0.37	0.34*
	(0.14)	(0.1)	(0.10)	(0.1)
PP	0.58	0.55	0.50	0.46*
	(0.31)	(0.26)	(0.3)	(0.35)
Group II (Ins + Placebo)				
CP (pmol/ml)				
Fasting	0.32	0.18	0.19	0.19**
	(0.13)	(0.05)	(0.06)	(0.09)
PP	0.51	0.40	0.41	0.36*
	(0.30)	(0.32)	(0.3)	(0.25)

Values in brackets are SD.
* < 0.05, ** < 0.01 compared to initial value

Table 2: **Insulin Doses U/day Used at Various Time Periods in the Two Responder Groups**

Period	1 During initial combination therapy	2 1st week	3 8th week	4 16th week	5 24th week
Group I (Ins + SU)	16 ± 6	18 ± 5	20 ± 10	23 ± 12	24 ± 10*
Group II (Ins + Plac)	18 ± 7	34 ± 12**	36 ± 14**	36 ± 16**	40 ± 18** +

p * < 0.05, ** < 0.01 vs Period 1, + p < 0.05 vs corresponding value of group I

Table 3: **Plasma Glucose, HbA1 and TG Values in the Two Groups of Responders**

	At entry	+ Ins	− Su	+ SU	1st week	8th week	16th week	24th week
Group I (Ins + SU)								
Plasma glucose (mg/dl)								
Fasting	222	164*	209	137*	120*	119*	124*	121*
	(28)	(32)	(35)	(28)	(18)	(15)	(16)	(7)
PP	322	196*	306	204*	190*	182*	185*	172*
	(38)	(23)	(62)	(20)	(22)	(25)	(15)	(13)
HbA1 (%)	10.8	–	–	–	–	9.7*	9.3*	8.9*
	(0.4)					(0.3)	(0.34)	(0.31)
TG (mg/dl)	147	–	–	–	–	92*	87*	88*
	(32)					(23)	(12)	(17)
Group II (Ins + Placebo)								
Plasma glucose (mg/dl)								
Fasting	272	161*	213	153*	148*	147*	139*	127*
	(41)	(11)	(27)	(13)	(19)	(16)	(12)	(12)
PP	329	181*	274	175*	196*	189*	186*	177*
	(58)	(19)	(22)	(14)	(22)	(18)	(14)	(10)
HbA1 (%)	11.2	–	–	–	–	9.9*	9.5*	8.9*
	(0.44)					(0.4)	(0.3)	(0.3)
TG (mg/dl)	125	–	–	–	–	91*	88*	86*
	(35)					(9)	(12)	(8)

*p < 0.001 compared to initial value
Values in brackets are SD.

Mild hypoglycaemic symptoms occurred in several patients, both in group I and group II, and the dose of insulin was adjusted accordingly. None of the patients had any other side reactions during the study period.

DISCUSSION

This study shows that a combination of glibenclamide and insulin is beneficial in the treatment of NIDDM patients with secondary failure to the OHA. In 76% (20/26) of the patients, beneficial effect of the combination therapy was evident, in that the plasma glucose concentration increased markedly on withdrawal of the tablets. The dose of insulin required to control the hyperglycaemia was significantly lower ($p < 0.05$) in the glibenclamide treated group (group I) than in the placebo group (group II). These findings agree with those of several previous workers,[6,11,12] justifying the use of the combination therapy in insulin-requiring NIDDM patients. The period of follow-up in this study was fairly long (24 weeks) and the beneficial effect was found to be sustained. Fasting and post prandial hyperglycaemia was significantly reduced with a significant reduction in the percentage of HbA1 also.

Lewitt *et al*[13] and Osei *et al*[6] had observed that the beneficial effect of combination therapy was only of short duration, the former group observing a deterioration after 2 months and the latter after 4 months of therapy. Lewitt *et al*[13] had included primary or secondary failures in the study and also noted that those with insulin therapy for > 8 years are unlikely to benefit by the combination therapy. The fact that in our study the duration of diabetes was similar in the responders and non-responders shows that the duration of diabetes did not adversely influence the response to combination therapy.

Many groups[13,14] have reported that the success of combination therapy is dependent on the presence of endogenous insulin secretion. We found that the non-responders had lower serum CP values compared to the responders, but the difference was not statistically significant. However, the CP values in either group were significantly lower than the values found in our NIDDM patients responding to OHA (which is usually ≥0.6 pmol/ml, 90 minutes after a meal). Our observations are in agreement with those of Kyllastinen *et al*[15] who also did not observe any change in serum C-peptide levels after glyburide treatment for 2 months despite improvement in glycaemic control. It is likely that the addition of glibenclamide improves the glycaemic control by its extra pancreatic actions.[16,17] Suppression of endogenous insulin secretion is observed to a greater degree in patients treated with insulin and placebo. Schwarz *et al*[18] observed that the suppression of CP secretion was absent in patients on combination therapy

group I and group II and this was probably related to the correction of hyperglycaemia. It is always desirable to use lower doses of exogenous insulin.[19] Addition of glibenclamide to the insulin treatment is advantageous in that it helps to achieve this goal. In developing countries like ours, reduction of insulin doses also reduces the cost of therapy. The evening injection can be avoided in some patients if OHA are used. These potential advantages make combination therapy with OHA and insulin a sensible form of treatment in our country, particularly if some pancreatic beta cell reserve is still present.

ACKNOWLEDGEMENT

We thank M/s Boehringer Mannheim, W. Germany for their help and support in this study.

REFERENCES

1. Krall LP, Bradley RF. "Secondary failures" in the treatment of diabetes mellitus with tolbutamide and with phenformin. *Diabetes* 1962; 11:88-91.
2. DeLawter DE, Moss JM, Tyroler S. Secondary failure of response to tolbutamide treatment. *JAMA* 1959; 171: 1786-92.
3. Shen SW, Bressler R. Clinical pharmacology of oral antidiabetic drugs. *N Engl J Med* 1977; 296: 787-93.
4. Groop LC, Pelkonnen R, Koskimies S, *et al*. Secondary failure to treatment with oral antidiabetic agents in non-insulin dependent diabetes. *Diabetes Care* 1986; 9: 129-33.
5. Maurerhoff T, Kiteisiegers JM, Lambert AE. Effect of glibenclamide in insulin treated diabetic patients with a residual insulin secretion. *Diabetes and Metabolisme* 1986; 12: 34-8.
6. Osei K, O'Doriso TM, Falko JM. Concomitant insulin and sulphonylurea therapy in patients with Type 2 diabetes. Effects on glucoregulation and lipid metabolism. *Am J Med* 1984; 77: 1002-9.
7. Mohan V, Ramachandran A, Viswanathan M. *Tropical Diabetes. In:* Alberti KGMM, Krall LP, Eds. Diabetes Annual I. Elsevier Science Publishers, Amsterdam 1985: 81-90.
8. WHO Expert Committee on Diabetes Mellitus.: Second Report. *WHO Tech Rep Ser*. Geneva, 646, 1980.
9. Eross J, Kreutzmann D, Jimenex M, *et al*. Colorimetric measurement of glycosylated protein in whole blood, red cells, plasma and dried blood. *Ann Clin Biochem* 1984; 21: 519-22.
10. Vanhandel E, Zilversmit DB. Micromethod for determination of serum triglyceride. *J Lab Clin Med* 1957; 50: 152-6.
11. Reaven GM, Fraze E, Chen NY, *et al*. The combined use of insulin and sulphonylurea therapy in patients with non-insulin dependent diabetes mellitus. *Horm Metab Res* 1989; 21: 132-6.
12. Bachmann W, Lotz N, Mehnert M. *Concluding remarks. In:* Bachmann W, Lotz N, Mehnert M, Eds. Insulin/sulphonylurea Symposium, Munich 1986, Basel: Karger, 1988L 154-8.
13. Lewitt MS, Yu VKF, Rennie GC, *et al* Effects of combined insulin-sulphonylurea therapy in Type 2 patients. Diabetes Care 1989; 12: 379-83.
14. Reich A, Abraira C, Lawrence-AM. Combined Glyburide and Insulin Therapy in type II diabetes. Diabetes Res 1987; 16: 99-104.
15. Kyllastinen M, Groop L. Combination of insulin and glibenclamide in the treatment of elderly non-insulin dependent (Type 2) diabetic patients. *Ann Clin Res* 1985; 17: 100-4.
16. Duckworth WC, Soloman SS, Kitabachi AE. Effect of chronic

, Lebovitz HE. Endocrine and metabolic effects of ...mide. Evidence for extra pancreatic mechanism of ac-...n. *Diabetes* 1971; 29: 745-55.
18. Schwarz O, Rosak C, Althoff PH, *et al.* Combined treatment of Type 2 diabetic patients with insulin and glibenclamide after secondary failure to tablets. *Diabetes* 1971; 29: 33-43.
19. Janka HV, Ziegler AG, Standl E, *et al.* Daily insulin dose as a predictor of macrovascular disease in insulin-treated non-insulin dependent diabetics. *Diabete and Metabolisme* 1987; 13: 359-64.