Oral insulin capsules: Clinical Highlights

Miriam Kidron PhD, Roy Eldor M.D. and Ehud Arbit M.D.
Oramed Pharmaceuticals, Jerusalem, Israel

www.oramed.com

INTRODUCTION

Apart from its indisputable convenience, orally administered insulin is projected to provide therapeutic advantages rooted in its direct delivery to the portal vein. By mimicking the physiological path taken by pancreatic insulin, oral insulin is expected to have a pronounced effect on the hepatic role in carbohydrate and lipid metabolism, hepatic inflammation and insulin resistance, while avoiding hyperinsulinemia and minimizing the risk of hypoglycemia. While the physiological advantages of oral-portal insulin remain to a large extent theoretical, evidence for these salutary effects is emerging from early clinical studies. Some of the evidence suggestive of the physiological advantages of oral–portal insulin is presented.

GLYCEMIC CONTROL

BACKGROUND Abnormal morning fasting blood glucose (FBG) is believed to be the result of unrestrained hepatic glucose output in the postabsorptive state. Impaired suppression of hepatic glucose production by insulin is the consequence of hepatic insulin resistance, which can be overcome by a relatively small increase in portal insulin directly delivered by way of an oral insulin formulation.

DESIGN Double-blind, randomized, placebo-controlled, single-center; 30 adult T2DM patients, inadequately controlled with diet and exercise and/or metformin. After a 5-day outpatient placebo run-in, patients were outfitted with a blinded continuous glucose monitor (CGM) and received a single, bedtime placebo dose on day 1, followed by a placebo or ORMD-0801 (460 IU) bedtime treatment in an inpatient setting every day for 7 days. Plasma glucose levels were measured for 5-hours postdosing.

RESULTS No hypoglycemic events, severe adverse events or abnormal laboratory findings were reported throughout the study. Mean nighttime (10PM-6AM) and daytime (6AM-10PM) glucose readings were consistently lower among ORMD-0801-treated versus placebo-treated patients, as were their fasting glucose (5-7AM) concentrations (Figure 1 and Table 1). Fasting CGM data demonstrated a mean reduction of -30.24 mg/dL between the last two days of active drug versus placebo treatment (Table 1).

Figure 1. Mean differences in nighttime glucose levels between day 8 and day 1 (baseline) Mean postdosing blood glucose levels of 10 T2DM subjects.

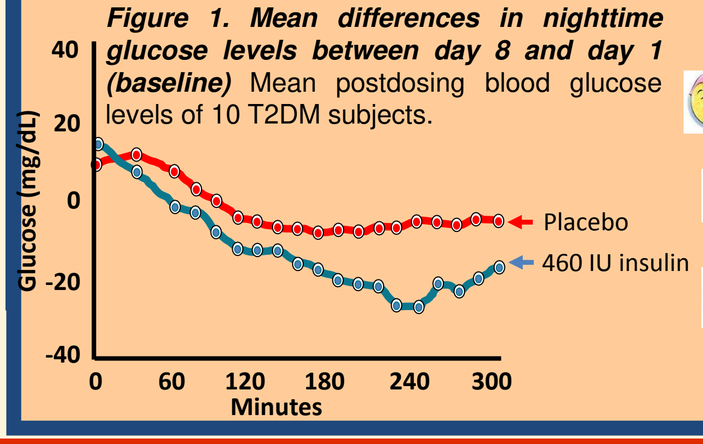


Table 1. Mean glucose concentrations (CGM)

Nighttime Mean (SD) CGM Glucose – mg/dL	Placebo N=10	ORMD-0801 460IU N=10	Difference (ORMD-0801 - Placebo)
Last 2 days of data	167.95 (64.172)	135.64 (39.400)	-32.31
All 7 days	165.85 (60.760)	139.73 (38.861)	-26.12
Daytime Mean (SD) CGM Glucose – mg/dL	**Placebo N=10**	**ORMD-0801 460IU N=10**	**Difference (ORMD-0801 - Placebo)**
Last 2 days of data	176.06 (63.698)	153.23 (40.160)	-22.83
All 7 days	175.99 (61.115)	152.55 (36.986)	-23.44
Fasted Mean (SD) CGM Glucose – mg/dL	**Placebo N=10**	**ORMD-0801 460IU N=10**	**Difference (ORMD-0801 - Placebo)**
Last 2 days of data	156.26 (58.622)	126.02 (27.264)	-30.24
All 7 days	154.37 (57.993)	129.27 (27.426)	-25.10

GLYCEMIC VARIABILITY

BACKGROUND The unpredictable behavior of uncontrolled type 1 diabetes often involves frequent swings in blood glucose levels which are often recalcitrant even to intensified insulin regimens. Increased frequency and magnitude of glycemic variability plays a role in the activation of oxidative stress and overproduction of mitochondrial superoxide, leading to vascular damage and to increased risk for the development of long-term diabetes complications.

DESIGN Open-label, single-center; 8 T1DM subjects (HbA1c (7.56- 11.04%)),regularly treated with insulin analog injections or subcutaneous insulin. Baseline blood glucose behavior was monitored over 5-day days, with a CGM. In the ensuing 10-day period, patients were monoitored with a CGM and 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 (1.99 ±0.88%)., when compared to the pretreatment phase (0.45 ±0.2%) 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 values, with the largest reductions measured between 5-7 PM (Figure 2).

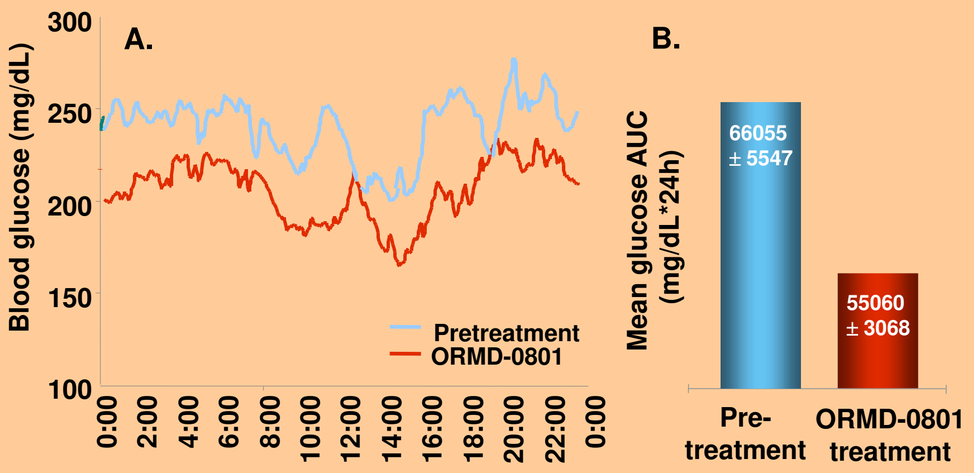


Figure 2. Mean glucose concentrations before and during ORMD-0801 oral insulin support therapy **A**. Mean blood glucose levels of six Type I diabetic subjects, during the pretreatment vs. ORMD-0801-treatment phases. **B.** Mean daily glucose AUC (±SD) of the pretreatment and ORMD-0801-treatment phases.

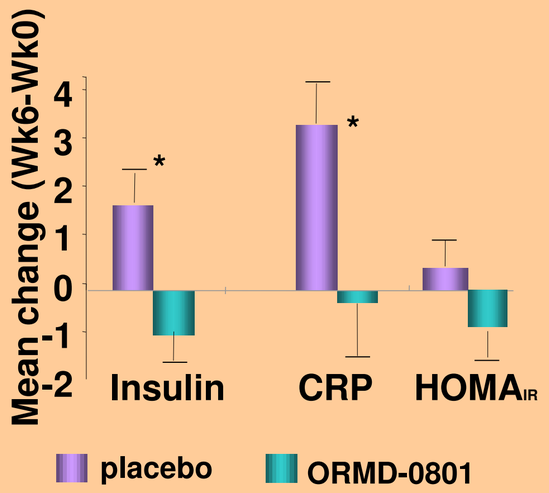
HEPATIC INSULIN RESISTANCE and CRP

BACKGROUND Insulin resistance (IR) underlies the development of T2DM and is also implicated in obesity, atherogenesis, metabolic syndrome, hypertension and inflammation. In parallel, increased levels of C-reactive protein (CRP), a marker of inflammation, have been associated with increased risk for cardiovascular disease (CVD) in T2DM patients. Some researchers have even suggested that CRP can act as a predictor of T2DM. Studies have suggested that chronic subclinical inflammation may be part of the insulin resistance syndrome.

DESIGN Multi-site, placebo-controlled, randomized, double-Blind; 21 T2DM patients; daily insulin treatment (8mg/capsule, 2 capsules/day/bedtime), six weeks; 8 patients received placebo. Blood samples were drawn from fasting subjects at the start and at the end of the study.

RESULTS ORMD-0801 induced significant decreases in morning plasma insulin levels, in contrast to the increase observed in the placebo-treated group (Figure 3, p=0.031). CRP levels dropped by a mean -0.22 mg/L in insulin-treated patients, versus a mean 3.05 mg/L rise measured among placebo-treated patients (Figure 3, p=0.042). The homeostatic model assessment index ($HOMA_{IR}$) showed a clear trend of decrease among ORMD-0801-treated patients in contrast to the placebo group (p=0.07).

Figure 3. Serum insulin and CRP responses to 6-week, bedtime ORMD-0801 dosing



CONCLUSIONS

- ORMD-0801 positively impacts FBG levels in T2DM patients.
- ORMD-0801 effectively improves glycemia in unstable T1DM patients.
- ORMD-0801 reduces $HOMA_{IR}$ and may impact chronic inflammatory states.