Glycemic Control in A Sample of Iraqi Patients with Type 2 Diabetes in Response to Nateglinide: Preliminary Study.

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ABSTRACT:

BACKGROUND:

Nateglinide, structural derivative of the amino acid D-phenylalanine, is a stimulator that controls the meal time spikes to restore of the early phase of insulin secretion lost in type II diabetes.

OBJECTIVE:

To evaluate the efficacy and tolerability of nateglinide in combination with metformin in a sample of Iraqi type II diabetic individuals,and to look for its side effects.

Setting: The Specialized Center of Endocrinology and Diabetes-Baghdad.

Design: During the period between September 2001 and January 2002 a sample of ten type II diabetic patients whose glycemic control is poor on metformin glibenclamide combination. Glibenclamide was replaced by nateglinide. Postprandial plasma glucose levels were checked frequently, and glycosylated hemoglobin (HBa1c) was evaluated in the 24th and 32nd week of the study period.

RESULTS:

It has been found that using nateglinide in a dose of 120 mg before each main meal three times daily does not reduce plasma glucose HBa1c to the desired levels, but using it in a dose of 180 mg before each meal results in gradual satisfactory decrement in plasma glucose and HBa1c. No adverse effects were recorded and metformin - nateglinide combination was well tolerated.

CONCLUSION:

Nateglinide and metformin improve overall glycemic control. Nateglinide decreases meal time glucose excursions. Their combination has a complementary effect, improving HBa1c and postprandial hyperglycemia. No adverse effects were recorded and metformin - nateglinide combination was well tolerated.

KEY WORDS: diabetes mellitus, nateglinide, glycemic control.

INTRODUCTION:

Owing to the fact that good control of postprandial hyperglycemia in type II diabetes is important with regard to reduction of macrovascular complications. The use of meglitinides as nateglinide, and repaglinide was advocated with other glucose lowering agents in order to achieve the best glycemic control. The most critical element of the treatment program is to define the goals.

Treatment must be based on results. Even when patients feel well and there has been lowering of glycemia, with a particular medication, if the treatment goal is unmet then change must be made.

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The American diabetic association advocates the following goals:

- Pre-prandial glucose = 80-120 mg/dl
- Bed time glucose = 100-140 mg/dl
- HBA1C (%) = less than 7% [1, 2]

In patients with established hyperglycemia, the major choices for monotherapy are sulphonylurea, metformin or thiazolidinedione. Combination therapy entails all permutations of these three, including patients increasingly being placed on triple therapy regimen. For patients with primarily postprandial hyperglycemia, acarbose or meglitinides are used. [3]

This study was conducted in order to find out the effect of nateglinide on meal time plasma glucose, and glycosylated haemoglobin (HBA1c). Meglitinides as nateglinide and repaglinide stimulate insulin secretion through a molecular effect similar to that of sulphonylurea by interacting with ATP-sensitive Potassium channels on the beta cells,

separate from the site occupied with high affinity by sulphonylureas. Similarly it stimulates glucose mediated insulin secretion. However it differs from sulphonylurea in its lack of inhibition of proinsulin biosynthesis. [4]

The greatest distinction comes from its pharmacokinetics. It is completely and rapidly absorbed. It has a rapid onset of action and short half life time (l hour). Consequently nateglinide has its dominant effect on postprandial glucose and lesser effect on fasting plasma glucose .An inherent advantage comes from temporal relation of dosing and action with meal consumption. The drug is intended to be taken from 0- 30 minutes before meals .If a meal is missed, nateglinide should not be taken. [5] Nateglinide has a fast on-of insulinotropic effect compared to sulphonylurea. [6]

PATIENTS& METHODS:

Ten poorly controlled patients with type II diabetes mellitus attending the specialized center of Endocrinology and Diabetes,during the period between September 2001 and January 2002 were enrolled in the study. They are two males and eight females. Their ages range from 47 to 62 years with a mean of 56.6 years. Their glycemic control is poor on the basis of high fasting plasma glucose (FPG), postprandial glucose (PPG), and glycated hemoglobin (HbA1c) thus their control doesn't fulfill the targets proposed by the European Diabetes Policy Group which are HbA1c < 7%, FPG < 128 mg/dl, and PPG < 135 mg/dl.

Their control also doesn't fulfill the targets proposed by the American Diabetes Association which are HbA1c < 7% and FPG < 131 mg/dl. Diabetic Patients who achieve the targets of glycemic control were excluded from the study. The enrolled subjects had at study entry a mean FPG of 283 mg/dl, mean PPG of 320 mg/dl and their mean HbA1c was 11.5%.At study entry they were treated with metformin 1.5 grams per day and glibenclamide 10 mg/day. Before changing their medications the details of the study were explained to the enrolled subjects. They were informed about Nateglinide action, benefit, and expected side effects.

After full explanation the patients accepted the idea and all subjects provided informed consent. At the first visit from the entire enrolled patient full story was taken followed by physical examination and blood samples were taken to check FPG, PPG, and HbA1c. Their treatment was modified by replacing glibenclamide with nateglinide 120 mg before each main meal, then FPG, and PPG were checked three times per week while HbA1c was checked at study entry, 24th week, and 32nd week. The dose of nateglinide was increased to 180 mg before each main meal at the 24 the week as the glycemic targets were not achieved by the starting dose of this drug despite being combined with metformin from the time of recruitment to the 32nd week of the study period.

RESULTS:

The studied subjects were found to be poorly controlled on the study entry despite being on metformin, thus their baseline meal time plasma glucose was 283 mg per deciliter and their HbA1c was 11.5% using nateglinide in a dose of 120 mg before each meal with metformin was found to be not useful with regard to achieving remarkable decrement in the level of mealtime plasma glucose and HbA1c. The results were promising after increasing the dose of nateglinide to 180 mg three times daily as shown in figure (1).

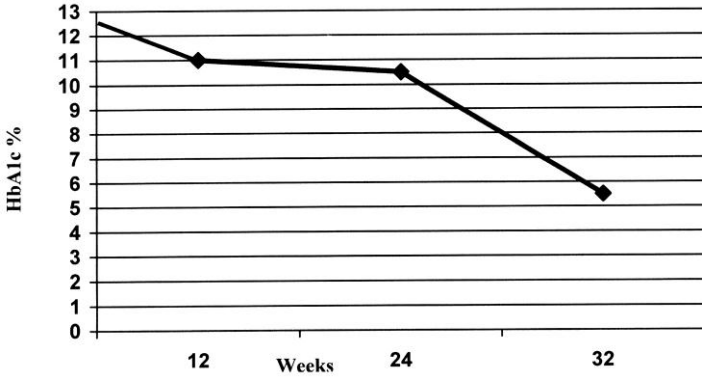

Figure 1: Changes in HbA1c through 32 weeks on metformin 1.5 grams per day and nateglinide 120 mg before each meal from study entry to the 24th week, and 180 mg three times daily till the end of the 32nd week.

After 32 weeks of substituting glibenclamide by nateglinide mark reduction of meal time glucose level was achieved thus metformin nateglinide combination is found to be promising when compared with metformin - glibenclamide combination, Figure (2) shows this observation.

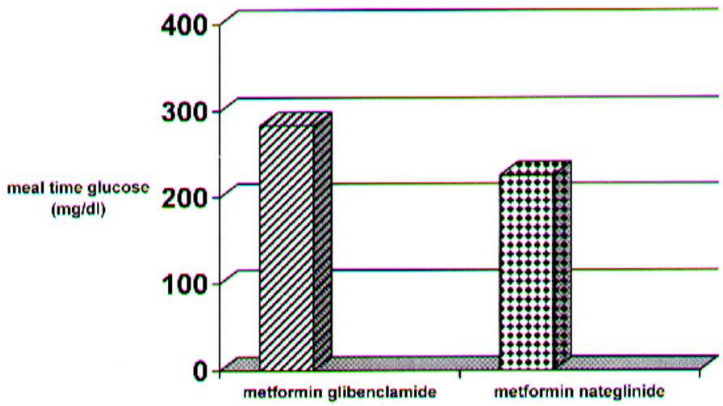

Figure 2: Reduction in meal time plasma glucose in response to metformin - glibenclamide combination on study entry versus metformin - nateglinide combination in the 32nd week of the study.
The response is remarkable particularly at the 32nd week of using nateglinide - metformin combination as shown in figure (3).

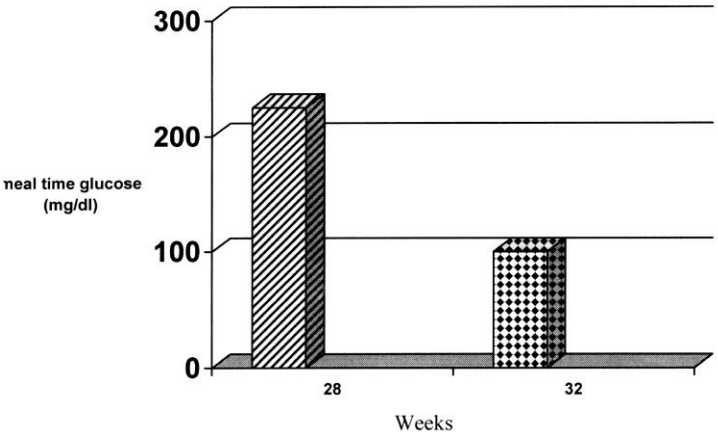

Figure 3: The response of meal plasma time glucose to metformin - nateglinide in the 24th week, the 32nd week of use.

The reduction of HBA1c was achieved only by the addition of nateglinide in a dose of 180 mg three times daily (tid) while using 120 tid fail to reduce HBA1c after substituting glibenclamide by nateglinide in combination with metformin , as shown in figure (4). Through out the 32 weeks of the study no hypoglycemic event or other adverse reactions were recorded.

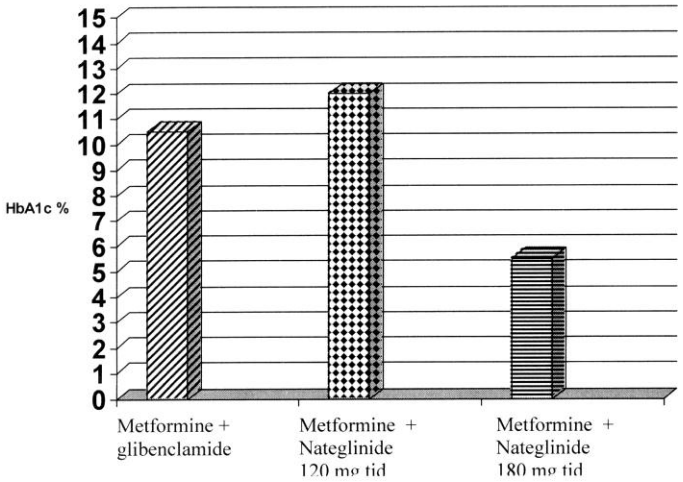

Figure 4: Mean HBA1c level in response to metformin - nateglinide combination and metformin - glibenclamide combination.

DISCUSSION:

Combined use of nateglinide with metformin has a complementary action thus they improve glycemic control by reducing meal time plasma glucose spikes as well as reducing glycosylated hemoglobin (HBA1C) levels. These targets are achieved only by using nateglinide in a dose of 180 mg/tid versus 120 mg/tid which fail to achieve the goal. Hypoglycemia is not recorded in the current study.

To compare the current study with other studies it has been found that nateglinide has a rapid stimulatory effect on insulin secretion, leading to a reduction in the post meal glucose spikes; this profile correspond to the physiologic response to meal. [7] Hollander had arranged eight weeks double blind randomized study comparing natiglinide (120 mg/tid), glibenclamide (5 mg once daily) for the first two weeks, then the dose of glibenclamide is increased to 10 mg/day from 2nd to 8th weeks of the study combined with placebo in stead of nateglinide. The 120 mg dose of nateglinide was well tolerated and the overall incidence of adverse events was similar during therapy with nateglinide.

The total number of adverse events attributed to studied medications by the investigator were not common in nateglinide and placebo groups while with glibencalmide such adverse effect were reported in almost one third of patients, with hypoglycemia the most frequent. In the current study hypoglycemia is not recorded despite full explanation of its symptoms to the enrolled patients.

There were no death and the incidence of serious or significant adverse events was very low. [8]

Events of hypoglycemia were observed in approximately 16% of nateglinide patients which, although higher than with placebo (approximately 4%) was substantially lower than with glibenclamide (36%). (8) When type II diabetic patients previously controlled by diet were treated with nateglinide 120 mg/tid or metformin 500 mg tid in monotherapy, hypoglycemia was found to be 4% with nateglinide alone, 8.4% with metformin - nateglinide combination.

Most of these hypoglycemic events were mild. [9] As a result no special dose adjustment is necessary for the elderly. Early phase insulin release is restored by administration of nateglinide in older patients just as effective as in younger age groups, thus resulting in desirable control of plasma glucose levels, and amelioration of the harmful meal time plasma glucose spikes. [10] At present nateglinide is not recommended for use in children because no clinical trials have been performed in this population.

In the United Kingdom Prospective Diabetes Study (UKPDS) intensive glycemic control in type 2 diabetes was shown to result in significantly increased treatment cost, substantially reduced costs of complications and increased time free complications. [11] The meal time glucose spikes have been found to be closely related to the occurrence of long term macrovascular complications and their

associated costs. [12] The link between meal time glucose spikes and the risk of cardiovascular disease have been proved ([13,14,15])

CONCLUSION:

1-The combination of nateglinide and metformin had a complementary effect improving FPG, PPG, and HbA1c.

2-Nateglinide in a dose of 120 mg three times daily fail to achieve the glycemic targets.

3-Increasing the dose of nateglinide to 180 mg three times daily results in marked improvement in the glycemic control.

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