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

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ABSTRACT
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. Fluoroscopic video imaging was used to assess oesophageal and gastric motility in rats using a buccal iodixanol 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. In rats, baseline oesophageal transit time was 2.23 ± 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.

RESULTS

Figure 1: Effect of Morphine on Oesophageal Transit Time in Rats

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 3 received 100g of canned food approximately 2 hours before the trial and the 3 other animals remained food deprived 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.

DISCUSSION AND CONCLUSION
Fluoroscopy monitoring of a semi-opaque meal or stainless steal 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.

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