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1976-PO

Basal Insulin Therapy in Type 2 Diabetes: A Prospective 18 Month Comparison of Insulin Glargine and NPH Insulin in Patients with a Multiple Injection Regimen


The UKPDS has established that long-term tight metabolic control delays the onset and progression of diabetic micro- and macrovascular complications. In most glycemic goals multiple injection regimens (MIC) are one practical option.

Age, duration of disease (60 yrs) and C-peptide (CP) levels did not differ significantly in both groups (IG age: 60 yrs, CP: 0.4-0.5 mg/dl; NPH age: 63 yrs, CP: 0.2-0.5 mg/dl). After 18 months of treatment the HbA1c level improved only in the IG group significantly from 7.4% to 7.0% (median: 7.0-8.0, p<0.001) compared to the NPH group (HbA1c from 7.4% to 7.2%; median: 7.0-8.0, p<0.001). We found no significant difference in the basal insulin doses (IG final dose: 29.8 IU/kg, median: 28.9 IU/kg; NPH final dose: 30.9 IU/kg, median: 30.8 IU/kg).

The also preprandial insulin doses did not differ significantly. Both groups did not show a significant increase of the mean body mass index. A significantly lower number of symptomatic hypoglycemia in the IG group was documented.

In an 18-month clinical trial patients with type 2 diabetes treated with a multiple injection regimen, IG once daily resulted in a significant improvement of metabolic control and no significant changes in body weight and insulin dose. IG provides a clinical advantage over NPH also with respect to the incidence of mild hypoglycemia.

1977-PO

Improved Treatment Satisfaction and Perceived Metabolic Control with Insulin Glargine, Regardless of Whether Injected before Breakfast, Dinner or Bedtime in Patients with Type 1 Diabetes

Louise Silvestre, Claret Braden, Elke Wittaukas, Nourmineva, France; Zygmans, United Kingdom; Francfort, Germany.

Insulin glargine (Lantus®) is a once-daily basal insulin with a duration of action beyond 24 hours. A recent study showed that glargine, plus prandial insulin, is effective when injected before breakfast, before dinner, or at bedtime in patients with type 1 diabetes. The effect of these administration times on treatment satisfaction and perceived metabolic control was presented. In this open-label, randomized, parallel group, multicenter, 24-week, study, 352 of the 378 treated patients completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at baseline and study endpoint. At baseline, 273 (73.8%) patients in the clinically evaluated population had an injection time preference (18.9%), breakfast (20.2%) dinner, 105 (28.2%) bedtime; 24 (6.7%) preferred a combination. Mean (±SD) treatment satisfaction scores, with most patients using NPH insulin, were 2.1 ± 0.5, 2.7 ± 0.5 and 2.8 ± 0.5 in the breakfast, dinner and bedtime groups, respectively, and increased in all groups from baseline to endpoint (P = 0.0079; 3.5, 0.0002; 1.8, 0.0009, respectively paired t test). The largest increase came from a change in the DTSQ convenience term (breakfast: 0.8, ± 0.0001; dinner: 0.7, ± 0.0001 and "wish to continue" (breakfast: 0.4, ± 0.0001; dinner: 0.6, ± 0.0001). In terms of perceived metabolic control, the perceived frequency of hypoglycemia decreased significantly at endpoint in the breakfast (-0.4, ± 0.012) and bedtime (-0.3, ± 0.0001) but not in the dinner group (0.3, ± 0.07). Perceived frequency of hyperglycemia decreased significantly in the 3 groups combined (-0.18, ± 0.04), but not in separate groups. These data complement the clinical study results and, in addition, show treatment satisfaction improved with glargine, regardless of injection time. Thus, insulin glargine can be used effectively according to individual patients' needs or preference, before breakfast, before dinner or at bedtime.

1978-PO

Synthesis and Crystal Structure of a PPARα agonist that Delivers Glycerone Control and Improved Lipid Profiles without Weight Gain

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We have previously shown that activation of the PPARα subtypes by simultaneous administration of combinatorial regimens of selective PPAR agonists produces synergistic effects in ZDF rats (recombinant model of type 2 diabetes, 69% AKA strain, 85, 566 and 567). These effects include normalization of post-glucagon plasma glucose and turnover of serum triglycerides and NEFAs without weight gain and less hyperinsulinemia. In addition, our single molecule that has agonist activity on PPARα, PPARγ and PPARβ/δ exhibits the same synergy as that reported for the combination of individual selective PPAR agonist molecules. The design, synthesis and in vivo data of such a PPARα agonist that is 5-methyl pyridine (C5) at PPARα and 40-methyl (C40) on PPARβ/δ in the transient transfection assay will be presented. In the ZDF rat model this piperazine-based compound is also significantly more effective on PPARδ suggesting that the beneficial effects of this molecule are due to the dual agonist activity.

The X-ray crystal structure of this independent component with the lady PPARα receptor shows that the piperazine occupies a pocket that is conserved in PPARα, PPARδ and PPARγ.

1979-PO

Combination of Repaglinide and Metformin Results in Greater Than Additive (Synergistic) Effects on Glucose Tolerance in Obese Zucker (fa/fa) Rats

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Combination therapy with repaglinide (RGL) and metformin (MFT) is an effective way to treat patients with type 2 diabetes. In this study, we specifically wanted to investigate whether the combination of RGL and MFT additively has additive or greater than additive synergistic effects on glucose tolerance in obese Zucker (fa/+) rats. Twenty overnight fasted Zucker rats were used in a 2x2 factorial design (5% per group). After-60 min steinar received each RGL to 300 mg/kg or vehicle (Veh) p.o., at-90 min animals received either RGL 5 mg/kg or Veh p.o., and at-60 min all animals received 2 g/kg glucose p.o. Tail-tip sampling for glucose measurements was performed at-90, -30, 0 (immediately prior to glucose dosage), 30, 60 and 120 min. The area under the glucose curve between 0 and 120 min (AUC0-120) were calculated for both baseline and with a two-way analysis of variance. The interaction term was used to test for synergy. Data are presented as mean±SEM. As demonstrated in the table, the threshold dose of RGL had no effect on either parameter when given alone, but a clear effect when combined with MFT dosage. This was confirmed by a significant main effect for glucose levels (GLU) among RGL, showing that RGL and MFT have greater than additive or synergistic effects on glucose tolerance in the male Zucker rat.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GTT (mmol/L)</th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
<th>AUC0-120 (mmol/L)*min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veh + Veh</td>
<td>8.1 ± 0.2</td>
<td>0.6 ±</td>
<td>0.9 ±</td>
<td>8.4 ±</td>
<td>49.2 ±</td>
<td>120.2 ±</td>
</tr>
<tr>
<td>RGL 5 mg/kg + Veh</td>
<td>7.9 ± 0.2</td>
<td>0.7 ±</td>
<td>1.0 ±</td>
<td>7.5 ±</td>
<td>34.7 ±</td>
<td>97.4 ±</td>
</tr>
</tbody>
</table>

* Statistical significance (p<0.05), showing that RGL and MFT have greater than additive or synergistic effects on glucose tolerance in the male Zucker rat.