M5044

Dynamic Change in pH by Low Buffer Capacity of Gastrointestinal Fluids Along The Human Gastrointestinal Tract: Implications For *In Vivo* Dissolution and Absorption of Ionizable Compounds

Bart Hens[1], Yasuhiro Tsume[1], Marival Bermejo[2], Paulo Paixao[3], Mark J. Koenigsknecht[1], Jason R. Baker[1], William L. Hasler[1], Robert Lionberger[4], Jianghong Fan[4], Joseph Dickens[1], Kerby Shedden[1], Bo Wen[1], Jeffrey Wysocki[1], Raimar Loebenberg[5], Allen Lee[1], Ann Frances[1], Greg Amidon[1], Alex Yu[1], Gail Benninghoff[1], Niloufar Salehi[1], Arjang Talattof[1], Duxin Sun[1], Gordon L. Amidon[1]

[1]University of Michigan, [2]Universidad Miguel Hérnandez, [3]Universidad de Lisboa, [4]U.S. Food & Drug Administration, [5]University of Alberta

Bart HENS, 428 Church Street, Ann Arbor, MI 48109-1065, USA - barthens@umich.edu

2017 AAPS ANNUAL MEETING & EXPOSITION

PURPOSE

In this report, both solution and total concentrations of ibuprofen in the GI tract (stomach, duodenum, proximal and mid jejunum) were determined as a function of time in aspirated GI fluids as well as plasma levels, **after oral administration of an 800 mg tablet of ibuprofen (IR dosage form) to healthy volunteers in fasting and fed state conditions**. In addition to intraluminal concentration-time profiling of ibuprofen, motility pressure recordings were simultaneously monitored via manometry along the GI tract. The measured concentrations of ibuprofen were linked with the existing pH and buffer capacity at the time of aspiration and, in turn, linked with the systemic availability of ibuprofen (plasma C_{max} and T_{max}).

OBJECTIVE

The broad aim of this project was to map the link between the gastrointestinal (GI) and systemic availability of an orally administered ibuprofen tablet (800 mg; RLD) with **the focus on fluctuations in pH, buffer capacity and GI motility along the GI tract for this acidic drug (BCS class 2a; pKa ~4.85).**

METHOD

Two experimental treatment arms were tested **in 25 subjects**: intake of one **IR tablet of ibuprofen** (IBU™ – Ibuprofen Tablets, USP, 800 mg, Dr. Reddy's Laboratories Limited, Shreveport, LA) **in fasted state with water or in fed state conditions simulated by intake of a liquid meal (Pulmocare®, Abbott Nutrition, Lake Forest, IL) prior to drug administration with water**. Of all 25 subjects, 12 individuals performed a second study visit in order to generate intra-subject data .

Upon arrival in the hospital, a **customized aspiration multi-channel catheter** (body length 292 cm; MUI Scientific, Mississauga, Ontario, Canada) was intubated via the mouth and positioned in the mid-jejunum, proximal jejunum, duodenum and stomach. **Each segment contains aspiration and motility channels to aspirate GI fluids and to monitor motility patterns via water-perfused manometry along the GI tract, respectively (Figure 1).** Positioning and guiding of the catheter were verified by fluoroscopy.

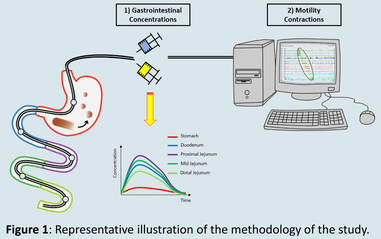

Figure 1: Representative illustration of the methodology of the study.

After checking the positioning of the catheter, volunteers were asked to take place in a hospital bed in a supine position. After performing a baseline motility test of 5 h, the **ibuprofen tablet was administered together with 250 mL of water** containing 25 mg of USP grade phenol red as a non-absorbable marker for monitoring GI fluid changes related to dilution, secretion, and absorption. In case of **fed state conditions, volunteers were asked to drink two cans of Pulmocare® (total volume of 474 mL) prior to dose administration. Volunteers were not obliged to drink the total amount of administered water and/or liquid meal to avoid any feeling of nausea at the start of the study.**

After oral administration of the drug, GI fluids were aspirated at specific predetermined time points for 7 h. The sampling volume was kept as small as possible (< 1 mL per time point). Immediately after aspiration of fluids, pH was measured *ex vivo* by using a pH meter (Mettler-Toledo LLC, Columbus, OH) and the sample preparation of dissolved and total ibuprofen was initiated. Gastric/intestinal fluids residing in the dead space was discarded prior to obtaining intestinal aspirations from each aspiration port at each temporal sample collection time blocks. Blood samples were collected for 24 h to monitor ibuprofen systemically. Samples were stored at -80°C until analysis. All samples were analyzed according to an accurate and precise bioanalytical LC-MS/MS method.

RESULTS

The time to appearance of the maximal concentration of ibuprofen in plasma (plasma T_{max}) is plotted as a function **of the time to appearance of the maximal solution concentration of ibuprofen in the duodenum (duodenal T_{max}; Figure 2A)** and in **the jejunum (jejunal T_{max}; Figure 2B)**.

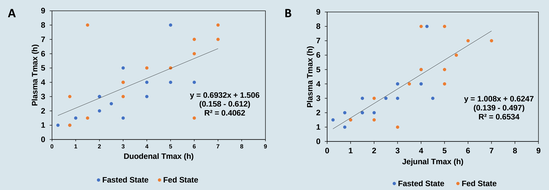

Figure 2: Plot of plasma T_{max} (h) as a function of (A) duodenal T_{max} (h) and as a function of (B) jejunal T_{max} (h). Fasted and fed state results are depicted by the blue and orange dots, respectively. Trendlines for both graphs are given by the black line and expressed by the slope and intercept. The Pearson Coefficient of Determination is expressed as R^2. Standard errors of slope and intercept, respectively, of the linear regression are indicated in parenthesis. Regression for both plots was significant with $p < 0.05$ (Analysis of Variance, ANOVA).

Figures 2A and 2B clearly **illustrate the link between the time of maximal concentrations of ibuprofen in solution (dissolved) appearing in the intestine and in blood.** Ibuprofen is a weak acid (pKa ~4.85) and dissolution of ibuprofen is favored at pH > 4.85, while very low intrinsic solubility concentrations are expected in the stomach in fasting state conditions (pH 1-2). The pH is highly variable and fluctuating along the GI tract, and this will have a major influence on the dissolution of the drug.

Gastric emptying of ibuprofen will likely be slowed in postprandial conditions, which is observed in the delayed plasma T_{max} in fed state conditions compared to fasting state conditions (2.97 h versus 4.88 h, respectively). **This is due to the later maximal concentrations of ibuprofen in the intestinal tract (Figure 3; orange dots). Further, the onset of phase III contractions was delayed in fed state conditions relative to the fasting state**, indicating the slow release of ibuprofen from the stomach to the small intestine. The plasma C_{max} values of all volunteers are depicted as a function of the post-dose appearance of phase III contractions in Figure 3.

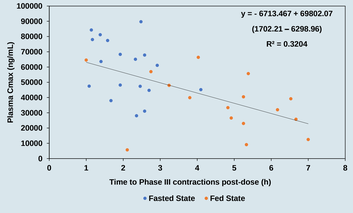

Figure 3: Plot of plasma C_{max} (h) as a function of time of appearance of phase III contractions after oral intake of ibuprofen. Fasted and fed state results are depicted by the blue and orange dots, respectively. The trendline is given by the black line and the Pearson Coefficient of Determination is expressed as R^2. Standard errors of slope and intercept, respectively, of the linear regression are indicated in parenthesis. Regression was significant with $p < 0.05$ (Analysis of Variance, ANOVA).

The pH along the GI tract is a dynamic physiological variable. The wide range of pH that has been measured in all volunteers will significantly affect drug dissolution of ibuprofen along the intestinal tract and thus the amount of drug in solution and available for absorption. **Figure 4 depicts the average profiles of solution concentrations of ibuprofen, total concentrations and pH as a function of time in fasted state duodenum (A) and jejunum (B), as well as in fed state duodenum (C) and jejunum (D).** Moreover, the **average time of appearance of post-dose phase III contractions (2.02 and 4.64 h in fasted and fed state, respectively) is indicated by the green line**, while the a**verage plasma T_{max} (2.98 and 4.88 h in fasted and fed state, respectively) is indicated by the dark blue line**.

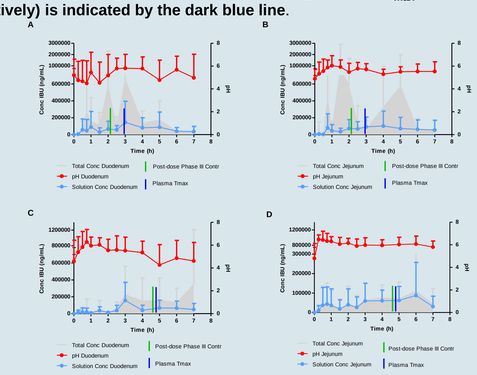

Figure 4: Average solution concentrations of ibuprofen (IBU) (blue line), total concentrations of IBU (gray area) and pH profiles (red line) of all subjects as measured in fasted state duodenum (A), fasted state jejunum (B), fed state duodenum (C) and fed state jejunum (D). The green line indicates the average time when phase III contractions occurred after intake of the tablet. The dark blue line represents the average plasma T_{max}. Data presented as mean + SD.

The **delayed appearance of phase III contractions in fed state conditions were positively linked with a decreased systemic exposure of ibuprofen** (in terms of C_{max}), clearly illustrating the effect of motility on variability in systemic drug exposure. **The changing intestinal pH** is determined by **the buffer capacity of these fluids.** Figure 5 depicts buffer capacity of the aspirated GI fluids as a function of time in fasted (A) and fed (B) state.

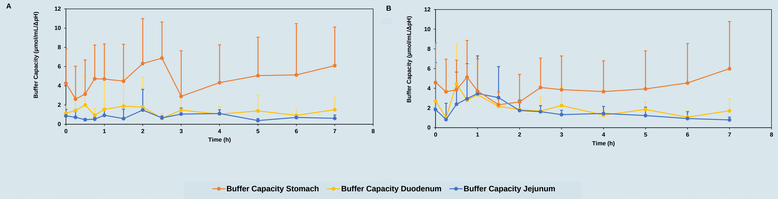

Figure 5: Buffer capacity values of the aspirated fluids in (A) fasting state conditions and (B) fed state conditions as a function of time (h). The yellow line represents buffer capacity data of the aspirated duodenal fluids; the blue line represents buffer capacity data of the aspirated jejunal fluids; the orange line represents buffer capacity data of the aspirated gastric fluids. Data presented as mean + SD.

CONCLUSION

The **dynamic pH and low buffer capacity along the GI tract** have been shown to be a **major determinant of inter- and intra-subject** variability in systemic exposure of ibuprofen **together with the appearance of the phase III contractions (TMMC) post-dose.**

FUNDING & ACKNOWLEDGMENT

This work was supported by **Grant # HHSF223201510157C and # HHSF223201310144C by the U.S. Food and Drug Administration (FDA)**; this report represents the scientific views of the authors and not necessarily that of the FDA.

PHARMACY UNIVERSITY OF MICHIGAN