COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: A Euglycemic Insulin Clamp Study in Type 1 Diabetic Patients With Oral Insulin (ORAMED

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TITLE: A Euglycemic Insulin Clamp Study in Type 1 Diabetic Patients with Oral Insulin (ORAMED)

BACKGROUND: Insulin therapy is an absolute requirement in type 1 diabetic patients. Multiple injections present a barrier to achieving normal/near-normal glucose control in diabetic patients (1). Therefore, there has been considerable interest in developing alternative routes of insulin administration. ORAMED has developed an oral insulin that, in preliminary studies, has shown promise. In the present study we will perform a pharmacodynamic/pharmacokinetic study to evaluate this novel insulin preparation as a potential therapeutic option in diabetic patients.

EXPERIMENTAL PLAN:

Subjects: 10 type 1 diabetic subjects between the ages of 18 to 70, in good general health by routine history and physical exam; A1c<10.0%; BMI = 18-40 kg/m2; on no meds known to affect glucose metabolism other than insulin; hematocrit ≥ 34 vol%; LFTs < 3 x ULN; plasma creatinine < 1.8 mg/dl.

Study Design: Each subject will be studied on three occasions with an interval of 3 days to 4 weeks between each study. During each study subjects will receive: (i) two 8 mg ORAMED capsule containing insulin; (ii) three 8 mg ORAMED capsules containing insulin; (iii) one 16 mg ORAMED capsule containing insulin. If the fasting plasma glucose is >200mg/dl on the procedure day, the procedure will be rescheduled.

Prior to each study subjects will refrain from eating (except water) after 10 PM and report to the Clinical Research Center at approximately 7 AM. A catheter will be placed in an antecubital vein and a prime (40 uCi x FPG/100) – continuous (0.4 uCi/min) infusion of tritiated (3-^{3}H-glucose) glucose will be started and continued until the end of the study. Plasma glucose

will be monitored and if necessary during the 1st hour of tracer equilibration, a small amount of IV regular insulin will be administered to obtain a fasting plasma glucose of 100-130mg/dl. The total amount of administered regular insulin will be <10 units. After a 3-hour tracer equilibration, subjects will ingest the ORAMED capsule containing insulin and a variable infusion of 20% glucose will be started to maintain the plasma glucose concentration between 100-120 mg/dl. Plasma samples for glucose, insulin, glucagon, and free fatty acid (FFA) concentrations and tritiated glucose radioactivity will be obtained every 5-15 minutes for 4 hours following the ingestion of the ORAMED capsule containing insulin.

Calculations: Following an overnight fast, steady state conditions prevail and the basal rate of glucose appearance (Ra) equals the rate of glucose disappearance (Rd) and is calculated as the tritiated glucose infusion rate (DPPM/min) divided by the tritiated glucose specific activity (DPM/min). Under postabsorptive conditions, Ra primarily reflects hepatic glucose production (2). Following the ingestion of oral insulin, non-steady state conditions prevail and Ra and Rd are calculated using Steele's equation (3). Endogenous (primarily reflects liver) glucose production (EGP) is calculated by subtracting the exogenous glucose infusion rate from the tracer-derived Ra. Rd reflects glucose uptake by all tissues in the body, but primarily reflects skeletal muscle (4).

Sample Size: The present study represents a pilot study to gain information about the absorption of oral insulin and its effect on hepatic and peripheral (skeletal muscle) glucose metabolism. This information will be used to determine whether the ORAMED oral insulin preparation represents a viable option to treat diabetic subjects, to gain information about the dose response effect of ORAMED insulin on glucose metabolism, and to provide quantitative

data about the effect of oral insulin on hepatic and peripheral (muscle) glucose metabolism. Therefore, we conservatively have set the sample size at 10.

REFERENCES

1. Polonsky WH, Fisher L, Guzman S, Villa-Caballero L, Edelman SV: Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. Diabetes Care 2005;28:2543-2545
2. DeFronzo RA, Ferrannini E, Simonson DC: Fasting hyperglycemia in non-insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. Metabolism 1989;38:387-395
3. Steele R: Influences of glucose loading and of injected insulin on hepatic glucose output. Ann N Y Acad Sci 1959;82:420-430

ORAL INSULIN CLAMP

TIME (min)	GLUCOSE (0.5 ml)		INSULIN (2.5 ml)	GLUCAGON (2.5 ml)	FFA (2 ml)	3-^{3}H-glucose (2.5 ml)
-180	Start 3-^{3}H-gucose					
-30	x		x	x	x	x
-20	x					x
-10	x		x	x	x	x
-5	x					x
0	x	Oral insulin	x	x	x	x
15	q 5 min		x			x
30			x	x	x	
45			x			x
60			x	x	x	x
75			x			x
90			x	x	x	x
105			x			x
120			x	x	x	x
135			x			x
150			x	x	x	x
165			x			x
180			x	x	x	x
195			x			x
210			x	x	x	x
220			x			x
230			x			x
235			x			x
240			x	x	x	x
Number	52		21	11	11	23
Volume	26		50.5	27.5	27.5	57.5

TOTAL – 189 ml