417-P

A Two-Week Randomized Active Comparator Study of Two HDV-Insulin Routes (SC and Oral) and SC Human Insulin in Patients With Type 1 Diabetes Mellitus

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Abstract

We evaluated the antihyperglycemic efficacy and safety of a novel SC and oral hepatic-directed vesicle insulin (HDV-I) formulations in comparison to SC regular human insulin (HI = Humulin-R) in a multicenter (3 sites), randomized, double-blind (SC HDV-I & SC HI) and open-label (oral HDV-I) study in adult type 1 diabetes patients on basal glargine therapy over a 14-day period. Patients (n=30), aged 40±11 years, with HbA_{1c} 7.9±1.5%, and BMI 26.2±3.5 kg/m^2, were titrated to stable doses of insulin glargine BID plus 3 pre-meal HI injections and HI prior to snacks over a 14-day baseline stabilization period. Patients were then randomized to receive either SC HI 0.07 U/kg (n=11) or SC HDV-I 0.07 U/kg (n=11) or oral HDV-I 0.1 U/kg (n=8) 15 min before breakfast, lunch and dinner if they had 3 consecutive days of FPG levels <120 mg/dl and 1-hour PPG levels <170 mg/dl. Patients measured/recorded daily FBG before breakfast, daily 2-hour PPG following lunch and dinner, a 7-point blood glucose test on Days 1, 4, 7 and 11, and adverse/hypoglycemic events in a patient diary.

Variable (Mean±SD Change from Baseline)	Oral HDV-I [A] (mg/dl) (n=8)	SC HDV-I [B] (mg/dl) (n=11)	SC HI [C] (mg/dl) (n=11)	p-Value		
				A vs. C	B vs. C	A vs. B
Mean Daily 7-point Blood Glucose	-24 ± 78	-16 ± 38	+26 ± 23	0.074	0.014	NS
FBG	-1 ± 99	-29 ± 42	+35 ± 101	NS	NS	NS
Mean Postprandial Blood Glucose	-42 ± 109	-43 ± 65	-14 ± 60	NS	NS	NS

Oral HDV-I and SC HDV-I significantly reduced (p<0.05), while SC HI increased (p=0.087) the overall mean daily 7-point blood glucose at endpoint. Only the mean change from baseline by SC HDV-I was significantly different compared to SC HI; the mean reduction by oral HDV-I approached (p=0.074) but did not achieve statistical significance, probably due to the small sample size. There were mean reductions from baseline in FBG and PPG by oral and SC HDV-I treatments that were not significantly different from the mean changes by SC HI. All 3 treatments were well tolerated and two hypoglycemic events (blood glucose <40 mg/dl) were observed in the same patient in the SC HI group. In conclusion, SC HDV-I and Oral HDV-I reduced mean daily 7-point blood glucose, the former significantly, in type 1 diabetes patients compared to SC HI when added-on to basal glargine therapy. SC HI increased blood glucose, however, it is noteworthy that this was a pharmacology study where same SC doses were used without titration.

Background

HDV-I administration by oral and subcutaneous (SC) routes have been shown to be effective and safe in controlling postprandial blood glucose levels in single-dose (SC HDV-I) and 3-dose one day (oral HDV-I) models in patients with type 1 and type 2 diabetes mellitus. The objective of this study was to investigate if these beneficial effects of SC and oral HDV-I in controlling postprandial blood glucose levels could be extended over a 2-week treatment period in patients with type 1 diabetes.

OBJECTIVES

- To compare the relative efficacy and safety of SC HDV-I and oral HDV-I to SC regular human insulin (HI = Humulin-R) in controlling plasma glucose levels in type-1 diabetes mellitus patients on basal glargine therapy during a 14 day trial.

Secondary objectives were:

- To evaluate the effects of SC HDV-I and Oral HDV-I by comparison to Humulin-R on HbA_{1c} levels, fructosamine levels, 7-point glucose test results, frequency of hypoglycemic events, body weight and lipid levels.
- To evaluate the safety and tolerability of SC HDV-I and oral HDV-I.

Subjects & Methods

This was a multicenter (3 sites), randomized, double-blind (for injectable insulin arms only = SC Humulin-R and SC HDV-I) and open-label (for oral HDV-I), active-controlled study that enrolled adult male and female type 1 diabetes mellitus patients (n = 30) aged 18 - 50 years (mean ± SD 40 ± 11 years), with at least a 1 year history of type 1 diabetes which was currently managed with at least 4 daily insulin injections. Also, patients were required to have a glycosylated hemoglobin (HbA_{1c}) of ≥6 to ≤10% (mean ± SD 7.9 ± 1.5%), BMI < 30 kg/m^2 (mean ± SD 26.2 ± 3.5 kg/m^2), C-peptide of <0.6 ng/ml, no clinically significant ECG abnormality, and if female of childbearing potential, must be non-pregnant and must be using a reliable form of contraception.

Baseline Stabilization Period: There was an initial 14-day baseline stabilization period, during which all patients received titrated basal insulin glargine (Lantus™) therapy to an optimal dose (split and given SC twice-daily) plus 3 premeal Humulin-R injections and Humulin-R prior to snacks, daily. At the end of the baseline stabilization period, patients were randomized by a 1:1:1 ratio to receive either SC Humulin-R 0.07 U/kg (n = 11) or SC HDV-I 0.07 U/kg (n = 11) or oral HDV-I 0.1 U/kg (n = 8) if they had 3 consecutive days of fasting blood glucose (FBG) <120 mg/dl and 1-hour postprandial blood glucose (PPG) levels <170 mg/dl. Patients assigned to oral HDV-I treatment had a qualifying oral glucose tolerance test (OGTT) on Day 0 to assure that they respond to oral HDV-I, if not they were assigned to the injection treatments.

Treatment Period: During the 14-day randomized treatment period, treatments were administered 15 min before breakfast, lunch and dinner each day. Patients consumed meals containing no more than 60 g of carbohydrate per meal. During this treatment phase, patients who did not achieve optimal blood glucose control following a meal or snack (defined as a 2-hour PPG level >200 mg/dl had the option to use a small bolus of their assigned injectable insulin – for patients in either SC Humulin-R or SC HDV-I treatment groups. Patients in the oral HDV-I group used Humulin-R (non-study medication vials) and adjusted their short-acting insulin accordingly. During the 14-day randomized treatment period, patients measured and recorded daily FBG before breakfast, daily 2-hour PPG following lunch and dinner, a 7-point blood glucose test on Days 1, 4, 7 and 11, and adverse and hypoglycemic events in a patient diary.

Statistical Methods: Demographic and baseline characteristics were summarized descriptively by treatment group. All blood glucose data are expressed as mean ± SD or Mean ± SEM. Mean blood glucose values were compared between treatment groups using either ANOVA or the Student's t-test. p-values of ≤0.05 were considered statistically significant.

Results

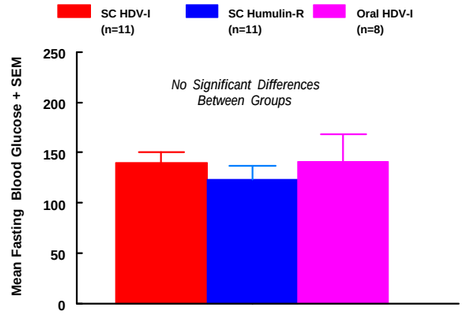

Figure 1. Mean±SEM Fasting Blood Glucose (Pre-Breakfast = Baseline) Values for All 3 Treatment Groups

Results

Figure 1 Comments: Patients in all three treatment groups (SC HDV-I, SC Humulin-R, and oral HDV-I) had similar mean FBG values at the pre-breakfast time point (baseline) on Day 1 that were not statistically significantly different - confirming effective randomization and a comparable baseline of FBG levels between the groups.

Table 1. Mean±SD Baseline Values and Mean±SD Changes from Baseline to Endpoint (Day 11) in Self-Measured Mean Daily 7-Point, Fasting, and Postprandial Blood Glucose Levels by Treatment in Patients With Type 1 Diabetes Mellitus

Treatment Group	Day 0/1 Mean±SD	Day 11/14 Mean±SD	Mean±SD Change from Baseline	p-Value	
				Day 1 vs. Day 11	A or B vs. C
Mean±SD Daily 7-Point Blood Glucose (mg/dl)					
Oral HDV-I (A) (n=8)	216 ± 73	192 ± 53	-24 ± 78	0.043	0.074
SC HDV-I [B] (n=11)	147 ± 24	131 ± 29	-16 ± 38	0.043	0.014
SC Humulin-R [C] (n=11)	126 ± 21	152 ± 33	+26 ± 23	0.086	NA
Mean±SD Fasting Blood Glucose (FBG) (mg/dl)					
Oral HDV-I (n=8)	141±78	140±78	-1±99	NS	NS
SC HDV-I (n=11)	140 ± 78	111 ± 48	-29 ± 42	0.015	0.13
SC Humulin-R (n=11)	123 ± 47	158 ± 72	+35 ± 101	0.206	NA
Mean±SD Postprandial Blood Glucose (PPG) (mg/dl)					
Oral HDV-I (n=8)	233 ± 99	187 ± 32	-42 ± 109	0.15	NS
SC HDV-I (n=11)	167 ± 78	144 ± 54	-43 ± 65	0.02	NS
SC Humulin-R (n=11)	151 ± 58	137 ± 57	-14 ± 60	0.38	NA

Comments: At endpoint (Day 11 of treatment), oral HDV-I and SC HDV-I both significantly (p<0.05) reduced the overall mean 7-point blood glucose value while SC Humulin-R insignificantly (p=0.086) increased the overall mean 7-point blood glucose value.

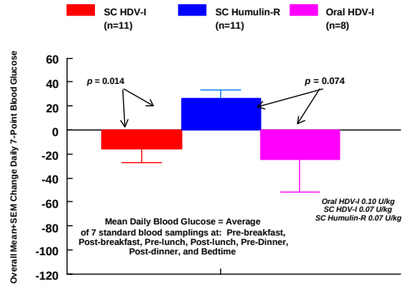

Figure 2. Comparison of the Overall Mean±SEM Daily 7-Point Blood Glucose Values Between the Three Treatment Groups.

Comments: Between the treatments, only the mean reduction in the overall mean 7-point blood glucose value by SC HDV-I treatment was significantly (p=0.014) different from the mean increase observed for SC Humulin-R treatment. The mean reduction by oral HDV-I treatment approached but did not achieve statistical significance (p=0.074) compared to SC Humulin-R, probably due to the small sample size.

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Results

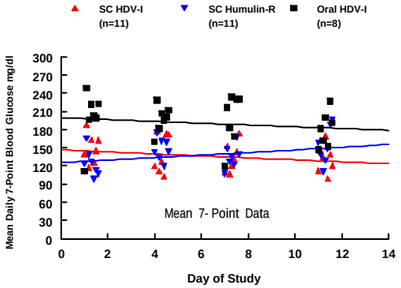

Figure 3. Scatterplot of the Mean Daily 7-Point Blood Glucose Values for subjects in All Treatment Groups on Treatment Days 1, 4, 7 and 11. Each point on the graph is the mean of 11 subjects for the injection groups and 8 subjects for the oral treatment group.

Comments: The mean 7-point blood glucose values improved from Day 1 to Day 11 following oral HDV–I and SC HDV-I treatment as indicated by the identical negative slopes of the best curve fits for the data points. In contrast, SC Humulin-R treatment was followed by a worsening of blood glucose control from Day 1 to Day 11, despite administration of the same dose as SC HDV-I, as indicated by the positive slope of its best curve fit.

Adverse Event (Verbatim Term)	Oral HDV-Insulin (n = 8)	SC HDV-Insulin (n = 11)	SC Humulin R (n = 11)
Patients With At Least 1 AE	3 (37.5%)	5 (45.5%)	5 (45.5%)
Achilles Decreased Bilateral	1 (12.5%)	0 (0.0%)	0 (0.0%)
Food Poisoning	0 (0.0%)	1 (9.1%)	0 (0.0%)
Headache	1 (12.5%)	1 (9.1%)	1 (9.1%)
Muscle Cramping	1 (12.5%)	0 (0.0%)	0 (0.0%)
Sinus Headache	0 (0.0%)	0 (0.0%)	1 (9.1%)
Shortness of Breath	0 (0.0%)	0 (0.0%)	1 (9.1%)
Head Cold	0 (0.0%)	0 (0.0%)	1 (9.1%)
Viral Diarrhoea	0 (0.0%)	1 (9.1%)	0 (0.0%)
Right knee Pain	0 (0.0%)	0 (0.0%)	1 (9.1%)
Back Pain	0 (0.0%)	1 (9.1%)	0 (0.0%)
Relative Hypoglycemia	0 (0.0%)	1 (9.1%)	0 (0.0%)

HDV = Hepatocyte-directed vesicle; SC = Subcutaneous; AE = Adverse event

Conclusions

- SC HDV-I and Oral HDV-I reduced mean daily 7-point blood glucose, the former significantly, in type 1 diabetes patients compared to SC Humulin-R when added-on to basal glargine therapy. In contrast, SC Humulin-R increased blood glucose, however, it is noteworthy that this was a pharmacology study where the same SC doses were used without titration.
- Oral HDV-I 0.1 U/kg treatment was associated with the same rate but lower magnitude of improvement in mean daily 7-point blood glucose levels as the same dose of SC HDV-I as indicated by an identical negative slope of the best curve fit.
- All 3 treatments were generally well tolerated, however, SC Humulin-R treatment was associated with hypoglycemic episodes despite showing an increase in the mean daily 7-point blood glucose level. These results suggests HDV-I treatment may be associated with lower incidence of significant hypoglycemic events and may be safer.

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