Oral insulin capsules toward management of Type 1 diabetes mellitus

oramed
Pharmaceuticals Inc
www.oramed.com

GTC Global Technology Community

DIABETES SUMMIT 2013
APRIL 29-30, 2013 • BOSTON, MA

[1]R. Eldor, [2]E. Arbit, and [2]M. Kidron
[1]Hadassah Medical Center, Diabetes Unit and Endocrinology Services, Jerusalem, Israel
[2]Oramed Pharmaceuticals, Jerusalem, Israel

INTRODUCTION

Orally administered insulin has been speculated to provide improved glycemic control, while offering the benefit of hepatic first-pass insulin metabolism, reduced systemic exposure and ease-of-use. Oral insulin (ORMD-0801), formulated with Oramed Pharmaceuticals' proprietary technology, has been previously shown to impart clinically relevant pharmacodynamic effects in both healthy and Type 2 diabetic volunteers. The studies presented here, describe a first exposure of patients with Type 1 diabetes (T1DM) to preprandially administered ORMD-0801 and of unstable T1DM patients to preprandially administered ORMD-0801 delivered over a 10-day period in conjunction with their anti-diabetes treatment regimen.

OBJECTIVES

- To evaluate the safety of ORMD-0801 when preprandially administered to T1DM patients.
- To assess the pharmacokinetics and pharmacodynamics of ORMD-0801 in T1DM patients
- To monitor the incidence of glucose swings in unstable T1DM patients

METHODS

Single-blind, single-center; 8 T1DM, male subjects (ages 24-41, diabetics for 2-28 years, HbA1c (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. A minimum 72-hr washout period was required between treatment sessions.

RESULTS

Significant increases in insulin levels were detected in 61% of the treatment sessions (T_{max} 40-180 min), with a mean C_{max} of 45.0±23.5% (range 22-91%) above baseline. An additional 26% reached insulin C_{max} at 6-13% above baseline values. 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 the timing of caloric intake. 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. Glucose C_{max} was reached at an approximate 100-min lag from start of meal (range: 60-150 min), which in 17/23 cases returned to basal levels before the end of the monitoring session (Table 1). Correlations between insulin and postprandial glucose profiles were weighed by coplotting the two monitored parameters for each treatment session (Figure 1). In most cases, even slight increases in plasma insulin concentrations proved sufficient in regulating glucose levels (Figure 1, meal: t-10 min).

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. Representative insulin versus post-prandial glucose levels following preprandial administration of 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.

METHODS

Open-label, single-center, home-based; 8 T1DM, subjects (ages 27-50 years, diabetics for 10-16 years, HbA1c (7.56-11.04%), regularly treated multiple daily insulin analog injections or subcutaneous insulin. Patients were monitored using a continuous glucose monitoring (CGM) device for a period of 15 days. Baseline patient blood glucose behavior was monitored over the initial 5-day period. In the ensuing 10-day treatment period, patients were asked to eat and continue diabetes treatment as usual and to self-administer, one ORMD-0801 capsule (8 mg insulin) three times daily, 45 min before main meals.

RESULTS

CGM data sufficient for analysis were collected from 6/8 subjects. Blood glucose recordings were more frequently below 70 mg/dL during the treatment phase, when compared to the pretreatment phase (1.99 ±0.88% versus 0.45 ±0.2%, respectively; p=0.06). In parallel, the frequency of glucose readings >200 mg/dL was 24.4% lower upon addition of ORMD-0801 to the treatment regimen (p=0.026). ORMD-0801 treatment led to a 16.6% decrease in glucose area under the curve (AUC) values, with the largest reductions (21.2%) measured between 5-7 PM (Figure 2).

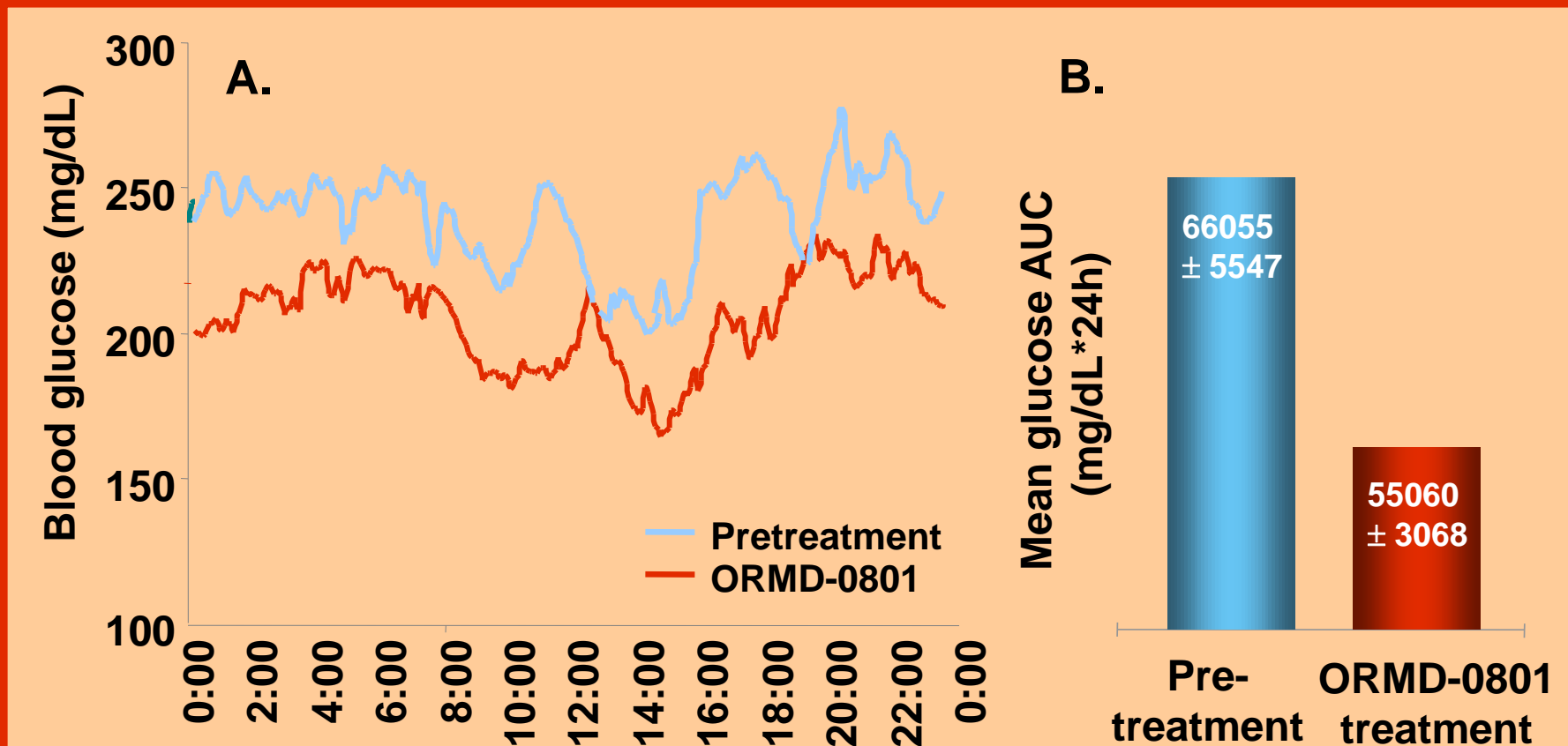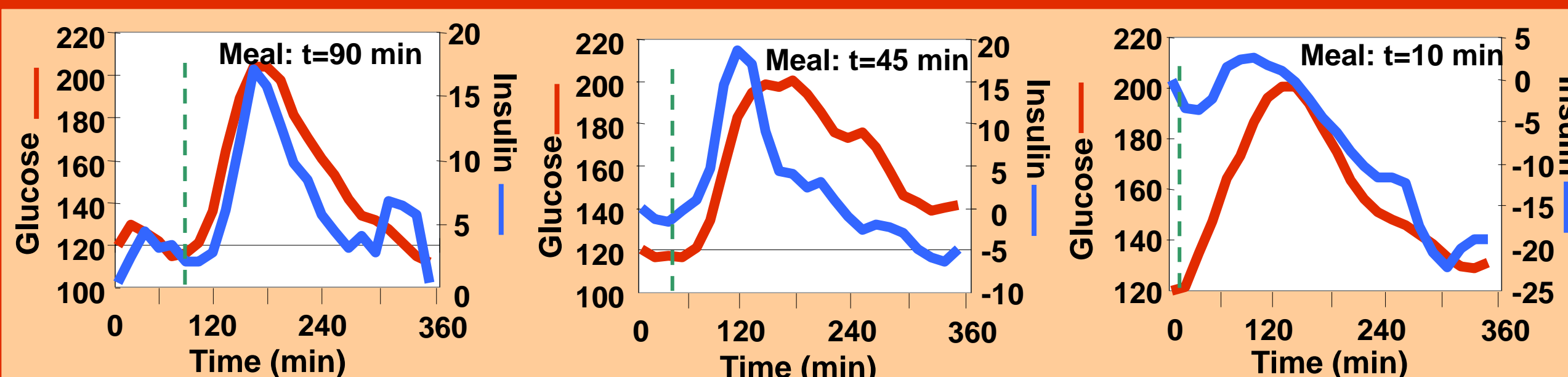**No adverse events or incidents of hypo-glycemia were reported in either study.**

Figure 2. Mean glucose concentrations before and during ORMD-0801 oral insulin support therapy A. Mean blood glucose levels of six Type I diabetic subjects, during the pretreatment vs. ORMD-0801-treatment phases. B. Mean daily glucose AUC (±SD) of the pretreatment and ORMD-0801-treatment phases.

CONCLUSIONS

ORMD-0801 imparts a prominent stabilizing effect on blood glucose concentrations among uncontrolled T1DM patients and blunts glucose excursions when delivered to T1DM patients before meals. Future studies will be required to measure the full hypoglycemic capacity of this new drug and to assess translation of this therapy into reduced levels of HbA1c and diabetes-related complications.