Pharmacokinetics (PK) and Pharmacodynamics (PD) of Oral Insulin in Healthy Subjects

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Summary

Oramed's orally delivered insulin can provide non-invasively a more physiological approach to regulate glucose levels in diabetic patients. The results of this study in healthy volunteers demonstrate reduction in plasma glucose levels and c-peptide.

Introduction

Novel non-parenteral routes of insulin administration are being investigated for their clinical relevance. Oramed is developing an oral dosage form of insulin based on its proprietary drug delivery technology, which facilitates the absorption of peptides and proteins across biological membranes. The objective of this study in healthy volunteers was to determine the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of four new formulations of oral insulin (OI). The formulations consisted of one capsule containing the 8 mg of insulin and four different concentration of Oramed's enhancing agents.

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Experimental Methods

Eight healthy male volunteers (mean age 25 years, BMI 20.1-17.7 kg/m^2) participated in this 4-period, cross-over study. During each visit, separated by a 72 to 96 hours washout period, and after an overnight fast, subjects were administered an oral insulin capsule containing 8 mg of insulin combined with varying doses of Oramed's enhancing agents (formulations).

The pharamcokinetic profile of each insulin formulation and its metabolic effects on glucose, insulin and c-peptide were assessed over a five hour period.

Results and Discussion

This Pk Pd study of four oral insulin formulations demonstrated that Oramed's oral insulin administered in one capsule is absorbed enterally and results in significant glucose reduction (7% - 37%), decrease in c-peptide levels (13%-87%), and increase in insulin. The onset of action of oral insulin is delayed due to the specific enteric coated formulation and the effect is sustained for approximately 300 minutes. The most apparent effects observed were on c-peptide and glucose with a lesser effect on the surge of plasma insulin. C-peptide may conceivably be a more accurate surrogate of insulin absorption because it is secreted from the beta cell in equimolar concentration with insulin, but is not extracted by the liver. In contrast insulin secreted into the portal circulation or in the case of oral insulin administration is absorbed into the portal vein undergoes a large and variable hepatic extraction (40–80%) before dilution into the systemic insulin pool.

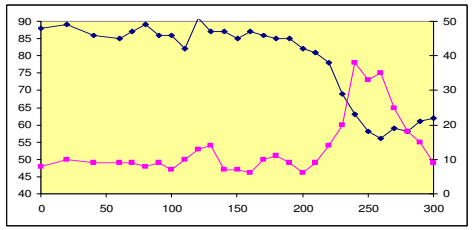

Figure 1. Case illustration - insulin (pink) rise and corresponding glucose response (blue).

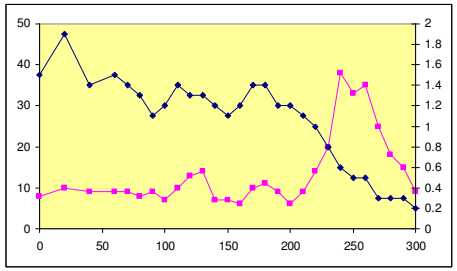

Figure 2. Same case as above - insulin rise (pink) and corresponding decrease in c-peptide.

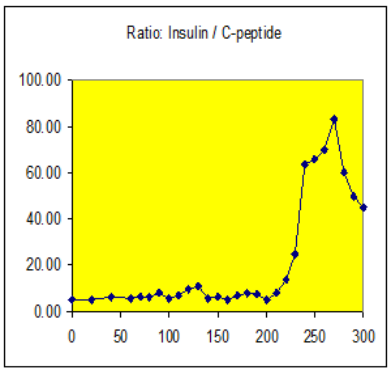

Figure 3. Ratio Insulin / C -peptide for illustrated case.

Acknowledgments

Authors would like to thank Tara Horn for her assistance.

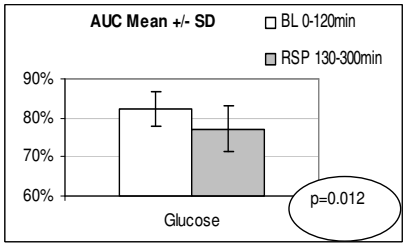

Figure 4. Mean AUC in glucose reduction in all 8 volunteers as a function of time.

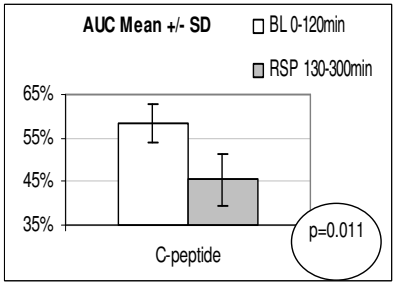

Figure 5. Mean absolute c-peptide reduction in all 8 volunteers as function of time.

Conclusions

The results of this study in healthy volunteers were positive and showed that insulin administered by Oramed's capsules;
A) Is absorbed and is biologically active.
B) It exhibits unique Pk and PD effects characterized by the delayed onset of action and a prolonged metabolic effect as compared with other oral or inhaled formulations currently under study. These encouraging results justify further clinical studies to assess the clinical potential of this formulation.
Conceivably, the potential clinical utility of the current prototypic formulation maybe in: playing a role in IGT and early stage T2DM where it will serves to supplement endogenous insulin, and thus reduce the burden of "overdrive" on islet cells, as suggested by the observed consistent reduction in c-peptide in this study.