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Back to Basics: pH-Dependent Drug Interactions with Acid Reducing Agents

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Gastric acid reducing agents (ARAs) such as antacids, proton-pump inhibitors, and histamine 2 receptor agonists are over-the-counter and prescribed medications used to treat a variety of gastric acid disorders (Table 1). Since ARAs can be available with unsupervised medical use, their gastric pH-increasing effect may pose a risk of harmful side effects or lack of efficacy when co-administered with other medications, as gastric pH is a physiological factor that can affect drug solubility and absorption. For instance, when pH rises above the pKa of a drug, the dissolution of a weak-base drug may decrease. pH-dependent drug-drug interactions (DDIs) may therefore result in loss of efficacy for weak-base drugs or increased adverse events for weak-acid drugs. To address the potential impact of such risks during the development of new drug candidates, FDA issued draft guidance in November 2020 entitled Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents [1].

Table 1. Gastric Acid Diseases

Conditions	Description
Aspirin-associated gastroduodenal mucosal injury	Prolonged use of aspirin can cause mucosal injury and induce gastric acid secretion [2].
Dyspepsia	Digestive disorders in which stomach acids or bile can irritate the esophagus lining, typically causing burning sensation (commonly termed heartburn)
Gastroesophageal reflux disease (GERD)	
Nocturnal acid breakthrough	Occurs in patients taking a proton-pump inhibitor yet continue to endure acid reflux and overnight intragastric pH< 4 [3].
Peptic ulcer disease	A sore that develops in the digestive tract and commonly caused by Helicobacter pylori (H. pylori). H. pylori inhibits acid secretion by downregulating hydrogen/potassium adenosine triphosphatase pump (H^+-K^+-ATPase) α-subunits.
Upper gastrointestinal bleeding	Can be a symptoms of other gastric diseases. Intravenous proton-pump inhibitor (PPI) may be administered to suppress stomach acids.
Zollinger-Ellison syndrome	A rare gastrinoma in which excessive levels of gastrin are secreted from a digestive tract tumor.

Drugs with low solubility, also known as Class II (low solubility, high permeability) and Class IV (low solubility, low permeability) according to the biopharmaceutical classification system (BCS) [4], will in particular be at risk for potential pH-dependent DDIs. The significance of the new FDA guidance can be inferred from the fact that ~30% of marketed drugs are BSC Class II compounds such as nonsteroidal anti-inflammatory drug ibuprofen, anti-lipemic agent ezetimibe and folic acid. An additional 10% of marketed drugs are represented by BSC Class IV compounds including for instance the diuretic furosemide and the antifungal agent bifonazole. Furthermore, a recent systematic review by Patel *et al*. identified 230 drugs that were screened for an ARA interaction and found that nearly half demonstrated a clinically meaningful drug interaction, in which 33% were attributed to gastric pH mechanisms [5].

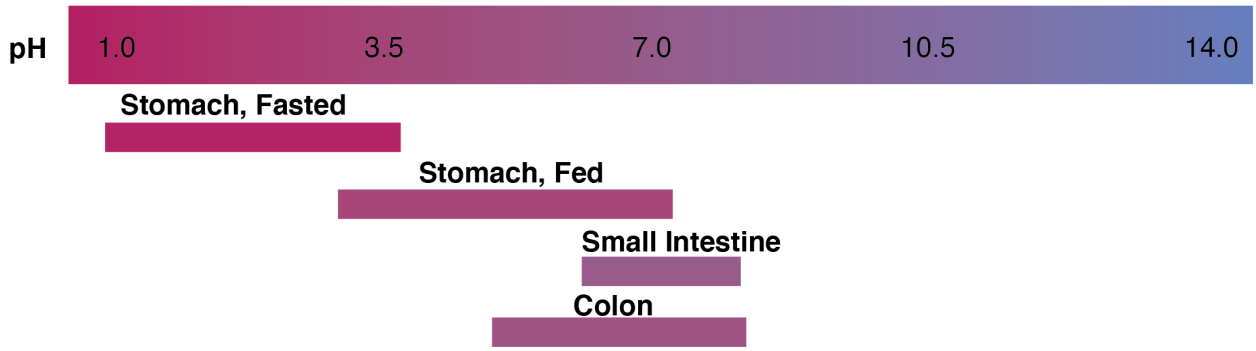
Although not covered by this new FDA Guidance, changes in gastric pH can also result from intake of chelating drugs and food intake. Moreover, infection with H. pylori, a bacteria associated with gastric ulcer disease and a predisposition to gastric cancer, is known to affect gastric pH. Because these factors are often studied/considered in conjunction to or as part of ARA DDI studies, these will also be discussed hereafter.

Brief Review of Gastric Acid Production

The acidic stomach environment serves to kill food-borne bacteria, facilitate food digestion and absorption of minerals [6]. Since overproduction of gastric acid can have harmful effects on the stomach lining, gastric acid secretion is highly regulated by hormonal and central mechanisms as well as local processes in the stomach. Briefly, gastrin, histamine, and acetylcholine promote the secretion of gastric acid by the parietal cells. A proton pump regulates exchange of cytoplasmic H^+ for extracellular K^+, and H^+ released into gastric lumen combines with luminal Cl^- to form HCL (gastric acid). Somatostatin reduces gastric acid secretion by inhibiting the release of gastrin in a feedback loop controlling gastric acid secretion, and pH of the stomach (reviewed in [7]). In this complex system, other gastric acid stimulators include ghrelin, apelin, motilin and glucocorticoids, while GLP-1, PYY, adenosine, prostaglandins, corticosterone releasing factor, neurotensin as well as nitric acid and hydrogen sulfide demonstrate inhibitory effects on gastric acid production [6].

Food can also alter stomach acid pH (Figure 1), increasing pH from 1.0 – 3.5 in the fasted state to 3.0 – 7.0 under fed conditions [5]. As a consequence, food can delay drug bioavailability and decrease PPI exposure by ~50% (reviewed in [8]). Therefore, fasting is typically recommended during a DDI study with proton-pump inhibitors.

Figure 1. pH Ranges of the Stomach, Small Intestine & Colon



Acid Reducing Agents

ARAs suppress gastric acid secretions and/or potentially raise gastric pH above 6.0. There are three types of ARAs with different mechanisms of action, including PPIs, histamine receptor antagonists (H_2 blockers) and antacids.

Proton Pump Inhibitors (PPI) irreversibly bind H^+-K^+-ATPase of gastric parietal cells, reducing acid production for >24 hours. Typically, a minimum of four days of repeat dosing is needed to observe maximal suppressive effect on pH. Common PPIs are omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole.

H_2 Blockers compete for receptor binding with histamine at H_2 receptors in gastric parietal cells resulting in reduced acid secretion. A peak effect of the increase in pH is typically observed after 2 hours of administration and lasts up to 12 hours. Common H_2 blockers are cimetidine, ranitidine, nizatidine, and famotidine. It is important to note that ranitidine is currently not on the market due to impurity issues [9].

Antacids are cationic bases that neutralize gastric acids, suppress gastric emptying and acid secretion. Common antacids are sodium bicarbonate, calcium carbonate, aluminum hydroxide, magnesium hydroxide. All but sodium bicarbonate also have chelating function.

As a consequence of an increase in pH, ARAs can result in a decrease in dissolution and absorption of weak bases and, thus, lead to pH-dependent DDIs. As an example, the bioavailability of atazanavir (a weak base), an HIV medication, is dramatically impacted by ARAs. A 95% reduction in exposure was observed after lansoprazole co-administration [10], thus requiring dosing recommendations in the label to separate intake from H_2 blockers and PPIs [11]. Conversely, ARAs can increase the solubility of weak acids leading to an increased absorption rate or extent, however, in practice the impact of ARAs intake on the exposure to weak-acid drugs is generally modest.

The FDA guidance focuses on immediate-release weak base drugs, and provides limited guidelines for immediate-release weak-acid drugs and modified-release products. Overall, if there is potential for a pH-dependent DDI, a study is recommended or justification for a waiver based on in silico, in vitro and clinical supporting data.

Physicochemical Framework for Immediate-Release Weak-Base Drugs

The guidance provides a helpful framework to assess clinical DDI risk through physiochemical analysis. First, consider if the investigational product (IP) has pH-dependent solubility within a pH range of 1.0-6.8. If so, is the solubility of the clinical dose of the IP in 250 mL at pH 6.0-6.8 less than the dose divided by 250 mL? A positive result signals a likely drug interaction with ARAs and an interaction study is recommended. A negative finding suggests an unlikely interaction. An optional step is to compare dissolution profiles at different media pH conditions. For drugs intended to be taken with food, a comparison of solubility at pH 6-6.8 versus pH 4-5 (high meal effect) and pH 2-3 (light meal effect) is recommended. See FDA guidance for framework details [1].

DDI Study Design Considerations

The recommended population to enroll can be healthy normal volunteers if safe to do so. The sample size should allow reliable estimation of the magnitude and variability of DDI. A crossover design (fixed sequence or randomized) is usually preferred, however, a parallel design is acceptable for investigational drugs with long half-lives. In order to mitigate any carryover effect by the ARA (and especially PPIs), a fixed sequence is most commonly used, with the ARA co-administered in the last study period (Table 2).

Administration of a single dose of the IP under fasting conditions is recommended for most studies, with both IP and ARA administered at the maximum recommended therapeutic dose. These recommendation may vary in the following scenarios:

- Dose regimen: Administration of multiple doses of the IP is recommended if multiple doses of the IP are expected to affect the drug absorption.
- Dose level: for weak-acid IP, a reduction in the dose may be considered if safety concerns due to potential increase is systemic exposure is anticipated.
- Food intake: For IP(s) recommended for administration under fed conditions, food intake should be consistent with procedures for late-phase clinical trials or approved labeling.

Assessment of the effect of ARAs on the IP is recommended through comparison of PK parameters $AUC_{0-\ inf}$ (or AUC_{0-tau} for multiple dose), C_{max}, T_{max}, and if clinically significant C_{min} for the IP, and relevant active metabolites, when co-administered with an ARA versus when the IP is administered alone.

Additional considerations:

- Additional mechanisms which may affect the systemic exposure of the IP, such as metabolizing enzymes, may be affected by the ARA. These effects should be taken into consideration when choosing the ARA. For example, omeprazole is an inhibitor of CYP2C19, and cimetidine inhibits CYP2D6, CYP3A4, MATE1 and MATE2/K.
- The prevalence of H. pylori in the general population is high, ranging from 19-88% depending on geographic area [12]. We recommend to assess H. pylori status using a breath test for potential post-hoc analysis.

Table 2. Common Study Design Considerations for ARA DDI Studies

Factor	Proton Pump Inhibitors	H_2 Blockers	Antacids
Effect on gastric pH	Long lasting	Intermediate lasting	Short lasting
IP administration	Co-administration	Staggered	Co-administration
Example of timing IP administration	IP and PPI co-administered	Famotidine dosing at -12 hours or -10 hours and at -2 hours of IP dosing	IP and antacid co-administered
Example ARA and dose	40 mg QD esomeprazole, 20 mg QD rabeprazole, 30 mg QD lansoprazole	20 mg famotidine	1000 mg calcium carbonate, 2000 mg aluminum hydroxide, 2000 mg magnesium hydroxide
Precautions due to CYP interactions	40 mg omeprazole (CYP2C19 inhibitor)	10 mg/kg BID cimetidine (CYP2D6, CYP3A4, MATE1 and MATE2/K inhibitor)	

Adapted from FDA draft guidance [1].

Reduced Study Design

The concomitant use of PPI represents the worst-case scenario and can guide label recommendations for ARAs as outlined in the FDA framework [1] and Table 3. In addition, results can be extrapolated to the same ARA drug class, but interacting mechanisms besides changes in gastric pH such as CYP or transport interactions should be noted.

Table 3. ARA DDI Label Considerations

DDI Study Findings	Suggested labeling		
	Proton Pump Inhibitors	H_2 Blockers	Antacids
No DDI effect with PPI	No pH-dependent interactions with PPIs, H_2 blockers, or antacids		
Clinically relevant DDI effect with PPI	Avoid use with PPIs	Avoid use with H_2 blockers	Staggered dosing with antacids (eg. 2 hours before or after antacid use)
	Alternative design options: Evaluate lower PPI doses or conduct a DDI study with an H_2 blocker	Alternative design options: Staggered dosing with H_2 blocker (eg. 2 hours before and 10 to 12 hours after dosing of H_2 blockers	Alternative design options: Evaluate shorter staggered dosing (<2 hours) with antacids

Adapted from FDA draft guidance [1].

Super-Size It: Adding a Food Effect Arm

In addition to PPIs, H_2 blockers, and antacids, additional non-medicinal ARAs may be of interest, such as food or acidic beverages (e.g. orange juice, coke). Assessment of DDI of both medicinal and non-medicinal ARAs may be combined in a single study design. As the effect of perpetrators such as food and acidic beverages is relatively short, the assessment can be conducted with the IP alone and IP and fed conditions/ co-administration with acidic beverage as a cross-over design, followed by the ARA co-administration as a fixed sequence.

Conclusion

The recent FDA draft guidance stresses the conceivable effects of ARAs on gastric pH, which may interfere with the dissolution of orally administered drugs if taken concomitantly with ARAs and, hence with their safety and efficacy. For new drugs in development, it is therefore recommended to evaluate the potential for DDIs with ARAs and conduct dedicated clinical trials. Depending on the IP and the Sponsor's preference, different options for DDI study designs are available. In practice, combination studies or innovative designs are often considered to assess a DDI for ARAs together with other conditions with potential impact on gastric pH in a single study.

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