

Pharmacokinetics of an Orally Delivered Antibody in Awake Dogs

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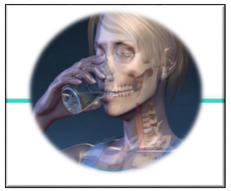


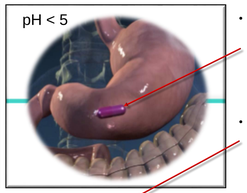
INTRODUCTION AND STUDY RATIONALE

Despite the therapeutic success of biologics, their delivery is problematic, as they can only be injected. As a consequence, patients must endure up to multiple painful injections daily, which may have a profound impact on their quality of life and compliance. The Oral Capsule (OC) is an ingestible device that delivers a payload - a dissolvable needle containing a drug in solid form - into the small intestinal wall. Since the intestine is insensate to sharp pain stimuli, injections into its wall are painless. This allows the delivery of biopharmaceuticals of any molecular weight, regardless of chemical structure or properties, making this OC a versatile delivery platform. We performed this study to evaluate the bioavailability of a large protein, human IgG, delivered via the OC to conscious dogs.

HOW THE ORAL CAPSULE WORKS

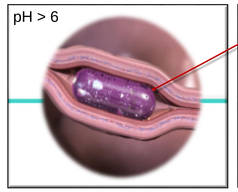
1. Enteric-coated Oral Capsule (OC) is Ingested

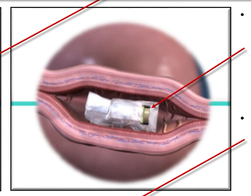




- The OC remains intact in the stomach due to an enteric coating resistant to the acidic gastric pH
- The coating disintegrates when OC encounters higher intestinal pH

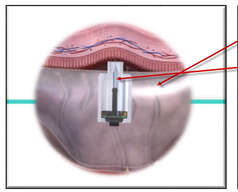
2. Enteric Coating Disintegrates in the Higher pH of the Intestine

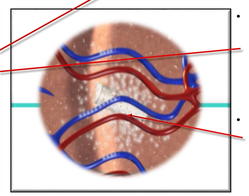




- Intestinal fluid ingress dissolves a reaction valve allowing a chemical reaction to generate CO_2
- The gas inflates a folded balloon which aligns the device for delivery of the payload

3. Drug is Delivered





- Pressure from CO_2 actuates a microsyringe 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

Animals and Test Articles

Study Group:	OC (n = 3)	SC (n = 2)	IV (n = 3)
Weight (kg)	8.3 (8.1, 7.8, 8.9)	8.4 (8.4, 8.4)	8.9 (8.7, 9.6, 8.4)
huIgG Dose (mg)	2.34 (2.33, 2.30, 2.38)	2.37 (2.39, 2.34)	2.40 (2.39, 2.40, 2.39)

Data are presented as Mean (Individual Data)

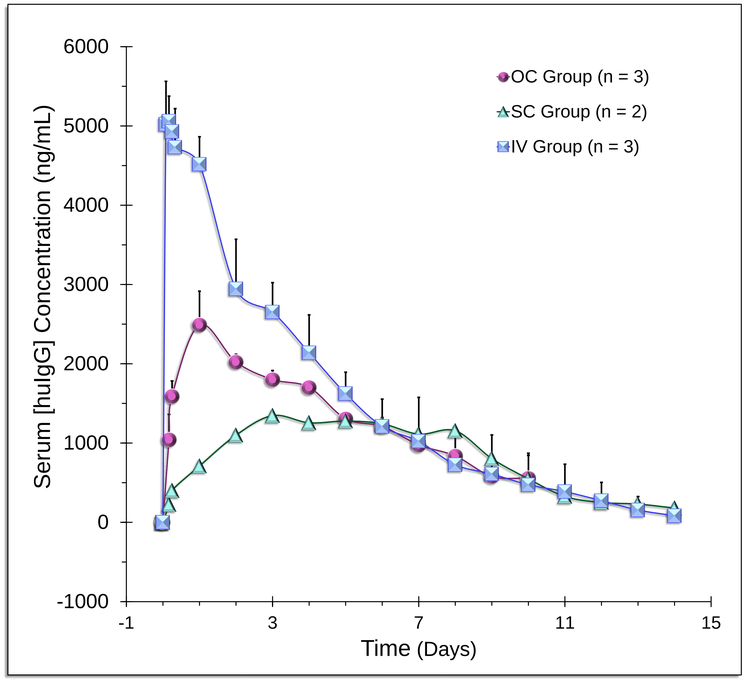
In this single-dose feasibility study, 8 awake, fasting beagles weighing 7.8 - 9.6 kg, received 2.3 - 2.4 mg of human immunoglobulin G (huIgG), divided into 3 groups:

1. OC group (N=3): Oral administration of the OC containing ~2.3 mg of huIgG in solid form (sealed inside a hollow dissolvable needle)
2. Subcutaneous (SC) group (N=2): SC injection of ~2.4 mg of huIgG in a volume of 2 ml
3. Intravenous (IV) group (N=3): IV injection of 2.4 mg of huIgG in a volume of 2 ml

The transit of the OC was tracked through the GI tract via fluoroscopy to confirm its successful passage and deployment in the small intestine. Serial blood samples were collected for up to 14 days to measure the serum concentrations of huIgG via a validated, sensitive and selective ELISA.

RESULTS

Figure 1. Pharmacokinetic (PK) profiles of all groups



Data are presented as Mean for SC group and Mean ± SD for OC and IV groups

Figure 2. Individual PK profiles of OC group animals

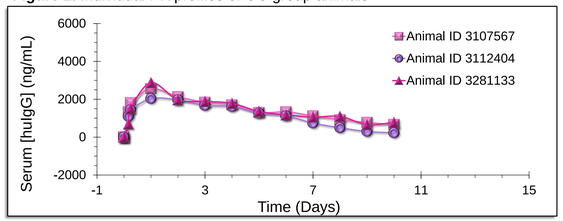


Figure 3. Individual PK profiles of SC group animals

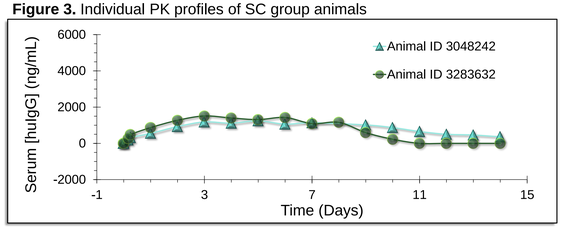
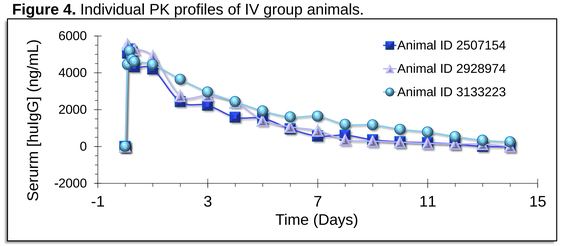


Figure 4. Individual PK profiles of IV group animals.



PHARMACOKINETIC DATA

Study Group:	OC (n = 3)	SC (n = 2)	IV (n = 3)
Bioavailability (%F)	**61** (64, 50, 68)	**51** (53, 49)	--
T_{max} (hr)	24 (24, 24, 24)	96 (72, 120)	3 (4, 2, 4)
C_{max} (ng/mL)	2491 (2558, 2036, 2878)	1378 (1246, 1510)	5339 (5289, 5538, 5191)

Data are presented as Mean (Individual Data)

Summary

- Bioavailability of huIgG was 61% in the OC vs 51% in the SC group.
- The T_{max} was shorter and C_{max} higher in the OC than the SC group.
- Absence of nociceptive or behavioral response by the dogs confirmed the painless delivery of huIgG in the intestinal wall.

DISCUSSION AND CONCLUSION

- This study demonstrated the successful delivery of a large antibody via OC, with absolute bioavailability similar to the SC route.
- The ingestible OC might be an ideal platform for oral delivery of therapeutic peptides and proteins, currently delivered by frequent, painful parenteral injections.
- These pilot observations need to be confirmed in a larger sample.

Contact

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