

Comparison of Bedtime NPH Insulin Or Metformin Combined with Glibenclamide in Secondary Suipphonylurea Failure in Obese Type H (NIDDM) Patients

Pages with reference to book, From 336 To 338

Rauf Niazi, Zarina Muzaffar (Department of Medicine, Pakistan Institute of Medical Sciences, Islamabad.)

Abstract

Objective: To compare the effects of bedtime NPH Insulin vs Metformin combined with Glibenclamide in patients who are obese and had secondary failure to suipphonylurea treatment.

Design and Methods: Prospective, randomized, comparative study of patients having type-II diabetes, without complications with associated obesity and secondary failure to suipphonylureas. Thirty-six obese patients who continued to have blood glucose values of fasting >150 mg/dl and/or random >220 mg/dl, after 8 weeks of intensive dietary and drug therapy.

Interventions: For the 20 weeks of study, the patients were randomised in two equal groups, one receiving 20 to 40 units of NPH Insulin at bed time and the second group, Metformin upto a maximum dose of 3 grams, along with Suipphonylureas.

Results: Both the groups showed, a significant reduction in the blood glucose values, with an average decrease of 50 mg/dl. The other monitored parameters, such as, serum cholesterol, triglycerides and blood pressure values, also demonstrated a similar downwards trend. However, the drop out rate was high in the Insulin treated group and the remainder group did show slight increase in weight and BMI, while the reverse, stood true, for the metformin group, with 100% compliance rate.

Conclusion: Metfonnin, in obese, type II diabetics, with secondary failure to Suipphonylureas, is an effective, safe and well tolerated treatment, which not only improves the metabolic control but also favourably modifies other parameters such as weight, total cholesterol and triglyceride values (JPMA 48:336,1998).

Introduction

Non-insulin dependent diabetes mellitus Type 2 (NIDDM) is a progressive disease in which endogenous insulin secretion gradually declines. In spite of all efforts to achieve normoglycaemia with diet, exercise and oral suipphonylurea treatment, 5 to 10% of these patients annually display inadequate metabolic control, i.e., (develop secondary failure to sulphonylurea)^{1,2}. Several different modalities and regimens have been tried in treating these patients, including pm-prandial insulin, NPH insulin at bed time and addition of Metformin, to Sulphonylureas along with dietary management²⁻⁹.

In a meta-analysis of 17 studies, the investigator concluded that combined suipphonylurea-insulin therapy leads to modest improvement in the glycaemic control compared with insulin therapy alone and that lower doses of insulin may be used in combination therapy to achieve a similar control⁷. Other studies have shown that bedtime as compared to the morning NPH⁸ is almost as effective as regular pre-prandial insulin, both in combination with Suipphonylureas, for a better glycaemic control and night NPH may be associated with less weight gain².

Other studies have shown, Metformin and Suipphonylurea combination to be more effective in achieving better glycaemic control and lowering lipid levels³, with additional effectiveness in increasing Insulin sensitivity at the receptor level¹⁰⁻¹² and in lowering Arterial Blood Pressure³. As a general observation, it is felt that type 2 diabetes and obesity coexist in majority of the patients.

Patients hesitate to use Insulin and have disbeliefs against the daily injection in our county. Secondary failure to Sulphonylureas is not only common, but may be undetected and untreated for a considerable amount of time. In this study, we compared combination of bedtime Insulin NPH, or Metformin, with maximum doses of Sulphonylureas in obese type 2 (NIDDM) patients with secondary failure to Sulphonylureas.

Other parameters such as effect on hyperlipidaemia, hypertension, weight and compliance to therapy were also closely monitored.

Patients and Methods

Forty-two subjects with type II diabetes and secondary failure to sulphonylureas in a maximum dose and a BMI > 27 were enrolled in the study during a period from 30-1-96 to 30-11-97. Inclusion criteria were fasting blood glucose > 150 mg/dl, or 2 HPP blood glucose > 220 mg/dl, high blood pressure without the use of anti-hypertensive treatment (> 140 mmHg systolic and/or > 90 mmHg diastolic), triglycerides > 200 mg/dl, cholesterol > 200 mg/dl, normal renal functions, normal LFTs, no cardiomyopathy, lung diseases, malnutrition, or acute intercurrent infections and no use of drugs that might interfere with the study.

This selected group was given special care for two months, reinforcing advice on diet and use of medication. At the end of this period, 36 patients had persistent secondary failure to prescribed Sulphonylureas. The patients enrolled had the diagnosis of type II diabetes with secondary failure to Sulphonylureas, established by fasting blood glucose > 150 mg/dl or 2 HPP blood glucose > 220 mg/dl, after regular compliance with Sulphonylureas and dietary management.

This was an open, prospective, randomised and comparative study. Selection of patients was at random and they were divided into two parallel groups (18 patients each). Each received Metformin 500 mg three times a day with meals (adjusted accordingly to a maximum of 3 G/day) or NPH Insulin (Humulin-N or Protaphane HM) 20 to 40 units at bed. time both with the maximum dose of sulphonylurea for 20 weeks, with subsequent visits every 4 weeks.

The dosages of Metformin and NPH Insulin were adjusted according to the patient response. Insulin NPH was injected subcutaneously in the lower abdominal wall and patients were given special instructions and training on how to prepare and inject insulin. Clinical evaluation was done every 4 weeks and consisted of examining the patients general condition measurement of weight and height for determining BMI, measurement of blood pressure and questioning for adverse, side effects. At each visit, patients were advised to have their fasting blood glucose and urine analysis done. At the beginning and at the end of the study, the following tests were conducted: complete blood picture, urea / creatinine / electrolytes, serum cholesterol, ECO, HbA_{1c}.

Results

The baseline characteristics of the 18 subjects in each group and which were noted at the start of the study are shown in Table I.

Table I. Baseline characteristics.

	Metformin group	Insulin group
n	18	18
Age (years)	50.2 $\pm$ 10.8	48.2 $\pm$ 11.2
Sex (M/F)	11/7	10/8
Weight (kg)	70 $\pm$ 5.2	71.3 $\pm$ 8.6
Duration of diabetes (in years)	6.2 $\pm$ 4.6	7.2 $\pm$ 3.5
Blood pressure (mmHg)	150 $\pm$ 10	145 $\pm$ 10
Blood glucose (fasting) mg/dl	180 $\pm$ 24	190 $\pm$ 26
Serum cholesterol(fasting) mg/dl	236 $\pm$ 22	230 $\pm$ 20
Serum triglycerides (fasting) mg/dl	256 $\pm$ 14	280 $\pm$ 26

Nine individuals from the Insulin group did not complete the study and dropped out after 8 weeks. The changes observed in the blood chemistry, blood pressure and BMI after completion of the study at 20 weeks can be seen in Table II.

Table II. Changes before and after the study.

	Metformin group		NPH-Insulin group	
Fasting glucose (mg/dl)	190 $\pm$ 26	126 $\pm$ 12.1	80 $\pm$ 24	130 $\pm$ 14
Fasting cholesterol (mg/dl)	236 $\pm$ 22	200 $\pm$ 10	230 $\pm$ 20	20 $\pm$ 18
Fasting triglycerides(mg/dl)	256 $\pm$ 14	180 $\pm$ 16	280 $\pm$ 26	276 $\pm$ 24
Glycosylated (Hb)	13 $\pm$ 3	8 $\pm$ 2	12 $\pm$ 2	9 $\pm$ 2
Serum creatinine (mg/dl)	1.0 $\pm$ 0.2	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1
Blood pressure (mmHg)	150 $\pm$ 10	135 $\pm$ 8	145 $\pm$ 10	140 $\pm$ 8
BMI	28.1 $\pm$ 2.2	26.6 $\pm$ 1.6	28.3 $\pm$ 2.9	29.1 $\pm$ 2.5

The decrease in serum cholesterol, triglycerides, glycosylated Hb and BMJ was more significant in the Metmorfin group. The only adverse effects noted were nausea and abdominal distension in two cases belonging to the Metformin group.

Five males and 4 females dropped out from the insulin group, at about 8 weeks, inspite of consistent encouragement and explanation. In the Metfonningroup there was nota single drop out.

Discussion

The results of the study indicate the advantage of Metformin in the obese patients with type II diabetes, who did not respond optimally to Suiphenylurea alone. Comparing the results of the two groups, acceptable metabolic control was achieved in both the groups with blood glucose values in the Insulin group showing an average decease of 50 mg/dl, compared to 60 mg/dl in the Metformin grout. This was in correlation with various international studies³. The decrease in glucose levels was proportionate to the insulin dose used. Many studies show lack of aggressiveness in increasing the dose of insulin, for

a better glycaemic control⁴⁻⁹, perhaps, under the belief that, larger doses of insulin may be harmful, by causing peripheral hypensulinaemia (though unproven yet). We kept the doses of insulin between 20 and 40 units.

Besides the glycaemic control, metformin had a positive modifying effect on other parameters such as body weight, triglycerides and cholesterol values, which were not so significant in the Insulin group.

This again was in concordance with the other international studies¹⁰⁻¹². These effects may be explained by the known actions of Metformin in improving glucose utilization by the peripheral insulin action at the receptor level and possibly reduction in intestinal glucose absorption.

Hyperinsulinaemia, resulting from insulin resistance, in type II diabetes is a cardiovascular risk factor and a major cause of death in these patients¹³. Metformin decreases insulin resistance, thus favourably modifying this risk. The decrease in blood pressure was not statistically significant in our population group, on Metformin, as has been observed in the other studies^{3,12}, but they did show a downward trend.

The high drop out rate in the insulin group showed the general attitude of the population towards insulin. It is a reflection of various myths and disbeliefs surrounding the use of insulin. Another minor reason was failure to lose weight and a slight gain and increased appetite with its usage.

The choice of Metformin has an added advantage of oral route of administration, as compared to insulin. It is also relatively inexpensive and has less likelihood of causing hypoglycaemia. The occurrence of lactic acidosis in patients, without renal or hepatic disease is 0.03 per 1000 patient years. No interaction with the Sulphonylureas¹⁴ has been reported.

In conclusion, Metformin, in obese, type II diabetics, with secondary failure to Sulphonylureas, is an effective, safe and well-tolerated treatment. It improves the metabolic control and favourably modifies other parameters, such as weight, total cholesterol and triglycerides levels. The reduction in weight is associated with a general lowering in blood pressure, which is an additional benefit.

References

1. Lebovitz H. Sulphonylurea treatment; In international text book of medicine; Alberti K, De Fronzo-Keen, H, Zimmet P. Eds; Chichester, Wiley, 1992, pp. 745-72.
2. Hallin LL, Adamson U, Amer P. et al. Comparison of bed time NPH or preprandial regular insulin combined with Glibenclamide in secondary sulphonylurea failure. *Diabetes Care*, 1995;18:1183-88.
3. Fanghanel G, Reyes LS, Taajillo C, et al. Metformin effects on glucose and Lipid metabolism in patients with secondary failure to Sulphonylurea. *Diabetes Care*, 1996;19:1185-89.
4. Yki-Jarvinen H, Kaupila M, Kujansuu E, et al. Comparison of insulin regimens in patients with NIDDM. *N. Engl. J. Med.*, 1992;327: 1426-33.
5. Lindstrom TH, Arniqvist H, Von-Schnack HR. Effect of conventional and intensified insulin therapy on free insulin profile and glycaemic control in NIDDM. *Diabetes Care*, 1992;15:27-34.
6. Henry RR, Gurnbinder B, Ditzler T, et al. Intensive conventional insulin therapy for type II diabetes. *Diabetes Care*, 1993; 16:21-31.
7. Pugh JA, Wagner ML, Sawyer S, et al. Is combination sulphonylurea and insulin therapy useful in NIDDM patients? *Diabetes Care*, 1992;15:953-59.
8. Groop L, Widen E, Ekstrand A, et al. Morning or bed time NPH insulin combined with Sulphonylurea treatment of NIDDM. *Diabetes Care*, 1992;15:831-34.
9. Lindstrom T, Eriksson P, Olsson AG, et al. Long term improvement of glycaemic control by Insulin treatment in NIDDM patients with secondary failure. *Diabetes Care*, 1994;17:719-21.
10. Nosadini R, Avogaro A, Trevisan R, et al. Effect of Metformin on Insulin binding to receptor in type II diabetes. *Diabetes Care*, 1987;10:62-7.
11. Klip A, Lieter LA. Cellular mechanism of action of Metformin. *Diabetes Care*, 1990;13:696-704.

12. Stumvoli M, Nurjhan N, Perriello G, et al. Metabolic effects of Metformin in non-insulin dependent diabetes mellitus. *Diabetes Care*, 1995;18:550-54.
13. Fuller JH. Shipley Mi, Rose G, et al. Coronary heart disease risk and impaired glucose tolerance. *Lancet*, 1980;1:1373-76.
14. American Diabetes Association Consensus Statement. The pharmacological treatment of hyperglycemia in NIDDM. *Diabetes Care*, 1995;18:1510-18.