Clinical Pharmacokinetics (2020) 59:447–462
https://doi.org/10.1007/s40262-019-00844-3

REVIEW ARTICLE

A Systematic Review of Gastric Acid-Reducing Agent-Mediated Drug–Drug Interactions with Orally Administered Medications

Divya Patel[1] · Richard Bertz[1] · Song Ren[2] · David W. Boulton[2] · Mats Någård[2]

Published online: 2 December 2019

Abstract

Background and Objective Several review articles have been published discussing gastric acid-related drug–drug interactions (DDIs) mediated by coadministration of antacids, histamine H_2 receptor antagonists, or proton pump inhibitors, but are not sufficiently comprehensive in capturing all documented DDIs with acid-reducing agents (ARAs) and tend to focus on gastric pH-dependent DDIs and/or basic drugs. Subsequently, several new drugs have been approved, and new information is available in the literature. The objective of this systematic review is to comprehensively identify oral medications that have clinically meaningful DDIs, including loss of efficacy or adverse effects, with gastric ARAs, and categorize these medications according to mechanism of interaction.

Methods An indepth search of clinical data in the PDR3D: Reed Tech Navigator™ for Drug Labels, University of Washington Drug–Drug Interaction Database, DailyMed, Drugs@FDA.gov, and UpToDate®/Lexicomp® Drug and Drug Interaction screening tool was conducted from 1 June to 1 August 2018. The PDR3D, University of Washington Drug–Drug Interaction Database, and DailyMed were searched with terms associated with gastric acid and ARAs. Conflicting findings were further investigated using the UpToDate®/Lexicomp® screening tool. Clinical relevance was assessed on whether an intervention was needed, and prescribing information and/or literature supporting the DDI.

Results Through the search strategy, 121 medications were found to clinically meaningfully interact with ARAs. For 38 medications the mechanism of interaction with ARAs was identified as gastric pH dependent, and for 83 medications the interaction was found to be not gastric pH mediated, with mechanisms involving metabolic enzymes, transporters, chelation, and urine alkalization. Additionally, 109 medications were studied and did not have a clinically meaningful interaction with ARAs.

Conclusion This review may provide a resource to healthcare professionals in aiding the care of patients by increasing awareness of interactions with ARAs and may also identify and potentially aid in avoiding clinically relevant DDIs and preventing risk of treatment failure and/or adverse effects. Advances in non-clinical predictions of gastric pH-mediated DDIs may guide the need for a future clinical evaluation.

Key Points

This review provides an evaluation of the effectiveness and safety of currently available medicines when taken with medicines used to control stomach acid.

For medications found to have meaningful interactions, ways of avoiding or reducing the effect of the acid-controlling medication are suggested.

Medicines that are not affected by gastric-acid controllers are also identified so prescribers and patients know they do not have to be concerned about altered effectiveness or safety when using them with gastric acid controllers.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40262-019-00844-3) contains supplementary material, which is available to authorized users.

✉ Mats Någård
mats.nagard@astrazeneca.com

[1] University of Pittsburgh School of Pharmacy, 37 S. New York Rd, Galloway, NJ 08205, USA

[2] Quantitative Clinical Pharmacology, Early Clinical Development, Innovative Medicines (IMed) Biotech Unit, AstraZeneca LP, One MedImmune Way, Gaithersburg, MD 20878, USA

1 Introduction

Gastric acid-reducing agents (ARAs) are commonly used among patients across all fields of medicine and are often recommended to treat conditions related to gastrointestinal disease [1, 2]. Because of the frequent use of ARAs, the potential for drug–drug interactions (DDIs) is an important consideration. The three ARA classes on the market include antacids, histamine H_2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs). These medication classes raise gastric pH through different mechanisms and with different durations of action: antacids are short acting, H2RAs are intermediate acting, and PPIs are long acting [3, 4]. The H2RA and PPI classes each include agents that differ in their interaction potential via cytochrome P450 (CYP) enzymes and active transporters, which could potentially affect the metabolism and/or excretion of other concurrently administered medications [5, 6]. However, each of these classes share the potential to interact through increased gastric pH, which may affect concurrently administered drugs with pH-dependent solubility, pH-dependent stability, or pH-sensitive release from a dosage form by influencing the rate and/or extent of absorption [5].

Most ARAs are available over the counter, which can be potentially problematic in terms of DDIs, especially in patients who are taking many concurrent medications without medical supervision of their ARA use [7, 8]. Polypharmacy, generally referring to the concurrent use of five or more medications, drastically increases the risk of DDIs. To ameliorate the challenge polypharmacy poses, prescribers and pharmacists often conduct comprehensive medication reviews, including non-prescription medications, and then counsel the patient on their medications and warn them of any adverse effects or potential drug interactions and how to mitigate them [7].

A comprehensive review of gastric acid-mediated DDIs using ARAs as the perpetrator might aid in the treatment of patients with polypharmacy and potentially avoid drug interactions that would otherwise affect their care. By further identifying the specific mechanism of interaction, possible mitigation strategies and alternative options can be chosen by the prescriber. This comprehensive review could save time for prescribers and pharmacists who are responsible for the care of many patients by providing a reference to help screen for ARA-mediated DDIs. In addition, this systematic review provides mitigation strategies for ARA-mediated DDIs.

Although several review articles have been published discussing gastric acid-related DDIs mediated by coadministration of antacids [1], H_2RAs [9], or PPIs [2, 10–12], these reviews are not sufficiently comprehensive in capturing all documented DDIs with ARAs and tend to focus on gastric pH-dependent DDIs and/or basic drugs. Subsequently, several new drugs have been approved, and new information is available in the literature. Thus, the objective of this systematic review is to comprehensively identify oral medications with clinically meaningful DDIs, including loss of efficacy or adverse effects with ARAs, and to categorize these medications according to mechanism of interaction.

2 Factors for Drug Disposition

ARAs may act as perpetrators (i.e., drugs that cause or are believed to have an effect on the substrate drug) with substrate medications (i.e., drugs whose systemic exposure may or may not be changed by a perpetrator drug) by affecting their absorption, metabolism, or elimination, and these mechanisms are discussed in this section.

2.1 Absorption

Following oral administration, medications typically are systemically absorbed through the gastrointestinal tract into the bloodstream to allow distribution to the target site(s) of action [13, 14]. The extent and rate of absorption is determined by both the properties of the medication and the gastrointestinal characteristics of the individual patient (e.g., food status, comedications, gastrointestinal disease, etc.). The intrinsic physicochemical properties of the medication are important factors for oral absorption, including stability, solubility, permeability, lipophilicity, particle size, shape and physical form of the active pharmaceutical ingredient, and formulation [15, 16].

To fully understand DDIs mediated by ARAs through increased gastric pH, it is important to review physiologic gastrointestinal pH. The range of pH varies widely in the human digestive tract. In the fasting state, the lower stomach secretes hydrochloric acid until it reaches a pH of 1.0–3.5, and a pH of 3.0–7 when in a fed state. The pH in the small intestine is 6.0–8.0, and in the colon the pH is 5.5–8.0 [14, 17, 18].

2.1.1 Weak Acids and Weak Bases

When gastric pH is raised by ARAs, the solubility of weak acids generally increases [19]. For clinical doses of weakly acidic drugs that are not completely dissolved in gastric fluid at physiologic pH, an increase in gastric pH may lead to an increased dissolution and likewise subsequent absorption rate and/or extent. For clinical doses of weakly basic drugs that are not completely dissolved at physiologic pH, an increase in gastric pH would result in a decrease in dissolution and also subsequent absorption rate and/or extent [19].

Most clinically meaningful DDIs caused by ARAs through this mechanism are with weak bases.

2.1.2 Formulation/Dosage Form Effect

There are many different formulations of oral dosage forms available on the market [20]. These include immediate-release (IR) dosage forms and modified-release (MR) dosage forms.

2.1.2.1 Modified-Release Dosage Forms MR dosage forms, often introduced to reduce dosing frequency [20], include extended-release (ER) and delayed-release (DR) forms. Examples of these ER dosage forms include controlled-release, sustained-release, timed-release, and long-acting forms. These ER dosage forms do not commonly interact with ARAs because of a lack of involvement of a pH component in drug release.

DR dosage forms include enteric-coated products, which pass through the stomach unaltered and are then triggered to release by the higher pH environment of the lower gastrointestinal tract [20]. DR dosage forms protect the drug from gastric fluids, reduce gastric irritation by the drug, and improve drug absorption in the desired location of the gastrointestinal tract. Enteric coatings are beneficial particularly in regard to drugs with chemical or physical instability in acidic conditions. For those medications designed to not release in the stomach, the pH of release can range from 5.0 to 7.0, depending on the intended location in the gut [21]. Notably, ARAs can raise gastric pH above 6.0 [22], which can lead to premature release of drug formulated in a DR dosage form. The implications of this are potential degradation of the drug in gastric fluid, gastric irritation by the drug, and altered absorption rate and/or extent [23]. DR dosage forms are most likely to interact with ARAs because of the inherent pH-related release profile. However, some DR formulations, such as time-based dosage forms, are independent of pH.

2.1.2.2 Immediate-Release Dosage Formulations IR dosage forms dissolve rapidly after oral administration. For these formulations, the acid–base characteristics of the substrate medication are important in determining its solubility and/or its chemical stability in gastric fluid [1]. ARAs have the potential to interact with IR formulations when a substrate medication exhibits pH-dependent solubility or pH-dependent chemical stability.

2.1.3 Chelation

Polyvalent cations in antacid formulations may form an insoluble chelate complex with medications [1]. Such chelates may be poorly absorbed, reducing bioavailability of the substrate medication. Chelation requires a net cation charge of +2 or +3; thus, calcium-, magnesium-, and aluminum-containing antacids are common culprits in regard to chelating effects with substrate medications. Sodium bicarbonate, the only metal ion-containing antacid with a net charge of +1, is not subject to chelation-based DDIs [24].

2.2 Metabolism

2.2.1 Cytochrome P450

CYP is a heme-containing superfamily responsible for the biotransformation of exogenous substances, including ~ 80% of medications [25]. With respect to ARAs, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are the most important from a DDI standpoint. CYP1A2 is predominantly expressed in the liver and is responsible for the metabolism of medications such as clozapine, olanzapine, theophylline, and derivatives thereof [25, 26]. Among the CYP2 enzymes, CYP2C9 is the most abundantly expressed CYP2 enzyme in the liver, accounting for the metabolism of ~ 20% of medications [26]. Because of the polymorphic potential of CYP2C9, variation in the metabolism and disposition of drugs is evident between individuals, which can be problematic for those drugs with a narrow therapeutic index [25, 26]. CYP2C19 is a clinically important enzyme that metabolizes several drugs, including omeprazole, diazepam, and propranolol [25–27]. Many clinically relevant interactions of ARAs with CYP-metabolized drugs occur via CYP2C19 [25]. The enzyme CYP2D6 is responsible for the metabolism of ~ 20% of medications [25, 26]. CYP3A4 is one of the major CYP3A enzymes in humans, which are involved in the metabolism of a wide range of substrate types and are, in fact, responsible for the metabolism of ~ 30 to 50% of medications [25, 26].

H2RAs and PPIs have the potential to act either as inhibitors or inducers of CYP enzymes [5]. When acting as an inhibitor of CYP, concomitant administration of an ARA may result in increased systemic exposure of a drug or decreased conversion of a prodrug to its active form. In fact, inhibition of CYP represents a common cause of DDIs seen in clinical practice [28]. Such inhibition of CYPs by H2RAs and PPIs occurs via reversible competitive inhibition, where the substrate medication and ARA (or inhibitor) both bind to the active site of the enzyme. The degree of inhibition depends on the concentration of the ARA at the active site, and the 'CYP profiles' of both the substrate medication and ARA [2].

In contrast to CYP inhibition, induction of CYP enzymes may occur, resulting in either increased activity of a prodrug or heightened elimination of the drug itself. Inducible enzymes include CYP2A, CYP2B, CYP2C, CYP2E, and CYP3A [29]. Notably, ARA-mediated CYP induction is less commonly seen with respect to clinically meaningful DDIs.

2.3 Elimination

2.3.1 Organic Cation Transporter 2

Organic cation transporters (OCTs) are expressed throughout the body; however, OCT2 is primarily localized in the proximal tubule of the kidney. OCTs work in tandem with efflux transporters to aid in drug excretion [6]. For example, OCTs function to secrete endogenous cations and remove positively charged drugs (e.g., ranitidine) from the body. On the basis of in vitro data, OCT2 can be inhibited by H2RAs, which may lead to decreased renal excretion of substrate medication and increased systemic exposure and potential toxicity [6].

2.3.2 *P*-Glycoprotein

P-Glycoprotein (P-gp), also known as multidrug resistance protein 1, is important for drug transport, aiding in the movement of the medication from the intestinal mucosa back into the gut lumen, thus contributing to first-pass elimination [30]. Intuitively, inhibition of this transporter would mean a medication would be absorbed to a higher degree, potentially leading to adverse effects possibly associated with attainment of toxic plasma concentrations of medications even when given at recommended doses.

2.3.3 Urine Alkalization

Antacids have the potential to increase urinary pH [1]. In a study of healthy men, increases in urine pH of 0.48 and 0.86 U were observed with administration of magnesium hydroxide and aluminum and magnesium hydroxide suspension, respectively, over a 7-day period [31]. Urinary pH can be a major factor for the renal excretion of medications. In alkaline urine, the renal clearance of weakly acidic drug molecules will tend to be increased. In an alkaline environment, weakly acidic drugs are polar (charged), and thus are less likely to pass through membranes for reabsorption into the systemic circulation, and weakly basic drugs will be rendered neutral and remain non-polar (uncharged), allowing them to be more likely to pass through membranes to re-enter the systemic circulation and increase their systemic exposure [32]. Increased urinary pH may lead to either toxic concentrations being reached for weakly basic drug molecules or reduced efficacy for weakly acidic drug molecules.

2.4 Implications

Therapeutic doses of ARAs can raise the gastric pH to > 6.0 [19]. It is important to differentiate the mechanism by which different ARAs work and the degree to which they affect gastric pH. In addition, it is important to identify other possible mechanisms of interaction between ARAs and substrate medications. By understanding such mechanisms, possible mitigation strategies can be investigated. Currently, common mitigation strategies include spacing of the dosing interval, avoidance of interaction, choosing an alternative agent, or monitoring of therapy [1, 2, 9].

3 Types of Gastric Acid-Reducing Agents and their Mechanisms of Interaction

3.1 Antacids

Antacids consist of basic substances coupled with a cation [1]. Antacids directly neutralize gastric acid, providing a quick onset of action and a short duration of acid suppression of ~ 2 h due to gastric emptying and gastric acid secretion. The most commonly available over-the-counter antacids are sodium bicarbonate, calcium carbonate, aluminum hydroxide, and magnesium hydroxide (Table 1). The possible mechanisms underlying DDIs for antacids are discussed in Sects. 3.1.1–3.1.4.

3.1.1 Gastric pH Elevation

Neutralization of gastric fluid by antacids may alter the dissolution, absorption, stability, or release of dosage forms of substrate medications [1]. However, the short duration of gastric pH elevation by antacids allows for the potential mitigation strategy of separation of doses apart in time of the antacid and substrate medication.

3.1.2 Chelation

Sodium bicarbonate is the only antacid containing a metal ion that is not known to chelate with substrate medications (Sect. 2.1.3) [24]. Accordingly, sodium bicarbonate can be used as an alternative antacid therapy over therapies containing magnesium and/or aluminum, metal ions that chelate with substrate medications. Again, separation of doses in time is a possible mitigation strategy to avoid chelation-based drug interactions. In addition, it is possible to switch to an H2RA or PPI to avoid such interactions, obviously as long as there is no new potential interaction.

3.1.3 Gastrointestinal Motility

Magnesium-containing antacids may promote gastric emptying and accelerate the rate of absorption of some drugs

Table 1 Clinically meaningful acid-reducing agent drug interaction potential and metabolic pathways

Drug	Absorption		Metabolism via CYP system						Transport systems		Excretion
	Gastric pH-dependent interaction	Chelation	CYP1A2	CYP2A6	CYP2C9	CYP2C19	CYP2D6	CYP3A4	OCT2[a]	P-gp[a]	Urine alkalization
Antacid											
Sodium bicarbonate	✓										✓
Calcium carbonate	✓	✓									✓
Aluminum hydroxide	✓	✓									✓
Magnesium hydroxide	✓	✓									✓
H2RA											
Cimetidine	✓		x			x	x	x	x		
Ranitidine	✓		s			s	s		x		
Famotidine	✓								x		
Nizatidine	✓										
PPI											
Omeprazole	✓		i	s	s	x, S′	s	s	x		
Esomeprazole	✓					x, S′		s			
Lansoprazole	✓		i		s	s		s	x		
Dexlansoprazole	✓					s		s			
Pantoprazole	✓					S′		s	x		
Rabeprazole	✓					S′		S′			

ARA acid-reducing agent, *CYP* cytochrome P450, *H2RA* histamine H_2 receptor antagonist, *I* inducer, *OCT2* organic cation transporter 2, *P-gp* P-glycoprotein, *PPI* proton pump inhibitor, *s* minor substrate, *S′* major substrate, *x* inhibitor, ✓ elicits pathway

[a]In vitro evidence only for OCT2 and P-gp

[1]. The clinical relevance of this is unclear. Notably, formulations containing magnesium alone are no longer used as antacids essentially because of the adverse effect of diarrhea. Combination products containing both magnesium and aluminum are now more common; aluminum counteracts the increase in gastric emptying observed with magnesium alone.

3.1.4 Alkalization of Urine

Since antacids are basic compounds, they have the potential to alkalize urine, altering the renal excretion of weakly acidic and weakly basic medications [32]. Possible mitigation strategies proposed in the prescribing information include selection of an alternative ARA (H2RA or PPI), monitoring for increased or decreased effects of substrate medication, and possible dose adjustment of the substrate medication. In this case, separation of dosing in time is less likely to be a successful mitigation strategy; however, this has not been well-studied.

3.2 Histamine H_2 Receptor Antagonists

Commonly used H2RAs available over the counter include cimetidine, ranitidine, nizatidine, and famotidine [9, 33, 34]. H2RAs compete reversibly with histamine at H_2 receptors in gastric parietal cells to reduce gastric acid secretion. Potential for DDIs with H2RAs should be considered in the context of their pharmacokinetic profile, which drives the effect on gastric pH, with a peak effect at 2 h and a duration of action of up to 12 h [35]. The possible mechanisms underlying putative DDIs with H2RAs are discussed in Sects. 3.2.1–3.2.3.

3.2.1 Gastric pH Elevation

Various mitigation strategies have been proposed, including avoidance of the H2RA, administering the substrate at least 2 h before the H2RA, dosing the substrate and H2RA simultaneously, and administering the substrate medication 10–12 h after the H2RA [19, 35]. When considering these mitigation strategies, thought must be given to the pharmacokinetics of the substrate medication and extent of the effect of increased gastric pH on the substrate medication.

3.2.2 The Cytochrome P450 Enzyme System

H2RAs have the potential to interact with substrate medications that undergo CYP enzyme metabolism [5]. H2RAs can inhibit CYP enzymes, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Cimetidine, the first approved H2RA, is an inhibitor of multiple CYP enzymes; however, newer H2RAs have less effect on CYP metabolism. For example, ranitidine is not as potent of a CYP inhibitor as cimetidine, and famotidine has a negligible effect on CYP enzymes [5].

Possible mitigation strategies when a clinically meaningful CYP-based interaction is seen with H2RAs include avoidance, monitoring for increased or decreased effects and possible dose adjustment of the substrate medication, or selection of an alternative ARA or substrate medication.

3.2.3 Organic Cation Transporter 2

H2RAs have the potential to inhibit OCT2, which is the most clinically relevant of the OCTs for H2RA-mediated DDIs [6]. Possible mitigation strategies when a clinically meaningful OCT2-based interaction is seen with H2RAs include avoidance, monitoring for increased or decreased effects and possible dose adjustment of the substrate medication, or selection of alternative ARA or substrate medication.

3.3 Proton Pump Inhibitors

Common PPIs include omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole, with many of these being available without a prescription [2, 10–12, 36–38]. PPIs irreversibly bind and inactivate the proton pump (i.e., the hydrogen/potassium adenosine triphosphatase system) at the secretory surface of gastric parietal cells. This results in suppression of gastric acid production for > 24 h, but 4 days of repeated dosing is required to reach maximal effect. Similar efficacy has been shown in acid suppression studies comparing omeprazole, lansoprazole, rabeprazole, and pantoprazole [4]. Esomeprazole has a stronger degree of acid suppression, with a longer period of intragastric pH > 4. However, the gastric pH-dependent interaction is class specific and does not appear to be markedly different among individual PPIs [4, 36]. The multiple possible DDI mechanisms of PPIs are discussed in Sects. 3.3.1–3.3.3.

3.3.1 Gastric pH Elevation

In contrast to other ARAs, the duration of raised gastric pH is sustained over the dose interval for PPIs. Therefore, there are fewer options for mitigation strategies for PPIs compared with antacids and H2RAs. The possible mitigation strategies for gastric pH elevation caused by PPIs include avoidance of the PPI, monitoring for increased or decreased effects of substrate medication, and setting a maximum dose of the PPI.

3.3.2 The Cytochrome P450 Enzyme System

PPIs can affect CYP2C19 and CYP1A2 activity [2, 11, 12, 38]. Omeprazole and esomeprazole reversibly inhibit CYP2C19 to a clinically meaningful degree, whereas other marketed PPIs inhibit CYP2C19 but not to a degree that is clinically relevant [39–41]. Omeprazole has been shown to clinically induce the activity of CYP1A2 in some studies but not others [2]. Possible mitigation strategies for CYP-mediated drug interactions with PPIs include avoidance of the PPI, monitoring for increased or decreased effect with possible dose reduction of substrate medication, or immediate dose reduction of substrate medication upon initiation of the PPI. While separation of dosing in time is sometimes an option for PPIs when a gastric pH–dependent mechanism is suspected, it is not recommended for CYP-only-based interactions.

3.3.3 *P*-Glycoprotein Efflux Transporter

It is unknown if clinically meaningful DDIs with PPIs are mediated through P-gp. One in vitro study concluded that omeprazole, lansoprazole, and pantoprazole are substrates and inhibitors of P-gp, but with only moderate potency [38].

4 Comprehensive Review of Gastric Acid-Reducing Agent-Mediated Drug–Drug Interactions

4.1 Methods

This review is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009-guided systematic review to identify oral medications that were substrates of an interaction with ARAs/perpetrators [42]. To conduct these analyses, four commercially available databases were used.

The initial search strategy was completed using the PDR3D: Reed Tech Navigator™ for Drug Labels, which is a database of prescribing information from a broad range of countries/regions. The 30 terms in Table 2 include generic names of antacids, H2RAs, and PPIs, as well as three common brands of combination antacid products. The first 27 terms listed in Table 2 were each searched in the "clinical pharmacology" and "drug interaction" sections of the prescribing information available through the database using the "OR" function. The last three terms in Table 2 related to dosage forms searched in "all" sections of the prescribing information. The PDR3D database was searched during the period of 1 June 2018–1 August 2018.

The University of Washington Drug–Drug Interaction Database (DIDB) was also searched from 15 June 2018 to 26 July 2018. The DIDB has the largest manually curated collection of in vitro and in vivo data related to drug interactions in humans primarily based on scientific literature. A query was created for the term "precipitant," which by the University of Washington database definition is the equivalent of a perpetrator. Each term in Table 3 was searched individually as a "precipitant" and specified for "in vivo" results only. Medications under all categories were evaluated for interactions, as follows: the query "in vivo no mechanism" aided in identifying substrates that do not interact with ARAs or do not have an interaction that is clinically

Table 2 PDR3D: Reed Tech Navigator™ and DailyMed search terms

PPI	Gastric acid
Proton pump inhibitor	Gastric pH
Omeprazole	pH dependent
Esomeprazole	Chelation
Lansoprazole	Antacids
Dexlansoprazole	Sodium bicarbonate
Pantoprazole	Calcium carbonate
Rabeprazole	Aluminum hydroxide
H2 antagonists	Magnesium hydroxide
H2 blockers	Maalox[a]
Cimetidine	Riopan[b]
Ranitidine	Gaviscon[c]
Famotidine	Enteric coated
Nizatidine	Delayed release
Acid-reducing	Modified release

PPI proton pump inhibitor

[a]Maalox®. Aluminum hydroxide 225 mg, magnesium hydroxide 200 mg

[b]Riopan®. Magaldrate oral suspension

[c]Gaviscon®. Aluminum hydroxide and magnesium carbonate suspension

Table 3 University of Washington Drug–Drug Interaction database search terms

Omeprazole	Nizatidine
Esomeprazole	Sodium bicarbonate
Lansoprazole	Calcium carbonate
Dexlansoprazole	Aluminum hydroxide
Pantoprazole	Magnesium hydroxide
Rabeprazole	Maalox[a]
Cimetidine	Riopan[b]
Ranitidine	Gaviscon[c]
Famotidine	

[a]Maalox®. Aluminum hydroxide 225 mg, magnesium hydroxide 200 mg

[b]Riopan®. Magaldrate oral suspension

[c]Gaviscon®. Aluminum hydroxide and magnesium carbonate suspension

meaningful, the query "in vivo other mechanism > 20%" aided in identifying substrates reported to have a gastric pH-based interaction with ARAs, the queries "in vivo no inhibition" and "in vivo no induction" covered any medications considered to be gastric pH based but not included in the "in vivo other mechanism > 20%" group, and the queries "in vivo induction > 20%" and "in vivo inhibition > 20%" covered medications that interacted via metabolic enzymes and transporters. Citations were provided to the prescribing information for the medication available at the Drugs@FDA webpage and/or PubMed publications evaluating the interaction.

Pharmaceutical companies with approved medications for marketing in the USA are required to have up-to-date prescribing information available to the public, and the DailyMed database contains this information. The search strategy used for PDR3D (see earlier in this section) was replicated for the DailyMed database from 28 June 2018 to 1 August 2018 (Table 2).

The information collected from each database was organized on the basis of the presence or absence of a clinically meaningful interaction. For medications exhibiting an interaction, the substrate drug name, ARA (perpetrator), clinical effect on substrate drug, mechanism of interaction, evidence of interaction (clinical data), and intervention strategy were complied. For medications without an interaction, the medication name, concurrent ARA name, directions of use, and clinical data supporting the lack of a clinically meaningful interaction were also compiled.

Throughout the search strategy described earlier, repeat medications, names of ARA products (omeprazole, ranitidine, Maalox®, etc.), non-oral dosage forms, and medications with no basis for a pharmacokinetic interaction were removed. The remaining medications were then evaluated to determine whether the drug was a substrate or a perpetrator, and perpetrators were removed. Potential substrates were subsequently evaluated for a clinically meaningful interaction or no interaction/no clinically meaningful interaction. A clinically meaningful interaction was defined as when the prescribing information recommended some intervention for either the perpetrator or substrate as a result of the interaction (e.g., spacing, avoidance, or change in dose). If a pharmacokinetic interaction was observed, but no action was recommended by the prescribing information, this was considered to be a non-clinically meaningful interaction. Substrates with clinically meaningful interactions were further evaluated for description of the mechanism(s) of interaction, which were typically claimed in the prescribing information; however, for the few medications that did not claim a probable mechanism in the label, PubMed was used to try to determine the mechanism. The greatest emphasis was placed on the prescribing information, while case reports were not considered a definitive source for an associated interaction. If there was conflicting evidence presented between databases, the UpToDate®/Lexicomp® Drug and Drug Interaction screening tool was used to resolve this.

The UpToDate®/Lexicomp® screening tool uses scientific literature and prescribing information to provide peer-reviewed clinical practice advice to healthcare professionals when different databases present conflicting evidence for the presence or absence of a clinically meaningful interaction for a particular medication pair. Conflicting evidence appeared ~ 10% of the time, mostly for interactions considered to be non-gastric pH based. This was resolved by using a decision-making sequence. First, the prescribing information was referenced for evidence of an interaction; if there was no evidence for a clinically meaningful interaction and scientific literature (PubMed) presented conflicting evidence for a potential interaction, the UpToDate®/Lexicomp® screening tool was used to evaluate current clinical practice along with any supporting information. In addition, this tool was used to cross-reference the interactions identified through PDR3D, the University of Washington DIDB, and/or DailyMed. This screening tool was used from 28 June 2018 to 1 August 2018.

4.2 Results

Figure 1 describes the PRISMA-compliant flow diagram of the search strategy conducted and the output that was further analyzed. 'Identification' used PDR3D, University of Washington DIDB, and DailyMed to compile a list of medications to be screened for an interaction with ARAs. 'Screening' allowed for the removal of repeat medications, names of ARA products, non-oral dosage forms, and medications not relevant to an interaction with ARAs. 'Eligibility' allowed for identification of medications to be potential substrates or perpetrators, with perpetrators being removed. Potential substrates were then analyzed for the presence or absence of a clinically meaningful interaction. Substrates with a clinically meaningful interaction were distinguished on the basis of their mechanism of interaction (gastric pH based or non-gastric pH based).

Medications with a gastric pH-dependent mechanism of interaction with ARAs deemed to be clinically significant are shown in Table 4. Table 1 in the Electronic Supplementary Material expands on each interaction, provides clinical data and references, and comments further on mitigation strategies.

Table 5 lists medications that interact with ARAs based on a non-gastric pH-based mechanism, including chelation, CYP-mediated interactions, transporter-mediated

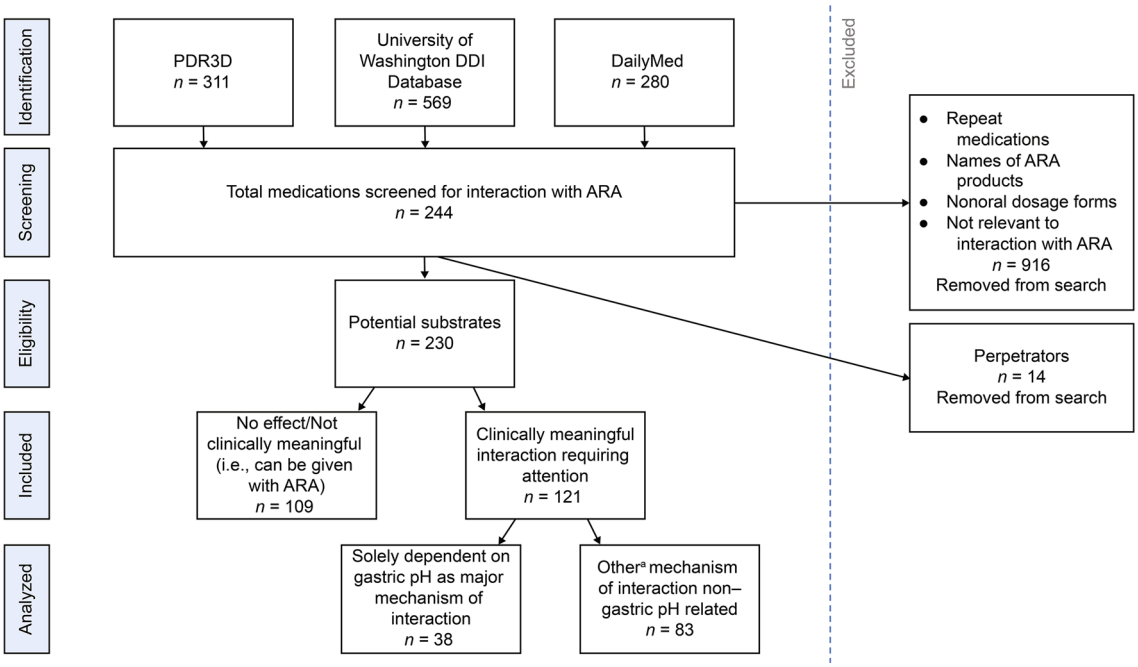

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA)-compliant methods output diagram. [a]'Other' means mediated by CYP, transporter, chelation, urine alkalization, etc. *ARA* acid-reducing agent, *DDI* drug–drug interaction

interactions, and urine alkalization. Table 2 in the Electronic Supplementary Material provides indepth information on the mechanism of interaction, clinical data, mitigation strategies, and references.

Table 6 shows medications with no clinically meaningful interaction with ARAs. Table 3 in the Electronic Supplementary Material provides supportive clinical data and references for these medications to support their use with ARAs without therapy change. All medications shown in Table 6 (and Table 3 in the Electronic Supplementary Material) have clinical data supporting lack of a clinically meaningful interaction with a designated ARA agent. Dependent on study design, it can reasonably be concluded that most of these mediations do not exhibit any gastric pH-dependent interaction.

5 Potential Strategies to Mitigate Gastric Acid-Reducing Drug–Drug Interactions

Figure 2 provides a decision-making sequence that prescribers and pharmacists can use to navigate through an interaction posed with an ARA. When an interaction is identified, the prescriber or pharmacist can choose to either change the ARA product or change the substrate medication. For example, changes would include either spacing of dosing in time, changing the dose, or selecting an alternative agent. When choosing to change the ARA, options include using a mitigation strategy or referring to Table 1 to select an alternative ARA. Table 1 shows the interaction profile of each ARA, and so selection of a non-interacting ARA would be made. When choosing to change the substrate medication, options include selecting an agent from a specific table depending on the mechanism of interaction. Strategies for both are shown for each mechanism of interaction.

6 Discussion

Current resources available permit identification of medications that may interact with ARAs; however, reference to multiple sources is required for a comprehensive examination, which becomes challenging in clinical practice. A single resource of DDIs with ARAs may support prescribers and pharmacists in avoiding or mitigating adverse drug combinations in patients undergoing ARA treatment. In this

Table 4 Substrates with a clinically meaningful gastric pH-dependent mechanism of interaction ($n=38$)

Drug	Antacid	H2RA	PPI
Acalabrutinib	Separate by 2 h	Take 2 h before H2RA	×
Atazanavir	Take 2 h before or 1 h after antacid	HIV treatment-naïve patients: take 2 h before or 10 h after H2RA in those unable to tolerate ritonavir; patients receiving ritonavir should take H2RA simultaneously with atazanavir and food or atazanavir 10 h after H2RA HIV treatment-experienced patients: take H2RA simultaneously with atazanavir and food or atazanavir 10 h after H2RA	× Can be administered with boosted atazanavir 12 h after PPI in patients that are treatment-naïve to atazanavir
Bisacodyl DR	Separate by at least 1 h	–	–
Bismuth subcitrate potassium, metronidazole, tetracycline hydrochloride	×	× with cimetidine and other inhibitors of CYP	✓
Bosutinib	Separate by minimum of 2 h	Separate by minimum of 2 h	×
Cefditoren pivoxil	×	×	×
Cefpodoxime proxetil	Separate by 2 h	Separate by minimum of 2 h	Monitor
Cefuroxime axetil	Take 1 h before or 2 h after antacid	×	×
Dabigatran etexilate mesylate	Canada: take 2 h before antacid; monitor	USA: ✓	USA: ✓
Dasatinib	Separate by minimum of 2 h	×	×
Delaviradine	Separate by 1 h	×	×
Digoxin	Monitor	–	Monitor
Emtricitabine, rilpivirine hydrochloride, tenofovir disoproxil fumarate (Complera®)	Take 4 h before or 2 h after antacid	Take 4 h before or 12 h after H2RA	×
Erlotinib	Separate by a few hours	Take 2 h before or 10 h after H2RA	×
Ferrous sulfate	Separate as much as possible, monitor	–	–
Gefitinib	Separate by 6 h	Separate by 6 h	× If necessary, separate by 12 h
Hyoscyamine	Administer before meals and antacid after meals	–	–
Indinavir	–	Monitor	Monitor
Itraconazole	Separate by 2 h; consider administering with non-diet cola	Separate by 2 h; monitor; administer with non-diet cola	Separate by 2 h; monitor; administer with non-diet cola
Ketoconazole	Take 2 h before or 1 h after antacid; monitor	Monitor; administer with non-diet cola	Monitor; administer with non-diet cola
Lapatinib	USA: ✓ UK: ×	USA: ✓ UK: ×	USA: ✓ UK: ×
Ledipasvir, sofosbuvir (Harvoni®)	Separate by 4 h	Time simultaneously or 12 h apart	Simultaneously under fasting conditions
Mefenamic acid	×	–	–
Mesalamine	×	–	–
Nelfinavir	–	Monitor	×
Neratinib	Take 3 h after antacid	Take 2 h before or 10 h after H2RA	×
Nilotinib	Separate by 2 h	Take 2 h before or 10 h after H2RA	×
Pazopanib	×	×	×
Phenytoin	Do not take at same time of day	–	–

Table 4 (continued)

Drug	Antacid	H2RA	PPI
Posaconazole oral suspension (Noxafil®)	✓	✓ for H2RA other than cimetidine; × for cimetidine	×
Raltegravir (Isentress®)	× for aluminum and/or magnesium antacids; × for calcium carbonate for high-dose raltegravir; ✓ for raltegravir	–	✓
Riociguat	Separate by 1 h	–	✓
Risedronate sodium (Atelvia DR)	×	×	×
Sofosbuvir, velpatasvir (Epclusa®)	Separate by 4 h	Time simultaneously or 12 h apart	× If necessary, take with food and 4 h before PPI

Medications were identified via searches and screens of the PDR3D: Reed Tech Navigator™, University of Washington Drug–Drug Interaction Database (DIDB), and DailyMed databases as detailed in Sect. 4.1

CYP cytochrome P450, *DR* delayed release, *H2RA* histamine H_2 receptor antagonist, *PPI* proton pump inhibitor, ✓ coadministration shows no interaction, × coadministration not recommended, – no information available

comprehensive review, 121 individual medications were found to clinically meaningfully interact with ARAs. Thirty-eight medications were identified to have a mechanism of interaction that was gastric pH dependent, and 83 medications were found to interact with ARAs with a non-gastric pH-mediated interaction (CYP/transporter/chelation/urine alkalization).

This review identified the mechanisms underlying DDIs, which allowed for the proposal of mitigation strategies. While mitigation strategies for introducing an ARA (perpetrator) and a substrate medication together are described in this review, it is also important to re-evaluate therapy changes when ARA (perpetrator) doses are decreased or stopped. For some medications, mitigation strategies recommended in prescribing information when H2RAs are perpetrators of a clinically meaningful gastric pH-dependent interaction are often inconsistent and sometimes debatable based on their pharmacodynamic properties. H2RA activity can persist for up to 12 h, with peak acid suppression occurring around 2 h. The prescribing information of some medications, such as bosutinib, indicates separation by 2 h before or after the H2RA. Although administering a substrate medication 2 h before an H2RA is appropriate, administering the substrate medication 2 h after the H2RA can be problematic because this is the time of the peak gastric acid raising effect. Waiting 10–12 h after an H2RA has been administered would strongly suggest mitigation of a gastric pH-dependent interaction based on the minimal pharmacodynamic effects of H2RAs at this time.

Specifically for chelation-based interactions, clinical data for substrate medications were often extrapolated to include other agents in the class or derivatives of the substrate medication. Although the clinical study may not have used the exact substrate medication and ARA combination, health authorities or manufacturers believed that alternative agents in the same class or substrate medication derivatives have potential for similar DDIs. For example, a common class of anti-infective medications are fluoroquinolones. Most antacids are known to chelate with fluoroquinolones; not all fluoroquinolones have been studied with antacids, but data for ciprofloxacin have been applied to other agents in the class, such as trovafloxacin, because of the similar chemistry prone to chelation among these agents.

Because gastric pH elevation is a characteristic shared among all three classes of ARAs, if no clinically meaningful gastric pH-mediated interaction is observed with one ARA, it is highly unlikely that no gastric pH-mediated interaction will be observed with any ARA. Similarly, if a clinically meaningful gastric pH-mediated interaction is observed with one ARA, it is highly likely that a gastric pH-mediated interaction will be observed with all ARAs. This allows for extrapolation of findings to different ARAs based on gastric pH alone. Because of individual characteristics of ARAs (antacids, H2RAs, PPIs), non-gastric pH-and chelation-based interactions, such as CYP, transporter, and urine alkalization, cannot be extrapolated between ARAs.

Interestingly, 109 medications were found to not have any clinically meaningful interaction with ARAs, suggesting that clinical DDI studies may have been conducted unnecessarily. It may be possible to identify drugs likely or not likely to have ARA-mediated drug interactions from their physicochemical characteristics, which would reduce the need for clinical gastric pH-mediated DDI studies. This also indicates the potential utility of a health authority

Table 5 Medications with a clinically meaningful other mechanism of interaction, not gastric pH-based ($n = 83$)

Victim drug	ARA/perpetrator	Mechanism of interaction
Anti-infectives		
Azithromycin	Magnesium-/aluminum-containing antacids	Likely chelation
Bictegravir	Antacids	Likely chelation
Chloroquine	Cimetidine	Inhibition of CYP
Ciprofloxacin	Magnesium-/aluminum-containing antacids	Chelation
Dolutegravir	Calcium-based antacids	Chelation
Doxycycline	Magnesium-/aluminum-/calcium-containing antacids, PPIs	Likely chelation
Gemifloxacin	Magnesium-/aluminum-containing antacids	Chelation
Levofloxacin	Magnesium-/aluminum-containing antacids	Chelation
Methenamine	Antacids	Urine alkalization
Minocycline	Magnesium-/aluminum-/calcium-containing antacids	Likely chelation
Moxifloxacin	Magnesium-/aluminum-containing antacids	Chelation
Norfloxacin	Cation-containing antacids[a]	Chelation
Quinine sulfate	Antacids/H2RAs	Chelation/inhibition of CYP3A4
Tetracycline	Magnesium-/aluminum-/calcium-containing antacids	Likely chelation
CNS agents		
Alprazolam	Cimetidine	Inhibition of CYP3A4
Carbamazepine	Cimetidine	Likely inhibition of CYP3A4
Citalopram	Cimetidine/omeprazole	Likely inhibition of CYP/inhibition of CYP2C19
Clobazam	Omeprazole	Inhibition of CYP2C19
Clozapine	Cimetidine	Inhibition of CYP3A4
Dalfampridine	Cimetidine	Inhibition of OCT2
Desipramine	Cimetidine	Likely inhibition of CYP
Doxepin	Cimetidine	Likely inhibition of CYP
Escitalopram	Cimetidine/proton pump inhibitors	Likely inhibition of CYP/inhibition of CYP2C19
Gabapentin	Antacid containing aluminum and magnesium	Possible chelation
Lisdexamfetamine	Sodium bicarbonate	Urine alkalization
Memantine	Antacids (sodium bicarbonate)	Urine alkalization
Mirtazapine	Cimetidine	Likely inhibition of CYP
Paroxetine	Cimetidine	Likely inhibition of CYP
Pramipexole	Cimetidine	Inhibition of OCT2
Sulpiride	Antacids	Unknown
Tizanidine	Cimetidine	Inhibition of CYP1A2
Zolmitriptan	Cimetidine	Likely inhibition of CYP
Cardiovascular agents		
Captopril	Antacids	Unknown
Carvedilol	Cimetidine	Likely inhibition of CYP
Diltiazem	Cimetidine	Likely inhibition of CYP3A4
Dofetilide	Cimetidine	Inhibition of renal tubular secretion
Felodipine	Cimetidine	Inhibition of CYP3A4
Fosinopril	Antacids	Unknown
Nifedipine	Cimetidine	Inhibition of CYP
Nimodipine	Cimetidine	Inhibition of CYP3A4
Nisoldipine	Cimetidine	Likely inhibition of CYP3A4
Nitrendipine	Cimetidine	Likely inhibition of CYP
Pindolol	Cimetidine	Likely inhibition of CYP or inhibition of renal clearance
Procainamide	Cimetidine	Likely inhibition of renal tubular secretion
Propafenone	Cimetidine	Likely inhibition of CYP

Table 5 (continued)

Victim drug	ARA/perpetrator	Mechanism of interaction
Quinidine	Cimetidine	Likely inhibition of CYP3A4
Rosuvastatin	Antacids	Possible chelation
Sotalol	Aluminum- and/or magnesium-containing antacids	Likely chelation
Verapamil	Cimetidine	Likely inhibition of CYP3A4
Immune suppressant agents		
Cyclosporine	H2RAs	Unknown
Mycophenolate mofetil	Antacids with magnesium and/or aluminum hydroxide	Chelation
Mycophenolic acid	Antacids with magnesium and/or aluminum hydroxide	Chelation
Tacrolimus	Proton pump inhibitors	Likely inhibition of CYP3A4
Blood-modifying agents		
Acenocoumarol	Cimetidine	Inhibition of CYP
Cilostazol	Omeprazole	Inhibition of CYP2C19
Clopidogrel	Proton pump inhibitors (esomeprazole, omeprazole)	Inhibition of CYP2C19
Eltrombopag	Cation-containing antacids[a]	Chelation
Warfarin	Cimetidine	Inhibition of hydroxylation in the liver
Metal chelators		
Deferasirox	Aluminum-containing antacids	Chelation
Deferiprone	Antacids	Chelation
Trientine	Antacids	Metal binding/chelation
Anti-diabetic agents		
Glimepiride	H2RAs (cimetidine, famotidine, nizatidine, ranitidine)	Inhibition of metabolism and/or renal transport
Glipizide	H2RAs (cimetidine, famotidine, nizatidine, ranitidine)	Inhibition of metabolism and/or renal transport
Metformin	Cimetidine	Likely inhibition of OCT2
Tolbutamide	Cimetidine	Inhibition of metabolism and/or renal transport
Bisphosphonate		
Alendronate	Antacids	Likely chelation
Antirheumatic		
Penicillamine	Antacids	Likely chelation
Chemotherapy		
5-Fluorouracil	Cimetidine	Likely a combination of inhibition of metabolism and decreased liver blood flow
Exchange resin		
Sodium polystyrene sulfonate	Antacids	Likely chelation
Gastrointestinal agents		
Alosetron	Cimetidine	Inhibition of CYP1A2
Respiratory agents		
Roflumilast	Cimetidine	Inhibition of CYP3A4
Urinary agents		
Tamsulosin	Cimetidine	Inhibition of CYP3A4
Lanthanum carbonate	Antacids	Unclear, possible chelation
Cholinergic agonist		
Varenicline	H2RAs (cimetidine, famotidine, nizatidine, ranitidine)	Possible inhibition of OCT2

Medications were identified via searches and screens of the PDR3D: Reed Tech Navigator™, University of Washington Drug–Drug Interaction Database (DIDB), and DailyMed databases as detailed in Sect. 4.1

ARA acid-reducing agent, *CNS* central nervous system, *CYP* cytochrome P450, *H2RA* histamine H_2 receptor antagonist, *OCT2* organic cation transporter 2

[a]It is suspected that 'cation-containing antacids' refer to polyvalent cations and not sodium bicarbonate when the mechanism of interaction is chelation

Table 6 Medications with no clinically meaningful interaction with one or more acid-reducing agents ($n = 109$)

Acitretin	Donepezil	Lisdexamfetamine	Sertindole
Alectinib	Dronedarone	Lopinavir and ritonavir (Kaletra®)	Sildenafil
Ambrisentan	Duloxetine	Losartan	Sodium oxybate
Amlodipine	Efavirenz	Meloxicam	Sorafenib
Aripiprazole	Elbasvir and grazoprevir (Zepatier®)	Metronidazole	Sulfasalazine
Asenapine	Eliglustat	Moexipril	Sulindac
Aspirin	Eprosartan	Naproxen DR	Tapentadol
Aspirin/extended-release dipyridamole (Aggrenox®)	Etravirine	Nebivolol	Telithromycin
Axitinib	Ezetimibe	Nevirapine	Temozolomide
Azacitidine	Famciclovir	Nifedipine	Topotecan
Betrixaban	Febuxostat	Nintedanib	Tramadol
Boceprevir	Fenofibric acid	Obeticholic acid	Trandolapril
Bortezomib	Fenoprofen	Osimertinib	Ulipristal acetate
Brexpiprazole	Fluconazole	Oxcarbazepine	Valacyclovir
Cabozantinib	Fluvastatin	Palbociclib	Valproic acid
Carvedilol	Fosamprenavir	Paricalcitol	Valsartan
Cephalexin	Gabapentin	Pioglitazone	Vandetanib
Ceritinib	Gabapentin enacarbil	Piroxicam	Venlafaxine
Cobimetinib	Garenoxacin	Ponatinib	Vilazodone
Crizotinib	Glecaprevir/pibrentasvir (Mavyret™)	Posaconazole delayed release capsules	Vismodegib
Dabigatran etexilate mesylate	Glimepiride	Prasugrel	Vorapaxar
Danoprevir	Imatinib	Propranolol	Voriconazole
Dapsone	Indinavir	Raloxifene	Zolpidem
Darunavir	Isavuconazonium sulfate	Ramelteon	
Diazepam	Isoniazid	Repaglinide	
Diclofenac	Itraconazole oral suspension	Risperidone	
Digoxin	Lamotrigine	Rivaroxaban	
Divalproex	Letrozole	Saxagliptin	

Medications were identified via searches and screens of the PDR3D: Reed Tech Navigator™, University of Washington Drug–Drug Interaction Database (DIDB), and DailyMed databases as detailed in Sect. 4.1

DR delayed release

guidance on this topic describing when a clinical study is, or is not, necessary.

Limitations of this review are that the search strategy was not replicated by a second individual, the risk for incomplete retrieval of interactions via the search strategy used, and that any additional information available after 1 August 2018 was not captured. The search strategy did not specifically include the names of the potassium-competitive acid pump antagonists revaprazan [43] and vonoprazan fumarate [44], which are approved in South Korea and Japan, respectively. Additionally, these drugs were not identified using the broad search terms, likely due to the limited number of countries in which they are approved.

7 Conclusions

This comprehensive review of DDIs using ARAs as a perpetrator will potentially aid in the treatment of patients receiving polypharmacy, permit avoidance of DDIs that would otherwise affect patient care, and save time for prescribers and pharmacists. Additionally, an effort was made to capture various mitigation strategies that were recommended by different health authorities (e.g., those in Canada and the European Union) to better apply this review outside of the USA.

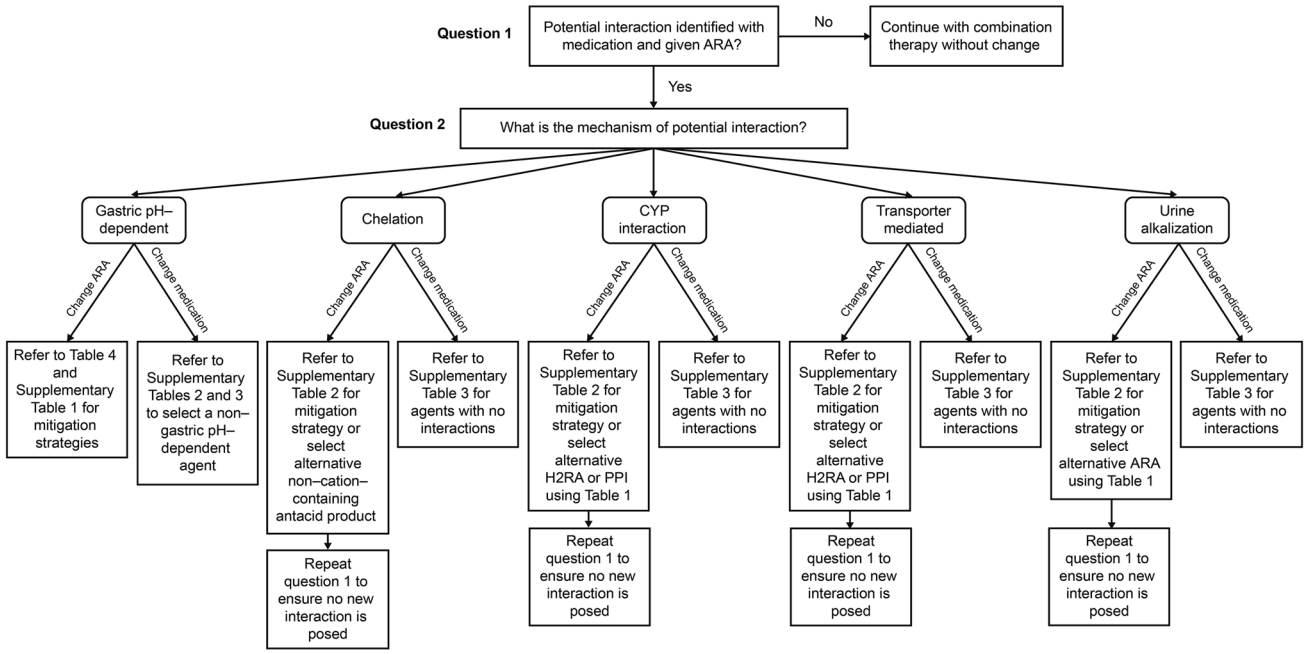

Fig. 2 Decision-making tree for selecting a mitigation strategy. *ARA* acid-reducing agent, *CYP* cytochrome P450, *H2RA* histamine H_2 receptor antagonist, *PPI* proton pump inhibitor

Acknowledgements The authors would like to acknowledge Deborah Anzalone, Kathryn DeStefano, Scott Tutak, Carol Moreno Quinn, Ian Sabir, Karin Mueller, Scott Adler, Mary Whealy, and Mary Beth DeYoung for their input and guidance. inScience Communications, Springer Healthcare (Philadelphia, PA, USA) provided editorial support funded by AstraZeneca.

Author Contributions All authors made substantial contributions to the analysis and interpretation of study data; wrote various drafts of the manuscript; and provided their final approval of the version to be published. All authors gave their agreement to be accountable for all aspects of the work.

Compliance with Ethical Standards

Funding Divya Patel completed a summer internship that was funded by AstraZeneca. inScience Communications, Springer Healthcare (Philadelphia, PA, USA) provided editorial support funded by AstraZeneca.

Conflicts of interest Divya Patel completed a summer internship funded by AstraZeneca. Mats Någård, Song Ren, and David Boulton are full-time employees and shareholders of AstraZeneca. Richard Bertz has no relevant conflicts of interest.

References

1. Ogawa R, Echizen H. Clinically significant drug interactions with antacids: an update. Drugs. 2011;71(14):1839–64.
2. Ogawa R, Echizen H. Drug-drug interaction profiles of proton pump inhibitors. Clin Pharmacokinet. 2010;49(8):509–33.
3. Feldman M. Comparison of the effects of over-the-counter famotidine and calcium carbonate antacid on postprandial gastric acid. A randomized controlled trial. JAMA. 1996;275(18):1428–31.
4. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008;10(6):528–34.
5. Humphries TJ, Merritt GJ. Review article: drug interactions with agents used to treat acid-related diseases. Aliment Pharmacol Ther. 1999;13(s3):18–26.
6. Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, et al. Membrane transporters in drug development. Nat Rev Drug Discov. 2010;9(3):215–36.
7. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother. 2007;5(4):345–51.
8. Trifirò G, Corrao S, Alacqua M, Moretti S, Tari M, Caputi AP, et al. Interaction risk with proton pump inhibitors in general practice: significant disagreement between different drug-related information sources. Br J Clin Pharmacol. 2006;62(5):582–90.
9. Sax MJ. Clinically important adverse effects and drug interactions with H_2-receptor antagonists: an update. Pharmacotherapy. 1987;7(6 Pt 2):110S–5S.
10. Johnson DA, Katz PO, Armstrong D, Cohen H, Delaney BC, Howden CW, et al. The safety of appropriate use of over-the-counter proton pump inhibitors: an evidence-based review and Delphi consensus. Drugs. 2017;77(5):547–61.
11. Mossner J. The indications, applications, and risks of proton pump inhibitors. Dtsch Arztebl Int. 2016;113(27–28):477–83.
12. Wedemeyer R-S, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. Drug Saf. 2014;37(4):201–11.

13. Kostewicz ES, Aarons L, Bergstrand M, Bolger MB, Galetin A, Hatley O, et al. PBPK models for the prediction of in vivo performance of oral dosage forms. Eur J Pharm Sci. 2014;57:300–21.
14. Sjögren E, Abrahamsson B, Augustijns P, Becker D, Bolger MB, Brewster M, et al. In vivo methods for drug absorption—comparative physiologies, model selection, correlations with in vitro methods (IVIVC), and applications for formulation/API/excipient characterization including food effects. Eur J Pharm Sci. 2014;57:99–151.
15. Bergström CAS, Holm R, Jørgensen SA, Andersson SBE, Artursson P, Beato S, et al. Early pharmaceutical profiling to predict oral drug absorption: current status and unmet needs. Eur J Pharm Sci. 2014;57:173–99.
16. Lahner E, Annibale B, Delle Fave G. Systematic review: impaired drug absorption related to the co-administration of antisecretory therapy. Aliment Pharmacol Ther. 2009;29(12):1219–29.
17. Fallingborg J. Intraluminal pH of the human gastrointestinal tract. Dan Med Bull. 1999;46(3):183–96.
18. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut. 1988;29(8):1035–41.
19. Zhang L, Wu F, Lee SC, Zhao H. pH-dependent drug–drug interactions for weak base drugs: potential implications for new drug development. Clin Pharmacol Ther. 2014;96(2):266–77.
20. Allen LV, Jr., Popovich NG, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems, ninth edition. J Pharm Technol. 2010;26(3):167–8.
21. Yoshida T, Lai TC, Kwon GS, Sako K. pH- and ion-sensitive polymers for drug delivery. Expert Opin Drug Deliv. 2013;10(11):1497–513.
22. Bendtsen F, Ovesen L, Rosenkilde-Gram B, Rune SJ. Effect of omeprazole on intragastric and duodenal bulb acidity in duodenal ulcer patients. Aliment Pharmacol Ther. 1989;3(2):151–8.
23. Abuhelwa AY, Williams DB, Upton RN, Foster DJ. Food, gastrointestinal pH, and models of oral drug absorption. Eur J Pharm Biopharm. 2017;112:234–48.
24. Maton PN, Burton ME. Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. Drugs. 1999;57(6):855–70.
25. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138(1):103–41.
26. Lee S-J, Shin J-G. The pharmacogenomics of cytochrome P450s: from molecular to clinical application. In: Yamazaki H, editor. Fifty years of cytochrome P450 research. Tokyo: Springer Japan; 2014. p. 345–70.
27. Inderal (propranolol hydrochloride) [prescribing information]. Philadelphia: Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.; 2017.
28. Lin JH, Lu AY. Inhibition and induction of cytochrome P450 and the clinical implications. Clin Pharmacokinet. 1998;35(5):361–90.
29. Kleinschmidt KC, Delaney KA. In: Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR, editors. Goldfrank's toxicologic emergencies. 10th ed. New York: McGraw-Hill; 2015. p. 155–67.
30. Trevor AJ, Katzung BG, Kruidering-Hall M. Katzung and Trevor's pharmacology: examination and board review. 11th ed. New York: McGraw-Hill; 2015. p. 35–40.
31. Gibaldi M, Grundhofer B, Levy G. Effect of antacids on pH of urine. Clin Pharmacol Ther. 1974;16(3):520–5.
32. Prescott LF. Mechanisms of renal excretion of drugs (with special reference to drugs used by anaesthetists). Br J Anaesth. 1972;44(3):246–51.
33. Bourdet DL. Differential substrate and inhibitory activities of ranitidine and famotidine toward human organic cation transporter 1 (hOCT1; SLC22A1), hOCT2 (SLC22A2), and hOCT3 (SLC22A3). J Pharmacol Exp Ther. 2005;315(3):1288–97.
34. Echizen H, Ishizaki T. Clinical pharmacokinetics of famotidine. Clin Pharmacokinet. 1991;21(3):178–94.
35. Nugent CC, Terrell JM. H2 blockers. StatPearls. Treasure Island: StatPearls Publishing; 2019.
36. Hatlebakk JG. Review article: gastric acidity—comparison of esomeprazole with other proton pump inhibitors. Aliment Pharmacol Ther. 2003;17(suppl 1):10–5.
37. Hitzl M, Klein K, Zanger UM, Fritz P, Nüssler AK, Neuhaus P, et al. Influence of omeprazole on multidrug resistance protein 3 expression in human liver. J Pharmacol Exp Ther. 2003;304(2):524–30.
38. Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF. Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. Naunyn Schmiedebergs Arch Pharmacol. 2001;364(6):551–7.
39. Kuzin M, Schoretsanitis G, Haen E, Stegmann B, Hiemke C, Grunder G, et al. Effects of the proton pump inhibitors omeprazole and pantoprazole on the cytochrome P450-mediated metabolism of venlafaxine. Clin Pharmacokinet. 2018;57(6):729–37.
40. Unge P, Andersson T. Drug interactions with proton pump inhibitors. Drug Saf. 1997;16(3):171–9.
41. Li XQ, Andersson TB, Ahlstrom M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos. 2004;32(8):821–7.
42. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
43. Lee JS, Cho JY, Song H, Kim EH, Hahm KB. Revaprazan, a novel acid pump antagonist, exerts anti-inflammatory action against Helicobacter pylori-induced COX-2 expression by inactivating Akt signaling. J Clin Biochem Nutr. 2012;51(2):77–83.
44. Yang X, Li Y, Sun Y, Zhang M, Guo C, Mirza IA, et al. Vonoprazan: a novel and potent alternative in the treatment of acid-related diseases. Dig Dis Sci. 2018;63(2):302–11.