

Effective Intajejunal Wall Delivery of Recombinant Human insulin via a Self-Deployed Ingestible Capsule in Anesthetized Swine: A Pharmacokinetic and Pharmacodynamic Study

Mir Hashim, Radhika Korupolu, Baber Syed, Kyle Horlen, Padma Karamchedu , Simret Beraki, Rodolphe Ruffy, Arvinder Dhalla, Mir Imran

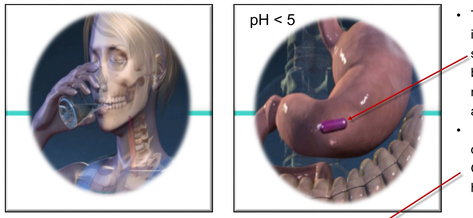
InCube Laboratories / Rani Therapeutics, San Jose, CA

INTRODUCTION AND STUDY RATIONALE

Oral delivery of biotherapeutic agents is challenging due to rapid digestion in the GI tract. Parenteral drug delivery is painful, cumbersome and compromises patient compliance. Rani Therapeutics has developed an oral capsule (OC) capable of injecting drugs in solid form into the jejunal wall. Disguised as a capsule, the OC transforms itself into an auto-injector upon dissolution in intestinal fluid and delivers its payload (in the form of a dissolvable needle containing solid drug) into the intestinal wall. The injection is painless as the GI tract is insensate to sharp stimuli. The objective of this study was to compare the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of recombinant human Insulin (RHI) delivered via the OC vs via subcutaneous (SC) injection.

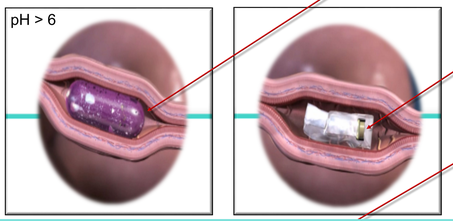
HOW THE ORAL CAPSULE WORKS

1. Enteric-coated Oral Capsule (OC) is Ingested



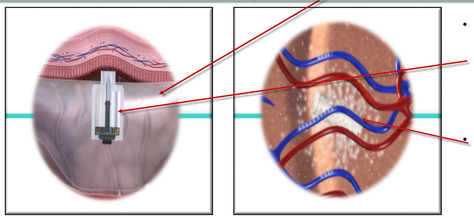
- The OC remains intact in the stomach protected by enteric coating resistant to the acidic gastric pH
- The coating disintegrates when OC encounters a higher intestinal pH

2. Enteric Coating Disintegrates in the Higher pH of the Intestine



- The intestinal fluid dissolves a reaction valve, allowing a chemical reaction to generate CO_2
- The gas inflates a folded balloon which aligns the device for delivery of the payload

3. Drug is Delivered



- Pressure from CO_2 actuates a micro syringe which injects the payload into the intestinal wall
- The needle and drug dissolve, and the drug is rapidly taken up by the microvasculature

MATERIALS AND METHODS

- In this single-dose feasibility study, 17 juvenile anesthetized pigs under a 60-80 mg/dl euglycemic glucose clamp received 20 IU RHI (Imgenex; Cat# IMR-232-250) as follows:
  - OC group (n=8): Intrajejunal insertion of the OC containing 20 IU of insulin in solid form (sealed inside a hollow dissolvable needle) for autonomous delivery to intestinal wall
  - SC group (n=9): Subcutaneous (SC) injection of 20 IU of solid RHI, dissolved in sterile water for injection
- In both study groups, blood samples were collected at 10-min intervals, over 7 hours after RHI administration
- Blood glucose concentrations were recorded using a handheld glucometer
- Serum Insulin concentrations were determined using a sensitive and selective ELISA for Human insulin (Alpha Diagnostics International)
- Data are presented as Means ± SEM

RESULTS

Figure 1. PK/PD of Human Insulin in OC Group

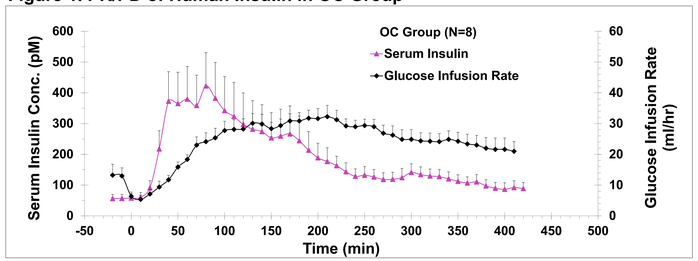


Figure 2. PK/PD of Human Insulin in SC Group

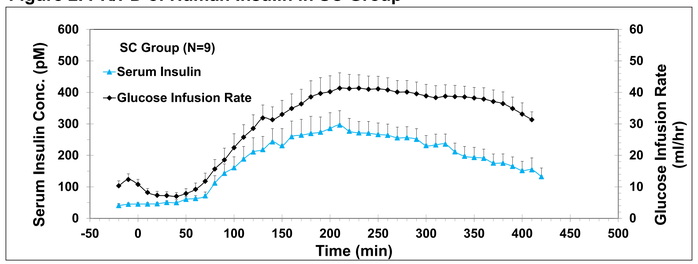


Figure 3. PK/PD of Human Insulin in SC Vs OC Group

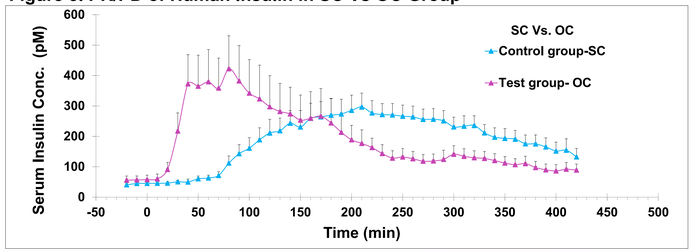


Figure 4. C_{max} for Serum Insulin

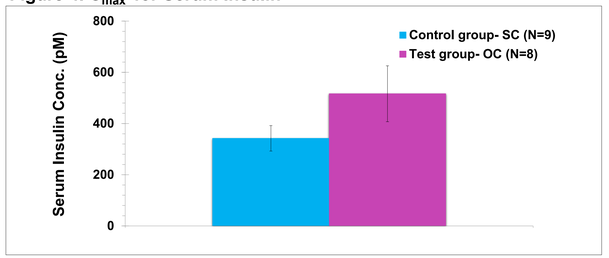


Figure 5. T_{max} for Serum Insulin

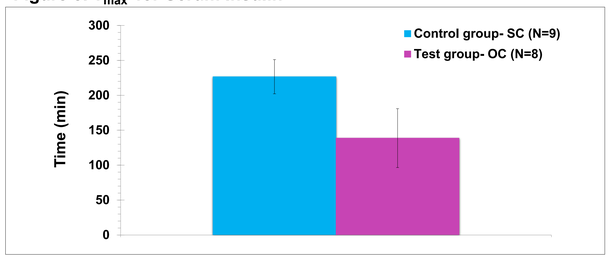
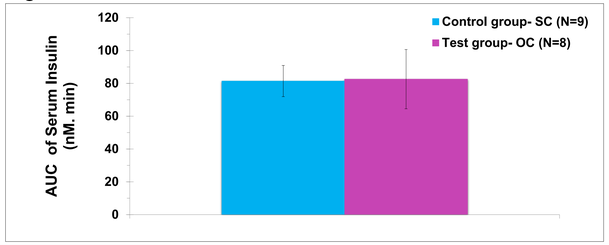


Figure 6. AUC for Serum Insulin



ANIMALS AND TEST ARTICLES

Study Group	Weight (kg)	RHI (IU)
OC Group (N=8)	17.0 ± 0.4	19.6 ± 0.3
SC Group (N=9)	17.4 ± 1.2	19.6 ± 0.3

PHARMACOKINETIC DATA

Group	T_{max} (hr.)	C_{max} (ng/mL)	AUC	
			Serum Insulin (nM.min)	Glucose Infusion (g/min²)
OC Group (N=8)	139 ± 42	517 ± 109	83 ± 18	85 ± 4
SC Group (N=9)	227 ± 24	342 ± 50	81 ± 10	106 ± 10

Data are Means ± SEM

SUMMARY

- AUCs for Insulin in the Test and Control Groups were similar
- Mean C_{max} in the Test Group was higher than in the Control Group
- T_{max} in the Test Group was shorter than in the Control Group

DISCUSSION AND CONCLUSION

- Insulin delivered by OC into the jejunal wall yielded PK-PD parameters similar to the subcutaneous route.
- Uptake of Insulin delivery was faster after OC than after SC delivery.
- The PD response confirmed that the dose of solid Insulin contained in the OC, was biologically active
- This study suggests that drugs such as basal insulin, currently administered parenterally, could be successfully delivered into the proximal intestinal wall via this ingestible robotic capsule

Contact

Stephanie McGrory
VP, Business Development
https://www.ranitherapeutics.com
Email: stephanie@ranitherapeutics.com
Phone: (408) 457-3730