Insulin glargine in combination with nateglinide in people with Type 2 diabetes: a randomised placebo-controlled trial

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Abstract

OBJECTIVE To evaluate the effect of adding nateglinide to therapy with insulin glargine in adults with Type 2 diabetes previously treated with insulin and with poor blood glucose control.

RESEARCH DESIGN AND METHODS In this 16-week, double-blind, placebo-controlled study, people with Type 2 diabetes (n = 55, HbA$_{1c}$ 8.2 ± 1.0 (±SD) %, duration of diabetes 12.8 ± 6.0 yr, duration of insulin treatment 6.0 ± 4.0 yr) were transferred to single bedtime injection of insulin glargine for a titration period of 4 weeks, and then randomised to nateglinide or matching placebo before meals in addition to insulin glargine. Metformin was continued if taken. Doses of insulin and oral medication were titrated to protocol for the treatment period of 12 weeks.

RESULTS Baseline-adjusted self-monitored capillary blood glucose concentration at 12 weeks was significantly lower with nateglinide + insulin glargine compared to placebo + insulin glargine after breakfast (difference -2.3 [95% CI -4.4, -0.2] mmol/l, $P = 0.030$), before lunch (-2.5 [-4.6, -0.3] mmol/l, $P = 0.029$), and after lunch (-2.3 [-4.3, -0.4] mmol/l, $P = 0.021$), but not at other times. Baseline-adjusted HbA$_{1c}$ was not lower with nateglinide + insulin glargine as compared to placebo + insulin glargine (7.8 ± 1.4 vs. 8.3 ± 1.0 %, difference -0.43 [-0.98, 0.12] %).

CONCLUSIONS Addition of nateglinide before meals to once-daily insulin glargine in people with long-standing diabetes already requiring insulin therapy improves blood glucose control in the early part of the day after breakfast and lunch, but does not provide good control of blood glucose levels overall.
Introduction

Studies have shown that intensive management of Type 2 diabetes reduces the incidence and progression of late-developing vascular complications (1, 2). In the management of Type 2 diabetes, treatment with oral glucose-lowering drugs (OGLDs) may not be sufficient as islet β-cell deficiency progresses, and the use of insulin has become standard practice in these circumstances. These people have often been managed on twice daily injections of premixed (biphasic) human insulin ('human pre-mix'), particularly where endogenous insulin secretion is unable to provide adequate meal-time insulin delivery. An alternative approach is to use insulin glargine, which can provide effective basal 24-h insulin replacement with a lower incidence of hypoglycaemia than NPH insulin (3-6), and requires just one injection. However, although pre-breakfast blood glucose levels can be lowered with such a regimen, meal-time glucose excursions may remain uncontrolled resulting in poorer overall control later in the day (7, 8).

There is also increasing evidence that postprandial hyperglycaemia makes a significant contribution to the overall glycaemic control and thus can potentially contribute to the development of late diabetic complications although the cause and effect relationship remains to be proven (9-14). Analysis from DECODE database shows that a high 2-h glucose response to an oral glucose tolerance test is associated with higher risk of death from CVD, ischaemic heart disease, stroke, and all cause mortality (15, 16). Also, since postprandial plasma glucose levels increase before fasting levels there may be an argument for detecting and treating postprandial hyperglycaemia early (17-20). Additionally, postprandial control of blood glucose is part of achieving better HbA1c levels, and indeed was actively used to improve blood glucose control in the DCCT (21).

Where it may be clinically relevant to control the problem of postprandial hyperglycaemia, a potential approach is the use of a rapid-acting insulin secretagogue. Nateglinide taken before meals has been shown to reduce postprandial blood glucose excursions both as monotherapy (22) and in combination with metformin (23).
The aim of the present study was to determine whether the use of a rapid-acting insulin secretagogue to control meal-time glucose excursions, together with insulin glargine to control post-absorptive glucose levels, could be effective in people who were previously managed on twice-daily insulin injections.

Participants and methods

The study used a 16-week, double-blind, randomised, parallel group design in people with Type 2 diabetes, studied at a single centre at the University of Newcastle upon Tyne, UK. Intervention treatment type (nateglinide or placebo) was allocated by formal concealed randomisation from a remote location. The local ethics committees approved the study before any trial activity, which was begun in each participant only after written informed consent was obtained.

Study participants

Sixty-nine people were recruited after preliminary screening of people on twice-daily insulin therapy attending the Newcastle Diabetes Centre. The people recruited were men and women age 39–83 yr with Type 2 diabetes (meeting the WHO definition of diabetes) who had been using a human premix or NPH insulin for at least 3 months and who had an HbA1c of 6.1-10.0 % and a BMI ≤42.0 kg/m² (Table1). Women of childbearing potential were required to be using adequate contraception. Significant hepatic or renal dysfunction, or active cardiovascular disease, were exclusion criteria.

Two people did not fulfil study inclusion criteria, five withdrew before entering the run-in period, and seven withdrew before randomization. Thus 55 people were randomised. Nine people in the placebo group withdrew during the treatment period, three because of perceived hyperglycaemia, four because of difficulty with injection devices, one because of nausea and one because of hospitalisation due to angina. Five people withdrew in the nateglinide group, three due to perceived hyperglycaemia, one due to hospitalisation for
angina, and one due to protocol violation. Thus endpoint data were available on forty-one people.

**Study design**

After a one week screening period during which previous insulin therapy was continued, participants entered a run-in period of 4 weeks during which once-daily insulin glargine was given at bedtime (OptiPen Pro, Sanofi-Aventis, Bridgewater, NJ.) Metformin was continued if taken. The commencing dose of insulin glargine was reduced by 20% from the previous daily dose as shown to be required in people with Type 1 diabetes transferring from twice-daily basal insulin to insulin glargine (24,25). The site of injection (either abdomen or thigh) was kept the same through the trial and the dose was titrated through telephone contact on days 3, 7, 14, and 21 to a target pre-breakfast capillary blood glucose level of 4.0-6.0 mmol/l, according to a pre-defined algorithm. At the randomisation visit after 4 weeks of run-in period, the participants started one capsule (60 mg) of nateglinide (Starlix, Novartis, Camberley, UK) or matching placebo before each meal, and the dose of insulin was reduced further by 20%. During the treatment period insulin glargine was titrated to a target pre-breakfast blood glucose level of <6.0 mmol/l and the number of nateglinide/placebo capsules was increased to two and then three before meals, in line with its European licence, according to a target 1-h postprandial blood glucose level of 5.0-7.5 mmol/l.

Participants were asked to perform frequent self-monitoring of blood glucose levels before breakfast and 1 h after meals using the OneTouch Ultra blood glucose meter (LifeScan, High Wycombe, UK). After randomization, further study visits occurred after 6 weeks and 12 weeks, with telephone contact in between visits on day 4, 7, 15, 30, 60 and 75. At each consultation, self-monitored blood glucose levels, hypoglycaemic events, insulin doses and trial medication doses were reviewed, and doses adjusted if necessary.
Biochemical measures

Eight-point self-monitored blood glucose profiles (pre- and 1 h post-meals, bed-time, and 0300-0500 h) were performed before randomization and at the end of the 12-week treatment period.

Hypoglycaemia was classified as symptoms-only (with glucose levels above 3.0 mmol/l [54 mg/dl] or no test data), minor (confirmed ≤3.0 mmol/l), or severe (requiring third party assistance).

HbA1c was measured by DCCT-aligned HPLC at the time of study entry, at randomisation and at the time of final visit. Body weight was measured at the same visits.

Statistical analysis

The primary endpoint was HbA1c, analysed by an ANOVA model using SPSS 12.0 for Windows (SPSS, Chicago, USA) on the intention-to-treat population (all people randomised).

Secondary endpoints included self-monitored glucose levels at each time point, body weight, and insulin dose. Hypoglycaemia was analysed as prevalence by Fisher’s exact test, namely the proportion of participants in each group having at least one episode of hypoglycaemia. Hypoglycaemia incidence (events per participant year) was analysed by the Mann-Whitney test.

From previous studies the SD for HbA1c in insulin glargine-treated people with Type 2 diabetes was taken as 0.8 %. In order to detect a difference in HbA1c of 0.6 % with a type 1 error of 5% and a statistical power of 80% we needed a sample size of 26 per group.

Data are given as mean ± SD and mean difference (95% CI) unless otherwise stated.
Results

Insulin and nateglinide doses, and use of metformin

The insulin dose in the nateglinide group at randomisation was 55 ± 28 U/day and increased to 58 ± 30 U/day by the end of study 12 weeks later. The matching data for the placebo group were 58 ± 29 and 62 ± 31 U/day (NS between treatments). By the end of the study 15 of 20 people in the nateglinide group were using nine capsules of nateglinide a day, whereas 17/21 people were using nine capsules of placebo in the other group. Metformin was used in 20/26 participants in the nateglinide group, and 19/29 participants in the placebo group.

Glycated haemoglobin and body weight

Baseline HbA\textsubscript{1c} in the nateglinide and placebo groups at randomisation (mean ± SD) was equal (8.2 ± 1.0 vs. 8.2 ± 1.0 %). At the end of treatment period HbA\textsubscript{1c} was 7.8 ± 1.4 % in the nateglinide group and was 8.3 ± 1.0 % in the placebo group. The baseline adjusted difference in mean change in HbA\textsubscript{1c} failed to reach statistical significance (-0.43 [95% CI − 0.98, 0.13] %, NS). The difference in change in body weight was also not significant (0.78 [95% CI −0.45, 2.01] kg, NS).

Blood glucose profiles

Already by the end of the run-in period 43 of 55 participants (78 %) had achieved target pre-breakfast self-monitored levels on insulin glargine. The blood glucose profiles at the end of the treatment period are shown in Figure 1. Visual inspection of the profiles reveals that the mean glucose levels are lower after breakfast, and before and after lunch, but that this difference is gradually lost through the rest of the day. The improvement in blood glucose concentration with the nateglinide was between 2.0-2.5 mmol/l after breakfast and before and after lunch, differences that were statistically significant (Table 2).
Hypoglycaemia

There was no episode of severe hypoglycaemia in the study. The proportion of participants experiencing minor (confirmed) hypoglycaemic episodes was similar for the two treatment arms (nateglinide 8% and placebo 7%, NS). The proportion of participants reporting episodes of symptoms-only (unconfirmed) hypoglycaemia was numerically greater for nateglinide than placebo treatment (19 vs. 14%, NS). For symptoms-only, minor and all episodes, the incidence was similar for nateglinide compared with placebo (1.5, 1.4, and 2.9 vs. 2.2, 3.3 and 5.5 events/pt-yr, all NS between treatments).

In general there were no major differences between the treatment periods in the distribution of hypoglycaemic episodes by time of day. In both groups, the proportion of people experiencing any type of Hypoglycaemia (major, minor and symptoms-only combined) was highest in the period before breakfast.

Adverse events

The number of people experiencing adverse events was similar in the two groups (nateglinide 9, placebo 11 participants). No treatment-related serious adverse events were recorded.

Conclusions

The participants in the present study were people with Type 2 diabetes of longer duration than average (12-13 yr) and already requiring insulin therapy for some years, in combination with metformin where tolerated and not-contraindicated. Despite this, their HbA1c levels were less than satisfactory (around 8.2 %) at randomisation suggesting fairly advanced islet β-cell failure. Their blood glucose profiles on insulin glargine plus placebo reveal the problem of blood glucose control that results, namely that while the basal insulin achieves good nocturnal blood glucose control, there is loss of control in the day-light hours, in this study of the order of +4.0 mmol/l between basal pre-breakfast and basal pre-dinner measurements. In some other studies this deterioration is also seen when using insulin glargine, perhaps
through waning of insulin delivery at that time, though in general of a lesser order of +2.0 mmol/l glucose in people earlier in their natural history of diabetes, starting insulin for the first time (7, 8).

In a further study more aggressive use of combination oral glucose-lowering drugs did abolish the day-time deterioration in glucose control in insulin glargine treated insulin starters (26). That study used metformin plus a sulfonylurea (glimepiride) with a peak glucose-lowering effect at 4-5 h. In the current study we attempted to obtain the same gain in people with more advance diabetes through the use of a rapid-acting insulin secretagogue at full dosage before each main meal, and while we were partially successful in that glucose levels were lowered by around 2.0 mmol/l for much of the morning and afternoon, the effect was entirely lost by the evening, a time when glucose control is often at its most difficult in this group of people, probably partly for physiological reasons and partly because the biggest meal of the day is taken at this time.

The gain in blood glucose control in the day with nateglinide would represent approximately a 10% drop in average blood glucose levels over 24 hours. A drop of glycated haemoglobin by the same order would then have been expected. While the baseline-adjusted change in HbA1c in the placebo group was as expected and as used in the power calculation, loss of numbers after recruitment meant the study was somewhat underpowered for this measure. This possibly explains the lack of statistical significance of the central estimate of a change of HbA1c of 0.43 % between treatments (approximately a 5 % relative change). A further contributory factor here might have been the length of study, as 12 weeks is only appropriate for HbA1c measurements if the gains in blood glucose control are fully established by 4 weeks after randomisation.

The lack of difference in hypoglycaemia outcomes was expected, largely because too few events occur in people with Type 2 diabetes to give significant differences in relatively small, short duration studies. Further reductions in hypoglycaemic events and thus study power will arise because rapid-acting insulin secretagogues like nateglinide are less prone to cause
inter-prandial hypoglycaemia than sulfonylureas in provocation studies (27), and because hyperglycaemia during the day was usual even in the nateglinide arm. The possibility nevertheless of a Type 2 statistical error is acknowledged.

Glucose control with these regimens in this group of people with relatively well-established insulin secretory deficiency was clearly not satisfactory. Alternative approaches to management are then likely to remain centred around optimal insulin regimens except in those people who might benefit from combination insulin-thiazolidinedione therapy (where drug licensing allows). The AT-LANTUS study found that meal-time insulin was a necessary accompaniment to insulin glargine if good blood glucose control was to be obtained in people changed from pre-mix insulin (28). Biphasic (pre-mix) insulin analogues may have an advantage here, but may need to be used more than twice-daily if the lunch-time glucose excursions seen in our patients are to be avoided (29). Meanwhile in people starting insulin for the first time an insulin secretagogue as well as metformin seems to be indicated (26), and nateglinide or repaglinide still remain to be studied in this context.

Thus, in people already taking insulin and exhibiting moderate blood glucose control the combination of nateglinide, metformin and insulin glargine results in improved blood glucose control compared with regimens without a secretagogue, but does so only during the earlier part of the day, and does not improve overall control substantially. At present insulin regimens using a prandial as well as a basal insulin still seem indicated in this situation.

Acknowledgements

For this study, insulin glargine was donated by Sanofi-Aventis and nateglinide was donated by Novartis. We are also thankful to Jan Gebbie and Jean Gerrard for technical assistance during the study.
Table 1. Characteristics of the people with Type 2 diabetes randomised and treated (the ITT set).

<table>
<thead>
<tr>
<th></th>
<th>Insulin glargine + Nateglinide</th>
<th>Insulin glargine + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Sex (male:female) (n)</td>
<td>14:12</td>
<td>15:14</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.8 ± 9.2</td>
<td>65.5 ± 8.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>87.0 ± 12.4</td>
<td>85.9 ± 15.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.0 ± 4.0</td>
<td>30.9 ± 5.5</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>8.2 ± 1.0</td>
<td>8.2 ± 1.0</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>12.3 ± 5.6</td>
<td>13.2 ± 6.4</td>
</tr>
<tr>
<td>Duration of insulin use (yr)</td>
<td>5.2 ± 3.8</td>
<td>6.7 ± 4.1</td>
</tr>
</tbody>
</table>

Mean ± SD, or n
Table 2. Comparison of baseline adjusted improvement in mean blood glucose (mmol/l) at different times of day and of HbA\textsubscript{1c} (%) (Insulin glargine + Nateglinide vs. Insulin glargine + Placebo)

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Difference</th>
<th>95% CI of difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before breakfast</td>
<td>0.53</td>
<td>-0.72, 1.78</td>
<td>NS</td>
</tr>
<tr>
<td>1-h after breakfast</td>
<td>-2.30</td>
<td>-4.36, -0.24</td>
<td>0.030</td>
</tr>
<tr>
<td>Before lunch</td>
<td>-2.45</td>
<td>-4.63, -0.27</td>
<td>0.029</td>
</tr>
<tr>
<td>1-h after lunch</td>
<td>-2.33</td>
<td>-4.30, -0.37</td>
<td>0.021</td>
</tr>
<tr>
<td>Before dinner</td>
<td>-1.03</td>
<td>-3.17, 1.10</td>
<td>NS</td>
</tr>
<tr>
<td>1-h after dinner</td>
<td>-0.57</td>
<td>-2.91, 1.76</td>
<td>NS</td>
</tr>
<tr>
<td>Bedtime</td>
<td>1.30</td>
<td>-1.26, 3.86</td>
<td>NS</td>
</tr>
<tr>
<td>0300-0500 h</td>
<td>-1.37</td>
<td>-4.24, 1.51</td>
<td>NS</td>
</tr>
<tr>
<td>HbA\textsubscript{1c}</td>
<td>-0.43</td>
<td>-0.98, 0.13</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Blood glucose in mmol/l, HbA\textsubscript{1c} in %

*Data analysis by baseline-adjusted ANOVA*
Figure 1. Self-monitored blood glucose profiles in people with insulin-treated Type 2 diabetes treated with bedtime insulin glargine with (♦) and without (■) nateglinide before main meals.
References


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