COMBINATION-THERAPY WITH BEDTIME NPH INSULIN AND SULPHONYLUREAS GIVES SIMILAR GLYCAEMIC CONTROL BUT LOWER WEIGHT GAIN THAN INSULIN TWICE DAILY IN PATIENTS WITH TYPE 2 DIABETES

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SUMMARY - Background: To study the effect on body weight and glycaemic control of two insulin treatment regimens in patients with Type 2 diabetes and moderate failure to oral hypoglycaemic agents.

Methods: Sixteen patients treated with oral hypoglycaemic agents (6 men and 10 women) were included in this open-label, randomized, parallel group study. Their age was 62 ± 2 (mean ± SEM) years (range 44-79 years), body weight 71.3 ± 2.9 kg, body mass index (BMI) 24.6 ± 0.8 kg/m². The patients were switched to insulin treatment with bedtime NPH insulin combined with daytime sulphonylurea (combination group) or twice daily injections of a premixed combination of regular human and NPH insulin (insulin twice daily group) with measurements as given below before and after 12 and 24 weeks of treatment.

Results: HbA₁c was lowered from 8.3 ± 0.3% to 7.0 ± 0.2% in the insulin twice daily group (p < 0.05) and from 8.3 ± 0.3% to 6.8 ± 0.5% in the combination group (p < 0.03; ns between treatment groups). Body weight increased from 71.7 ± 4.0 kg to 77.6 ± 4.4 kg in the insulin twice daily group (p < 0.001) and from 70.8 ± 4.6 kg to 72.7 ± 5.1 kg in the combination group (ns; p < 0.02 between groups). The dose of insulin at 24 weeks in the insulin twice daily group was 45.8 ± 4.2 U and 29.4 ± 5.4 U in the combination group (p = 0.03). Combination treatment reduced fasting and stimulated C-peptide levels.

Conclusions: Both treatments improved glycaemic control to the same extent but the combination of bedtime NPH insulin and daytime sulphonylurea gave a very small increase of body weight over a 6 months period. We conclude that combination therapy is an attractive alternative when starting insulin treatment in patients with Type 2 diabetes as this is a critical period for weight gain in such patients.

Key-words: type 2 diabetes, insulin, sulphonylurea, body weight, body mass index, C-peptide.

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RÉSUMÉ. - Le traitement combiné par insuline NPH au coucher et sulfonylurées donne un contrôle glycémique similaire mais une moindre prise de poids que l’insuline deux fois par jour chez les diabétiques de type 2.

Contexte : Étudier l’effet sur le poids corporel et le contrôle glycémique de deux protocoles d’insulinothérapie chez des diabétiques de type 2 en échec modéré de traitement hypoglycémiant oral.

Méthodes : Seize patients traités par hypoglycémiant oraux (6 hommes et 10 femmes) ont été inclus dans cette étude ouverte, randomisée en groupes parallèles. L’âge était de 62 ± 2 ans (moyenne ± SEM) (extrêmes 44-79 ans), le poids 71,3 ± 2,9 kg, l’index de masse corporelle (IMC) 24,6 ± 0,8 kg/m². Les patients ont été placés sous insulinothérapie avec insuline NPH au coucher combinée à la prise de sulfonylurées la journée (groupe traitement combiné) ou injections deux fois par jour d’un prémélange d’insuline humaine ordinaire et de NPH (groupe insuline deux fois par jour) avec mesures comme décrit ci-dessous avant et après 12 et 24 semaines de traitement.

Résultats : L’HbA₁c a été réduite de 8,3 ± 0,3 % à 7,0 ± 0,2 % dans le groupe insuline deux fois par jour (p < 0,05) et de 8,3 ± 0,3 % à 6,8 ± 0,5 % dans le groupe traitement combiné (p = 0,03 ; ns entre les groupes). Le poids a augmenté de 71,7 ± 4,0 kg à 77,6 ± 4,4 kg dans le groupe insuline deux fois par jour (p < 0,001) et de 70,8 ± 4,6 kg à 72,7 ± 5,1 kg dans le groupe traitement combiné (ns ; p < 0,02 entre les groupes). La dose d’insuline à 24 semaines dans le groupe insuline deux fois par jour était de 45,8 ± 4,2 U et de 29,4 ± 5,4 U dans le groupe traitement combiné (p = 0,03). Le traitement combiné a réduit le C-peptide à jeun et sous stimulation.

Conclusions : Les deux traitements ont amélioré le contrôle glycémique à un niveau similaire mais la combinaison d’insuline PH au coucher et de sulfonylurées la journée a conduit à un très faible gain de poids sur une période de 6 mois. Nous concluons que le traitement combiné est une alternative attractive pour la mise en route de l’insulinothérapie chez le diabétique de type 2 dans la mesure où il s’agit d’une période critique quant à la prise de poids chez ces patients.

Mots-cés : diabète de Type 2, insuline, sulfonylurées, poids corporel, index de masse corporelle, C-peptide.
type 2 diabetes is a slowly progressive disease [1, 2] in which treatment with diet, physical activity and oral hypoglycaemic agents will eventually prove insufficient [3, 4]. Insulin treatment improves blood glucose control in this situation but also increases body weight [5-7]. A majority of patients with Type 2 diabetes have overweight, a condition which is considered to aggravate the metabolic disturbances. Combination-therapy with insulin and oral agents such as sulphonylureas, metformin, acarbose and glitazones has been tried to diminish these potentially negative effects as lower insulin doses then can be used with similar effect on glycaemic control [8-17].

There is today no general consensus on how to treat Type 2 diabetes with insulin. The most commonly used treatment is one or two injections of insulin alone administered before breakfast and dinner or before breakfast in the case of a single daily injection. In the present study we chose to use such treatment with two daily doses of premixed regular and NPH insulin as a reference treatment. Bedtime insulin administration is recommended when combination therapy with insulin and oral agents is given. In patients with poor glycaemic control such combination with metformin has shown improvement of glycaemic control with only a small increase of body weight [17]. Also combination with bedtime NPH insulin with daytime sulphonylureas, as in the present study, has been tried with different results which will later be discussed [10, 17-19]. There are also studies of the combination with acarbose and with glitazones showing improvement of glycaemic control while body weight is increased during combination of insulin and glitazones in comparison with insulin treatment alone [16].

The aim of our study was to investigate the effect on body weight and glycaemic control of bedtime NPH insulin combined with daytime sulphonylurea in patients with Type 2 diabetes and failure to oral hypoglycaemic agents. This was defined as HbA1c between 7.0 and 10.0%. As comparison, treatment with two daily injections of a premixed combination of regular human and NPH insulin alone was used.

**PATIENTS AND METHODS**

**Study design**

Patients with Type 2 diabetes who were referred from primary care physicians owing to failure to oral hypoglycaemic agents defined as HbA1c values between 7.0-10.0% were invited to participate in the study. The patients had participated in the regular primary care diabetes programme with education on diet, exercise and self-monitoring of blood glucose and had been treated with oral agents for a minimum of 12 months. The study design was a randomized parallel group study. The patients were randomized to receive a prefixed combination of 30% regular human insulin and 70% NPH insulin (Mixtard 30/70 Penset® 100 U/ml; Novo-Nordisk AS, Bagsvaerd, Denmark) given before breakfast and dinner or to addition of NPH insulin given at bedtime (Insulatard Penset® 100 U/ml; Novo-Nordisk AS, Bagsvaerd, Denmark) to their daytime sulphonylureas. The patients treated with two daily insulin injections without any oral hypoglycaemic agents will be referred to as the insulin twice daily group and the patients treated with the combination of bedtime NPH insulin and daytime sulphonylureas as the combination group. All insulin injections were given subcutaneously in the thigh 30 min before breakfast and dinner or at bedtime respectively. During the study all patients performed home blood glucose measurements and the insulin doses were adjusted according to these. We aimed at preprandial blood glucose concentrations of 4-7 mmol/l and postprandial values (1.5-2 hrs after a main meal) below 10 mmol/l. Before starting insulin treatment and after 12 and 24 weeks of insulin treatment fasting blood samples as specified below were collected. The patients were also given 1 mg glucagon intravenously and C-peptide concentration was measured 6 minutes later. All patients gave informed consent prior to inclusion and the study was approved by the local ethics committee.

**Patients**

Sixteen patients (6 men and 10 women) were included in the study. Their age was 62 ± 2 (mean ± SEM) years (range 44-79 years), body weight 71.3 ± 2.9 kg, body mass index (BMI) 24.6 ± 0.8 kg/m² and they had been treated with oral hypoglycaemic agents for 7.1 ± 1.3 years (range 2-19 years). The patients randomized to the insulin twice daily group were previously treated with sulphonylureas (glibenclamide n = 6 or glipizid n = 2) and in 4 of the patients combined with metformin. Previous treatment in the combination group was sulphonylureas (glibenclamide n = 6 or glipizid n = 2) and in 3 patients combined with metformin. Metformin was withheld during the study.

**Analytic methods**

Blood glucose was measured using a hexokinase glucose-6-phosphate dehydrogenase method. HbA1c (normal range 3.9-5.3%) was analyzed with the hospitals routine method using high-performance liquid chromatography. C-peptide in plasma was determined by a radioimmunoassay (Euro-Diagnostica, Sweden; detection limit 0.10 nmol/l). Venous blood samples were drawn after overnight fasting for determination of lipoproteins which were analyzed with the hospital’s routine method.
6.6 had been treated with oral hypoglycaemic agents for 3.6 years (both non-significant between groups). During the study in the insulin twice daily group and with 1.8 ± 0.33 U/kg body weight and only an increase of 0.1 ± 0.4 kg in the combination group (ns). There was an increase with 5.8 ± 0.95 kg during the study in the insulin twice daily group and with 1.9 ± 1.0 kg in the combination group (p < 0.02 between treatments).

Statistics

The results presented are means ± SEM. Differences between baseline and 24 weeks values were tested with two-tailed Student’s t-test for paired data or Wilcoxon’s test where appropriate. Differences between baseline values between the groups were tested by two-tailed Student’s t-test for unpaired data. Correlations between baseline C-peptide concentrations and change of HbA1c was calculated by linear regression.

RESULTS

Patient characteristics

The patients randomized to treatment with two daily insulin injections were 63 ± 3 years of age and had been treated with oral hypoglycaemic agents for 7.5 ± 2.1 years while the patients randomized to combination treatment were 61 ± 3 years of age and had been treated with oral hypoglycaemic agents for 6.6 ± 1.6 years (both non-significant between groups).

Insulin dosage, glycaemia, body weight and determinations of C-peptide

The patients in the insulin twice daily group were treated with a total insulin dose of 42.1 ± 3.6 U after 12 weeks and with slightly higher dose at week 24; 45.8 ± 4.2 U (p < 0.01). The corresponding insulin doses in the combination group were 17.0 ± 2.0 U after 12 weeks and 29.4 ± 5.4 U after 24 weeks. They were thus significantly lower in the combination group than in the insulin twice daily group (p = 0.0001 and 0.03 respectively). In the insulin twice daily group an insulin dose of 0.56 ± 0.07 U/kg body weight at week 12 and 0.61 ± 0.07 at week 24 was given while in the combination group 0.25 ± 0.03 U/kg body weight and 0.33 ± 0.05 U/kg body weight were given respectively (in both instances p < 0.01 between treatments). No case of severe hypoglycaemia occurred during the study.

HbA1c was markedly lowered in both groups as shown in Table I. There was no significant difference between the insulin twice daily and combination groups. One patient in the insulin twice daily group had HbA1c above 8% (8.8%) and one patient in the combination group (9.6%) showing unsatisfactory glycaemic effect in these patients.

Body weight increased with 4.6 ± 0.85 kg in the insulin twice daily group and with 1.8 ± 1.0 kg in the combination group (p < 0.05) during the first 12 weeks of insulin treatment (Fig. 1). During the period between 12 and 24 weeks there was a further increase of 1.1 ± 0.55 kg in the insulin twice daily group but only an increase of 0.1 ± 0.4 kg in the combination group (ns). There was an increase with 5.8 ± 0.95 kg during the study in the insulin twice daily group and with 1.9 ± 1.0 kg in the combination group (p < 0.02 between treatments).

Table 1. Different variables in 8 patients with Type 2 diabetes treated with a premixed combination of regular and NPH insulin twice daily and in 8 patients treated with bedtime NPH insulin in combination with daytime sulphonylureas before starting insulin and 24 weeks after starting insulin therapy. Results are presented as means ± SEM. Differences within the groups were calculated with two-tailed Student’s t-test.

<table>
<thead>
<tr>
<th></th>
<th>Insulin twice daily</th>
<th>Bedtime insulin + sulphonylurea</th>
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<tbody>
<tr>
<td></td>
<td>before 24 weeks</td>
<td>Sign.</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 ± 0.3</td>
<td>7.0 ± 0.2 &lt; 0.05</td>
</tr>
<tr>
<td>Insulin dose (U)</td>
<td>45.8 ± 4.2</td>
<td>29.4 ± 5.4</td>
</tr>
<tr>
<td>Insulin dose/body weight (U/kg)</td>
<td>0.61 ± 0.07</td>
<td>0.33 ± 0.05</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3 ± 1.0</td>
<td>25.1 ± 1.2 &lt; 0.001</td>
</tr>
<tr>
<td>Fast C-peptide (nmol/l)</td>
<td>0.66 ± 0.24</td>
<td>0.70 ± 0.18</td>
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<tr>
<td>Stimulated C-peptide (nmol/l)</td>
<td>1.23 ± 0.47</td>
<td>1.23 ± 0.22 &lt; 0.01</td>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.6 ± 0.54</td>
<td>5.4 ± 0.34</td>
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<tr>
<td>Total triglycerides (mmol/l)</td>
<td>2.6 ± 0.58</td>
<td>2.2 ± 0.86</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.2 ± 0.13</td>
<td>1.1 ± 0.10</td>
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The C-peptide concentrations are given in Table I. Both fasting and glucagon stimulated concentrations decreased significantly after 24 weeks in the combination group and the changes in the insulin twice daily group were similar although they did not reach statistical significances. There was a significant correlation between the baseline C-peptide concentration and the change of HbA1c between baseline and week 24 in the combination group (Fig. 2) but no such correlation was found in the insulin twice daily group (R^2-value 0.003).

**DISCUSSION**

In this parallel group randomized study we compared the effects of bedtime NPH insulin in combination with daytime sulphonylurea (combination group) with the commonly used twice daily injections of regular human and NPH insulin (insulin twice daily group) in patients with Type 2 diabetes. Glycaemic control was improved similarly in both groups but while there was a marked increase of body weight in the insulin twice daily group the increase of body weight in the combination group did not reach statistical significance.

The majority of patients with Type 2 diabetes have overweight defined as a body mass index over 25 kg/m^2 but at the time when insulin is introduced a decrease of body weight has often occurred probably related to poor glycaemic control with glucosuria in many patients [20]. Probably also weight-reducing efforts by the patient with some changes of diet have influence. When insulin treatment is introduced there is a rapid increase of body weight in agreement with that 79% of the weight gain of the insulin twice daily group in our study occurred during the first 12 weeks. During a long-term study of patients with Type 2
diabetes treated with insulin alone we found that there is little change of body weight after 12 months of insulin treatment [21].

As in our study, combination treatment with bedtime insulin and daytime sulphonylureas have been studied in patients previously treated with oral hypoglycaemic agents. Wolffenbuttel et al. compared three treatment regimens including the two used in our study and also a morning injection of NPH insulin combined with sulphonylurea [18]. No differences in glycaemic control or body weight was found between the regimens after 6 months. In the FINFAT study lower weight gain was found with bedtime insulin combined with metformin but there was no significant difference in glycaemic control or body weight between the patients treated with bedtime NPH insulin and sulphonylurea compared with morning and bedtime NPH insulin [17]. The patients taking part in that study differed from our patients as they had more pronounced impairment of glycaemic control and were much more obese when starting insulin therapy. Clauson et al. [10] gave intensive insulin treatment for 6 weeks to patients with failure to oral hypoglycaemic agents and then randomized these patients to continued intensive multi-injection insulin therapy or to combination of bedtime NPH insulin and daytime sulphonylurea. Lower increase of body weight was found after 1 year in the combination group with similar glycaemic control in both groups. Interpretation of the study is, though, complicated by the fact that glycaemic control differed after 6 months insulin treatment and by a seemingly greater weight gain during the 6 week run-in period with intensive insulin treatment in the group that was later randomized to continue multi-injection insulin treatment. In another study using a rapid-acting insulin analog, lispro, in a multi-injection regimen with NPH insulin at bedtime there was similar glycaemic improvement as with NPH insulin at bedtime combined with daytime sulphonylurea [19].

Most studies where combination therapy with insulin and sulphonylureas have been given to previously insulin-treated patients have not shown a difference between combination treatment and insulin treatment in body weight but in many cases differences in glycaemic control complicate the comparisons [16]. The combination treatment seems an attractive alternative when introducing insulin treatment; a situation when dietary intake remains unchanged but caloric waste by glucosuria is heavily diminished [22]. In more obese patients the combination with metformin showed good results in the FINFAT study [17] but in patients with normal body weight or slight overweight when exhibiting secondary failure the present combination of bedtime insulin and daytime sulphonylureas might be a successful choice of initial treatment. Change to combination treatment with sulphonylureas in already insulin-treated patients is more doubtful and such patients with more advanced Type 2 diabetes might also have higher degrees of beta-cell failure [4, 23].

Both treatments markedly improved glycaemic control and there was no difference between the groups in agreement with what has previously been generally found with these combinations [17, 18] or with multi-injection regimens in comparison with bedtime insulin and daytime sulphonylureas [10, 19].
Both fasting and glucagon-stimulated C-peptide levels in the morning were lowered in agreement with improvement of glycaemia by insulin treatment [24]. In the combination group a significant correlation was found between the baseline C-peptide concentration and the subsequent change in HbA1c but no such correlation was found in the insulin twice daily group. This suggests that a better preserved betacell function gives a more pronounced glycaemic response to combination therapy but that betacell function is of lesser importance for the glycaemic response when an insulin regimen which covers 24 hours, such as the twice daily insulin treatment, is used. There are previous studies supporting that patients with higher C-peptide levels show greater improvement of glycaemia than those with lower levels during combination therapy but it should also be noted that in a large study comprising 175 patients [25] no such relation was found. None of the lipid variables changed significantly.

In summary, our study shows improvement of glycaemic control to the same extent over a 6 months period with premixed regular and NPH insulin before breakfast and dinner and with a combination of bedtime NPH insulin and daytime sulphonylurea. In spite of this we found considerably lower weight gain with the combined treatment. We conclude that combination therapy might be an attractive alternative of starting insulin therapy in patients with Type 2 diabetes and preserved betacell function when failure to oral hypoglycaemic agents evolves as it is also easily conceived by the patients.

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