Single-Blind, Placebo-Controlled, Dose-Ranging Trial of Oral HDV-Insulin in Patients With Type 2 Diabetes Mellitus

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Abstract

The addition of one instead of 2SC insulin to one type 2 diabetes treatment in patients with suboptimal glycemic control due to resistance against normal insulin and represents a significant advance. The dose-response of postprandial glycemia to add-on a mean one-hexadecylated vesicle-insulin (HDV-I) was evaluated using a 2 meal model. 127 adult type 2 diabetes patients, aged 56-67 years, with HbA1c 6.5-7.9%, BMI of 27.6-36.3 kg/m2 on oral antidiabetic therapy with suboptimal glycemic control were enrolled and received treatment in a single-blind, placebo-controlled, dose-escalating trial. Each dosing day was preceded by overnight euglycemic low-dose insulin infusion stopped 1 hour prior to dosing. Each patient received their ongoing oral antidiabetic therapy plus add-on single doses of HDV-I capsules each day, 30 min before breakfast (Time 0 min) lunch and dinner as follows: Day 1 – placebo capsules; Day 2 – 0.05 U/kg; Day 3 – 0.1 U/kg; Day 4 – 0.2 U/kg; Day 5 – 0.4 U/kg. Treatment was performed according to a prespecified schedule from Time 0 min before breakfast dosing to 4.5 hours after the dinner dose (Time 0 min). Postprandial blood glucose (PGC) AUC and incremental AUC were determined for each dose of HDV-I treatment and compared with placebo. Safety was assessed by adverse events and clinical laboratory tests.

Subjects and Methods

This was a single-blind, placebo-controlled, dose-ranging trial of HDV-I in patients with type 2 diabetes mellitus. Included were 67 adult patients with a current diabetes duration of type 2 diabetes mellitus, aged 18–65 years, currently managed with oral antidiabetic drugs (OAD) for at least 3 months, with BMI of 28 kg/m2, glucose intolerance levels (HbA1c 6-12%) ± ±(± or < 12%), hemoglobin levels of < 12% and a feeling blood glucose (FBG) level of < 120 mg/dl. Preparatory Period: Following Screening for the study, each eligible type 2 diabetes patient arrived at the metabolic ward (study center) the evening before the Treatment Period. The subjects were admitted to the metabolic ward and placed on an overnight regular insulin dose so that the morning FBG was approximately 100 mg/dl. The intraindividual insulin was withdrawn one hour before beginning the Treatment Period. The subjects were maintained on their usual oral antidiabetic therapy during the fall day. Treatment Period: During the Treatment Period (one day per dosing group), all patients were treated with placebo capsules on Day 1, oral HDV-I on Day 2 (0.05 U/kg), oral HDV-I on Day 3 (0.1 U/kg), oral HDV-I on Day 4 (0.2 U/kg) and oral HDV-I on Day 5 (0.4 U/kg). Each morning, the subjects were taken off the insulin drip and administered the treatment 1 hour later at each individual’s daily dose based on the body weight in kg and then given all OAD’s carbamylated in the morning. Blood glucose AUC was performed according to a prespecified schedule from Time 0 min before breakfast dosing to 4.5 hours after the dinner dose (Time 0 min). Postprandial blood glucose (PGC) AUC and incremental AUC were determined for each dose of HDV-I treatment and compared with placebo. Safety was assessed by adverse events and clinical laboratory tests.

Background

Hexadecylated vesicle-insulin (HDV-I) on HDV-I (hypothesis: subcutaneous single - SC) and orally administered forms, is an investigational liposomal insulin drug delivery system (Diason Pharmaceuticals, Conshohocken, PA). It is designed to provide insulin in a manner that more closely mimics the normal physiological delivery of insulin in patients with type 1 or type 2 diabetes mellitus. Based on the results of studies conducted in various animal models of diabetes, and in Phase 1 clinical trials in patients with diabetes which have demonstrated significantly improved glycemic control during on oral and insulin tolerance test (OGTT) and diabetic meals, HDV-I is expected to improve enhanced blood glucose control with a lower risk of hypoglycemic episodes at much lower doses compared to conventional insulin therapy. This study was designed to characterize the dose-response of postprandial blood glucose to oral HDV-I and thereby establish a minimum effective dose in patients with type 2 diabetes mellitus.

OBJECTIVES

• To determine the dose-response of postprandial plasma glucose to escalating doses [increased daily] of oral HDV-I given as single doses before breakfast, lunch and dinner, in addition to the diabetes medication patient’s oral antidiabetic therapy.

• To compare the daily glycemic profile of oral HDV-I over the treatment days.

• Secondary objectives were to evaluate the safety, tolerability, and efficacy of the last materials.

Results

All 4 HDV-I doses statistically significantly lowered mean and incremental mean blood glucose AUC compared to placebo, with the 0.10 U/kg dose effect at the 0.05 U/kg dose to a maximum at the 0.4 U/kg dose. The 0.05 U/kg dose was the minimum effective dose of oral HDV-I in the dosage range studied. Postprandial blood glucose (PGC) AUC and incremental AUC were determined for each dose of HDV-I treatment and compared with placebo. Safety was assessed by adverse events and clinical laboratory tests.

Table 2. Adverse Events By Subjects, Study Day of Occurrence and Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Study Day</th>
<th>Treatment</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right forearm IV infiltration</td>
<td>Day 5</td>
<td>Oral HDV-I 0.4 U/kg</td>
<td>1</td>
</tr>
<tr>
<td>Right forearm IV site</td>
<td>Day 5</td>
<td>Oral HDV-I 0.4 U/kg</td>
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</tbody>
</table>

Figure 1. Mean SEM Blood Glucose AUC Values By Treatment and Dose. Asterisks indicate significant differences (*** = p < 0.001; ** = p < 0.01) in mean incremental blood glucose AUC versus the corresponding value for the Placebo + OAD treatment. AUC = area under the plasma glucose concentration-time curve. OAD = oral antidiabetic drug.

Figure 2. Mean SEM Incremental Glucose AUC Values By Treatment and Dose. Asterisks indicate significant differences (** = p < 0.01 and * = p < 0.05, in each case) of mean incremental glucose AUC versus the corresponding value for the Placebo + OAD treatment. AUC = area under the plasma glucose concentration-time curve. OAD = oral antidiabetic drug.

Conclusions

• Add-on single doses of oral HDV-I 0.05 to 0.4 U/kg to oral antidiabetic therapy significantly lowered postprandial blood glucose AUC and incremental glucose AUC compared to placebo in type 2 diabetes mellitus patients.

• The peak effect of oral HDV-I in lowering postprandial blood glucose occurred at 0.1 U/kg with significant but lesser magnitude of effect at 0.2 U/kg followed by 0.4 U/kg.

• The minimum effective dose of oral HDV-I in the dosage range studied was 0.05 U/kg.

• Oral HDV-I in the dosage range 0.05 to 0.4 U/kg was generally safe and well tolerated.

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