Oral Insulin: Type I Diabetes (T1DM) Patient Response Upon Preprandial Administration

[1]Roy Eldor, M.D.; [2]Ehud Arbit, M.D.; [3]Yanitsa Miteva; [3]Rudiger Freier, Ph.D., [2]Miriam Kidron, Ph.D.
[1] Hadassah Medical Center, Diabetes Unit, Jerusalem, Israel; [2] Oramed Pharmaceuticals, Jerusalem, Israel; [3] Swiss Caps A/G, Kirchberg, Switzerland

INTRODUCTION

Oral insulin (ORMD-0801) formulated with Oramed Pharmaceutical's proprietary technology has been previously shown to be absorbed and to impart clinically relevant pharmacodynamic effects in both healthy and Type 2 diabetic volunteers. This Phase IIa study describes a first exposure of Type I diabetic (T1DM) patients to Oramed's oral insulin, evaluation of the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug and assessment of the influence of time to food ingestion on ORMD-0801 absorption.

OBJECTIVES

- To evaluate the safety of ORMD-0801 when administered preprandially to T1DM patients.
- To evaluate the PK and PD of ORMD-0801 in T1DM patients.

METHODS

Single-blind, open-label, single-center; 8 T1DM, male subjects (ages 24-41, diabetics for 2-28 years, HgA1C 6.63-8.63%), regularly treated with no-peak insulin. Two capsules of ORMD-0801 (8 mg insulin each) were orally administered to fasting subjects. A standard 400 kcal meal was served at 10, 45 or 90 min thereafter. Blood samples were routinely collected over the 6-hr post-ORMD-0801 administration to monitor insulin levels. In parallel, at each sampling time, mean glucose levels were calculated from the readings of two different glucometers. A minimum 72-hr washout period was required between treatment sessions.

RESULTS: SAFETY

No serious adverse events were recorded throughout the study. In 1/24 sessions, the subject used injectable insulin due to high glucose levels. The data of this session was not included in the analysis.

RESULTS: INSULIN

Significant increases in insulin levels were detected in 61% of the treatment sessions (T_{max} 40-180 min), irrespective of timing of meals. In these cases, C_{max} values were a mean 45.0 ± 23.5% (range 22-91%) above baseline. An additional 26% reached insulin C_{max} at 6-13% above baseline values. Fluctuations in insulin levels were undetectable in only 3/23 sessions. In all cases, insulin levels returned to baseline within 45-300 minutes of peak recordings, demonstrating full clearance from the bloodstream. In addition, the potency of insulin absorption did not demonstrate dependence on caloric intake initiated at different intervals after drug administration.

Correlations between insulin and postprandial glucose profiles were weighed by coplotting the two monitored parameters for each treatment session (Figure 1). In most cases, classic ORMD-0801 uptake and peaking mirrored tight control of postprandial glucose levels. Even slight increases in plasma insulin concentrations proved sufficient in regulating glucose levels (Figure 1, meal: t-10 min).

RESULTS: GLUCOSE

Plasma glucose levels rose after meal ingestion but were effectively kept in check in all sessions, regardless of the time lapse between ORMD-0801 administration and mealtime. C_{max} was reached at an approximate 100-min lag from start of meal (Table 1, range: 60-150 min), which in 17/23 cases returned to basal levels before the end of the monitoring session. Failure to resume normal glucose levels after caloric intake was often paralleled with undetectable insulin absorption or low or fluctuating absorption patterns.

Table 1. Summary of average glucose responses of eight T1DM patients

Treatment session	Blood sample (t*)	Glucose (mg%)	Blood sample (t*)	Glucose (mg%)	Blood sample (t*)	Glucose (mg%)
10min[&]	20	118	90	215	360	132
45min	40	136	165	244	360	192
90min	90	120	225	200	360	181

***: t=0=administration of ORMD-0801 capsules, [&]: means derived from n=7 subjects**

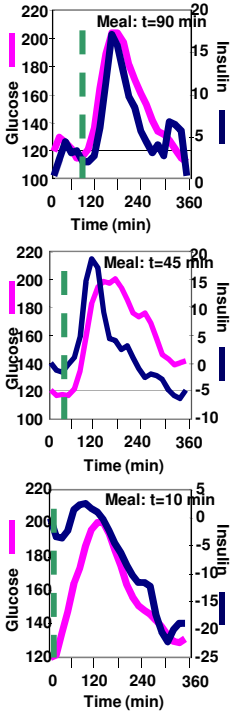

Figure 1. Insulin versus post-prandial glucose levels in T1MD patients pretreated with ORMD-0801: Moving averages of insulin (mU/ml) and glucose (mg%) levels of subject #5 were co-plotted to illustrate the temporal relationship between the insulin peak and glucose response. Values were normalized to 120 mg% glucose and 0 mU/ml insulin at baseline.

RESULTS: RATE OF GLUCODYNAMIC CHANGES

As the expected rise of plasma glucose in fasting T1DM patients is 45.1 ± 9.7 mg/dL·hr-1 upon withdrawal of insulin (Clement et al, 2002, Diabetes Technol Ther 4(4):459), a calculation of the effect of ORMD-0801 on the rate of glucodynamic changes was made. Patients receiving a meal 90 min post-drug administration demonstrated declining glucose concentrations during the 0-90 min post-drug interval (Table 2). In two cases, a glucodynamic rise at a rate of 5.5-11 mg/dL·hr-1 was observed, namely, 4-8-fold lower than that expected in fasting, insulin-deprived T1DM patients. Only Subject #1 demonstrated rising glucose levels similar to those reported for fasting T1DM patients. However, in this single case, ORMD-0801 effectively regulated glucose concentrations even after food intake, as seen by the measured glucose which leveled off within the monitoring session. These data further demonstrate both ORMD-0801 uptake and bioactivity through its effective prevention of the expected rise of glucose levels in fasting T1DM individuals.

Table 2. Glucodynamic rates in pre-prandial period post-ORMD-0801 administration

Subject	Rate in glucose chan (mg/dl·hr^{-1})	Time of insulin pea (min)
1	43.7	150
2	-0.7	60
3	-15.5	45, 225
4	10.9	165
5	-6.1	165
6	-28.7	165
7	-18.4	75
8	5.5	-

Glucodynamic rates were calculated for the t=0-90 interval.

CONCLUSIONS

- ORMD-0801 is safe for use in T1DM patients.
- ORMD-0801 is cleared within 300 min.
- ORMD-0801 is biologically active upon oral, preprandial administration.
- ORMD-0801 prevents the expected rise of glucose levels in fasting T1DM individuals upon insulin withdrawal.

Oramed's technology supports preprandial drug administration without compromising bioactivity.

Acknowledgments: The authors thank Dr. Yehudit Posen for her technical assistance.

For more information please contact: office@oramed.com or www.oramed.com