**Gastrointestinal Motility:**

Motility and Motor Migrating Complex (MMC) Evaluations in Rats, Dogs and Non-Human Primates

Raluca Kubaszky, Simon Authier, Hai-Ming Tang, Alexis Ascah, Mylene Pouliot, Samir Abtout, Kim Bujold, Roy Forster, Eric Troncy and Michael Pugsley

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**TOXICOLOGY SERVICES**

- General toxicology:
  - Rodents
  - Non-rodents: dogs, NHPs and minipigs
- Inhalation
- Dermal
- Ocular
- Immunotoxicology
- Reproductive toxicology including minipigs and NHPs
- Carcinogenicity studies also in rasH2 and p53/-/- mice
- Genetic toxicology: ICH compliant package
- In vitro toxicology: BCOOP, MUSST, OPRA, Photo 3T3, Epison™
- Agrochemical / Chemical / REACH
- Physical chemistry
- Ecotoxicology: wide range of test species

**SAFETY PHARMACOLOGY**

- Integrated Safety Pharmacology in Toxicology Studies
  - CV (JET), BP
  - Respiratory (JET), plethysmography
  - CNS (FOB) and JET-EEG
- Safety pharmacology core battery
- Early safety pharmacology screening
- Rodent and non-rodent LVP telemetry
- Anaesthetized models: ECG, ABP, LVP and QA

**DMPK AND BIOMARKERS**

- Radiolabeled DMPK in all species
- Bioanalysis LC-MS/MS, GC-MS/MS, LC-ICP/MS, ELISA, RIA
- Toxicogenomics, miRNA: Affymetrix™ Accredited service provider, Next Generation Sequencing (Illumina™)
- Immunology: 10-color flow cytometry, Luminex, Mesoscale
- Safety Pharmacology in Toxicology Studies
  - CV (JET), BP
  - Respiratory (JET), plethysmography
  - CNS (FOB) and JET-EEG
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  - CV (JET), BP
  - Respiratory (JET), plethysmography
  - CNS (FOB) and JET-EEG

**SPECIALIZED EXPERTISE**

- Juvenile studies including minipigs
- Fertility studies in rodents and NHPs
- Radiation safety and efficacy studies
- Tissue Cross Reactivity: human and animal tissue banks
- Gene therapy vector biodistribution via qPCR
- ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
- Lead optimization and predictive toxicology services: Leadscreen™
- DmpK AnD BiomArKers
  - radiolabelled DmpK: in all species
  - Bioanalysis LC-MS/MS, GC-MS/MS, LC-ICP/MS, ELISA, RIA
  - Toxicogenomics, miRNA: Affymetrix™ Accredited service provider, Next Generation Sequencing (Illumina™)
- Immunology: 10-color flow cytometry, Luminex, Mesoscale

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Gastrointestinal Motility: Motility and Motor Migrating Complex (MMC) Evaluations in Rats, Dogs and Non-Human Primates

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INTRODUCTION
Drug-induced effects on gastrointestinal motility are observed with a number of approved drugs but a relatively narrow range of non-clinical assays is available in drug development.

MATERIALS AND METHODS
Test System: Five (5) Sprague Dawley rats were fasted overnight and were given 100 mg of food supplemented with a radio-opaque agent and oesophageal transit of the bolus was monitored during normal feeding using fluoroscopy.

Two (2) to eight (8) Cynomolgus NHPs were given semi-liquid radio-opaque meal by oral gavage. Intestinal motility was assessed by gastric emptying time and intestinal transit time using fluoroscopy imaging. NHPs were administered Mosapride (1 mg/kg) or Morphine (2 mg/kg and 10 mg/kg) prior to intestinal motility assessment. Six (6) Beagle Dogs were fasted for at least overnight and were given 100 g of canned food approximately 2 hours before the trial and the 3 other animals remained fasted during the trial. Stainless steel beads (10 x 2mm diameter) were delivered to the stomach using gelatin capsule size #1, followed by 5 ml of reverse osmosis water.

Fluoroscopy imaging was used to monitor the location of the stainless steel beads in the digestive tract to determine the gastric emptying time. Fluoroscopy evaluation was performed just before the administration of the capsules and then approximately every 20 min up to 4 hours after ingestion. The gastric secretion pH was also measured.

Methodology: Fluoroscopic video imaging was used to assess oesophageal and gastric motility in rats using a buccal iodinated radio-opaque meal. In Beagle dogs and cynomolgus monkeys, this methodology was used to monitor gastric and intestinal motor migrating complexes and gastric emptying times using 10x2 mm radio-opaque beads and/or barium solution. In dogs, gastric pH was sequentially measured from fasted animals or after a wet food meal.

RESULTS
In rats, baseline oesophageal transit time was 2.33 ± 0.54 sec and a significant increase was induced by morphine (20 mg/kg). Baseline gastric motor migrating complexes (MMC) in non-human primates during the day was 2.82 ± 0.50 contractions per minute with an average gastric emptying time of a semi-solid meal at 206.3 ± 63.9 min. Mosapride (1 mg/kg) decreased gastric and intestinal emptying time. Morphine (2 mg/kg and 10 mg/kg) decreased the number of gastric contractions per minute in cynomolgus monkeys. In dogs, feeding was shown to significantly increase gastric emptying time compared to the fasted state but also significantly decreased gastric pH for a period of 5 hours.

DISCUSSION
MMC present circadian cycle patterns and controlling for day time is an important factor in functional evaluations. Large animals presented individual MMC patterns and comparison of drug-treated sessions with a time-matched control period from the same animal yielded optimal sensitivity. In large animals, a cross-over study design is preferable whenever possible.

CONCLUSION
Fluoroscopy monitoring of a semi-opaque meal or stainless steel beads was used in rodents and large animals to evaluate oesophageal, gastric and intestinal transit and emptying times. Pharmacological effects were identified in all segments. Group size when conducting GI motility assessments needs to be proportional to the high intrinsic variability of these functional measures.