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Research paper

Exploring the link between gastric motility and intragastric drug distribution in man

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ABSTRACT

In drug development, the stomach is often considered to be a simple, one-compartmental organ, a waiting room for transfer of an orally administered dosage form to the duodenum. However, factors such as gastric acidity and hydrodynamics in the gastric environment may influence drug disposition. Although a link between gastrointestinal drug behaviour and gastric motility has often been hypothesized, they have not been simultaneously investigated in humans yet. In this proof-of-concept study, the combination of a well-established intraluminal sampling technique with high-resolution manometric measurements in the gastrointestinal tract was evaluated. This new combination of *in vivo* techniques proved to be feasible from a practical point of view and yielded valuable additional information regarding intraluminal drug behaviour. As a first application, the link between fasted state gastric motility and (in)homogeneous distribution of an orally administered drug in the stomach was investigated in healthy subjects. To this end, drug concentrations were measured in different regions of the stomach after oral administration of a commercially available drug product (Gabbroral®, 250 mg paromomycin) during a specific period of gastric contractile activity. A clear trend towards better mixing of an orally administered drug with gastric contents was observed when dosed in the presence of gastric contractions, resulting in a more homogeneous distribution of the drug throughout the stomach compared to dosing in the absence of gastric contractions.

1. Introduction

After oral administration, most drugs travel along the gastrointestinal tract to eventually be absorbed at the level of the small and/or large intestine. Before reaching these sites of absorption, a drug first has to migrate through several other sites (e.g. oral cavity, oesophagus and stomach). As passage through the mouth and oesophagus occurs rapidly, the stomach is typically the first compartment in which a drug resides for a longer period of time [1–3].

Although several anatomical regions in the stomach have since long been identified [4,5], these are seldom recognized in drug development. When evaluating drugs and formulations, the stomach is often considered to be a simple, one-compartmental organ in which a drug awaits transfer to the duodenum relatively undisturbed. This is illustrated by the fact that most *in vitro* dissolution tools use a single vessel to mimic the gastric environment and only account for the acidity of the stomach, hereby neglecting other gastric physiological factors that potentially affect drug disposition. For instance, hydrodynamics are often introduced in these systems by means of stirring bars, creating fluid flow patterns which are not at all representative for the *in vivo* situation [6,7]. By oversimplifying the dynamic gastric environment regarding motility, processes such as dosage form disintegration, drug - gastric fluid mixing and gastric emptying may be incorrectly simulated in *in vitro* systems.

Gastric motor function is characterized by predominant tonic contractions in the proximal region and peristaltic contractions in the distal region of the stomach [8]. Peristaltic contractions originate in the midcorpus region and migrate towards the pylorus, meanwhile increasing in both amplitude and velocity [9]. During the interdigestive state, periods of contractile quiescence alternate periods of contractile activity in a continuous cycle called the '*Migrating Motor Complex (MMC)*' [10,11]. Generally, this cyclical pattern consists of three phases. The absence of contractions is

Abbreviations: MMC, Migrating Motor Complex; TIM, TNO Intestinal Model; Fmoc-Cl, 9-fluorenylmethoxy-carbonyl chloride; C_{max}, Maximal drug concentration; f_{sim}, average similarity factor; MRI, Magnetic Resonance Imaging.

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characteristic for MMC phase I. Moderate peristaltic contractions (mean: 39.7 ± 14.4 mmHg; n = 40) with irregular frequency mark the beginning of MMC phase II activity. As phase II transitions into phase III activity, the amplitude of these contractions further increases (mean: 88 ± 31.7 mmHg) [12]. MMC phase III can either originate in the stomach or the small intestine. In the stomach, this phase is generally of short duration (2–6 min) and is characterized by a regular contraction frequency (2–3 contractions.min^{-1}) [11,12]. Although marked variation within and between subjects has been observed, mean duration of one MMC cycle is often reported to range between 1.5 and 2 h [12–16].

As the presence, amplitude and frequency of gastric contractions under fasted state conditions fluctuates in a time-dependent manner, an orally administered drug may exhibit variable behaviour (e.g. disintegration, distribution) depending on the time of administration relative to the MMC phase. Although gastrointestinal motility itself has been the subject of extensive research efforts, both in animal species and humans, the direct link between motility and drug disposition can still be considered mainly uncharted territory [9,10,17–19]. In recent years, wireless motility capsule studies have yielded important information regarding biorelevant pressures exerted on non-disintegrating dosage forms and their relation to gastric emptying [20–22]. Furthermore, some work has been performed to visualize tablet erosion in the stomach due to mixing of the dosage form with gastric contents [23]. Efforts have been made to translate the *in vivo* obtained data to *in vitro* predictive tools to be used during drug development, in order to better reflect *in vivo* gastric motility (e.g. dynamic gastric model, TIM-advanced gastric compartment) [24–27]. Nevertheless, a clear need still exists to better understand fundamental drug disposition processes such as dosage form disintegration and drug distribution in relation to gastric motor function. Although the link between drug behaviour and gastric motility has often been hypothesized, it has not been demonstrated *in vivo* so far. To this end, this study assessed the feasibility of combining intraluminal sampling of gastrointestinal fluids after oral drug administration, a well-established approach to elucidate gastrointestinal drug behaviour [28], with simultaneous motility measurements. As a first application of this new combination of *in vivo* techniques, the link between fasted state gastric motility and (in)homogeneous distribution of an orally administered drug in the stomach was investigated in healthy subjects.

2. Materials and methods

2.1. Chemicals

Paromomycin sulfate, glycine and 9-fluorenylmethoxycarbonyl chloride (Fmoc-Cl) were purchased from Sigma-Aldrich (Diegem, Belgium). Boric acid was acquired via Acros Organics (99.5%, for analysis; Geel, Belgium). Chem-Lab (Zedelgem, Belgium) supplied acetic acid, while sodium acetate trihydrate ($NaOAc{\cdot}3H_2O$) was ordered from VWR (Leuven, Belgium). Acetonitrile and methanol were purchased from Fisher Scientific (HPLC grade; Leicestershire, UK) and Acros Organics (HPLC grade; Geel, Belgium), respectively. Purified water for analytical purposes was obtained using a Maxima system (Elga Ltd., High Wycombe Bucks, UK).

2.2. Clinical trials

2.2.1. Clinical trial approval

Clinical trials followed the tenets of the Declaration of Helsinki and were approved by the Federal Agency for Medicines and Health Products (FAMHP; EudraCT reference number 2013-000297-30) and the Medical Ethics Committee of the University Hospitals Leuven (ML9149).

2.2.2. Clinical trial medication

Clinical trial medication, i.e. Gabbroral® (250 mg paromomycin; Pfizer, New York City, NY, USA), was ordered via the hospital pharmacy of the University Hospitals of Leuven (UZ Leuven, Belgium).

2.2.3. Preliminary clinical trial

In a pilot study with healthy human volunteers, gastric fluids were collected from different regions of the stomach, i.e. corpus and antrum, as a function of time at predetermined time-points after oral administration of one tablet of Gabbroral® (250 mg paromomycin) with 240 mL of tap water. Gastric fluids were aspirated using the well-established intraluminal sampling technique [28]. This technique comprises the positioning of double-lumen catheters (Salem Sump™ PVC Gastroduodenal Tube, 14 Ch (4.7 mm) × 108 cm; Covidien, Dublin, Ireland) via nose and/or mouth in a region of interest in the gastrointestinal tract using fluoroscopic guidance. Subsequently, gastrointestinal contents can be aspirated as a function of time providing valuable information regarding intraluminal drug disposition [29–32].

2.2.4. Clinical trial investigating drug distribution

Based on results obtained from the preliminary clinical trial, a cross-over trial was conducted including eight healthy volunteers (6 males, 2 females; age range: 20–26 years old). Candidate subjects were excluded from participation in case of (potential) pregnancy, frequent exposure to ionizing radiation in the previous year, history of gastrointestinal pathology and/or illness at the time of the study. Furthermore, hepatitis B/C- or HIV-infected subjects were not allowed to participate in order to ensure the safety of the personnel conducting the study.

Volunteers were asked to refrain from eating and only consume water 12 h prior to the start of the study in order to ensure fasted state conditions. After providing written informed consent the day of the study, double-lumen catheters were positioned in the corpus and antrum region of the stomach, respectively (*cfr. 2.2.3. Preliminary clinical trial*). Additionally, a high-resolution manometry catheter (diameter 4.2 mm; Acertys, Aartselaar, Belgium) was introduced in the subject's duodenum via passage through the nose and the stomach. This catheter consists of 36 pressure sensors spaced 1 cm apart, providing the possibility of measuring regional pressures in both stomach and duodenum. By connecting the outer end of the catheter to a computer console, specialized computer software (Manoview Analysis™, version 2.0.1, Los Angeles, CA, USA) generates a high-resolution pressure map, facilitating real-time monitoring of pressure events and enabling drug administration during a specific phase of gastric contractions. Based on the generated high-resolution pressure map, quantification of the contraction amplitude is theoretically possible. However, due to limitations in the instrumentation available and as this study aimed to qualitatively assess the link between gastric motility and intragastric drug distribution, quantification was not pursued.

Following conditions were tested on different days with a minimum wash-out period of two days:

- Oral administration of one tablet of Gabbroral® (250 mg paromomycin) with 240 mL of tap water during MMC phase I (i.e. absence of contractions).
- Oral administration of one tablet of Gabbroral® (250 mg paromomycin) with 240 mL of tap water during MMC phase II (i.e. period of gastric contractions).

In both test conditions, gastric fluids were collected from both the corpus and antrum region of the stomach for 3 h at predeter-