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Article

pH-dependent drug interactions with acid reducing agents

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SUMMARY

Gastric acid reducing agents (ARAs) are drugs used for treating peptic ulcer disease. The higher gastric pH caused by ARAs can decrease solubility and absorption of the drugs co-administered with ARAs. The study examines the relationship between solubility and pharmacokinetic (PK) changes of cancer drugs concurrently used with ARAs, and the subsequent dose adjustment of cancer drugs to account for drug interactions. We hypothesize that (1) cancer drugs with pH-dependent solubility are evaluated more for drug interactions with ARAs, as compared to those with pH-independent solubility, (2) a decrease in the area-under-the-concentration curve (AUC) and maximum drug concentration (C_{max}), the PK measurements indicative of drug absorption, is observed more in drugs with pH-dependent solubility that sharply decreases at pH 3-5, and (3) dose adjustment is recommended more for drugs with a ≥45% decrease in AUC and C_{max}. The results showed no significant difference in the proportions of drugs where drug interactions were evaluated between drugs with pH-dependent solubility versus those with pH-independent solubility. A decrease in AUC and C_{max} was observed more in drugs with pH-dependent solubility that sharply decreased at pH 3-5 than those without such property (50% vs. 0%; p=0.04). Dose adjustment was recommended more for drugs with a ≥45% decrease in AUC and C_{max} than for those with a <45% decrease or no change (100% vs. 0%; p=0.002). These findings may help identify drugs with a higher risk of drug interactions with ARAs and assess the need for comprehensive evaluation of drug interactions and dose adjustment.

INTRODUCTION

Acid reducing agents (ARAs), including proton pump inhibitors (PPIs), H_2 receptor antagonists and antacids, e.g., calcium carbonate, are commonly used to treat peptic ulcer disease. Studies have reported that concurrent use of PPIs results in significant decrease in the efficacy of gefitinib and afatinib in the treatment of lung cancer (1, 2). The mechanisms of action of ARAs are inhibiting gastric acid secretion (PPIs and H_2 receptor antagonists) or neutralizing gastric acid (antacids) (3). It has been shown that a week of dosing with 20 mg of omeprazole or of rabeprazole increased gastric pH from 1.5 to 4.2 and 4.7, respectively (4). When oral drugs, including cancer drugs, are administered together with ARAs, the higher gastric pH caused by ARAs can lead to lower solubility (Le Chatelier's principle) and therefore decrease the absorption and bioavailability of the drugs (5). To ensure appropriate evaluation of pH-dependent drug interactions during drug development, the Food and Drug Administration (FDA) issued a guidance document on the evaluation of gastric pH-dependent drug interactions with ARAs (5). According to FDA guidance, the potential for an interaction with ARAs can be assessed in a stepwise manner, depending on whether the drug's solubility is pH-dependent or pH-independent (5).

The purpose of the present study is to examine the relationship between solubility, pharmacokinetic (PK) changes, i.e., changes in the area-under-the-concentration curve (AUC) and maximum drug concentration (C_{max}), of cancer drugs concurrently used with ARAs, and dose adjustment of cancer drugs for drug interactions, based on the data collected from the package inserts or FDA reviews. AUC is a measure of the average drug concentration in a given period of time, whereas C_{max} is the peak drug concentration after drug administration, both of which are measurements indicative of drug absorption (**Figure 1**) (6). Only oral cancer drugs approved from April 2020 to January 2023 were included in our study because all new oral cancer drugs were listed chronologically on a dedicated FDA website (7). This ensured that we evaluated all drugs in this category in an unbiased manner.

We hypothesize that (1) cancer drugs with pH-dependent solubility are evaluated more for drug interactions with ARAs, as compared to those with pH-independent solubility, (2) a decrease in AUC and C_{max} is observed more in drugs with pH-dependent solubility that sharply decreases at pH 3-5 than those without such property, and (3) dose adjustment is recommended more for drugs with a ≥45% decrease in AUC

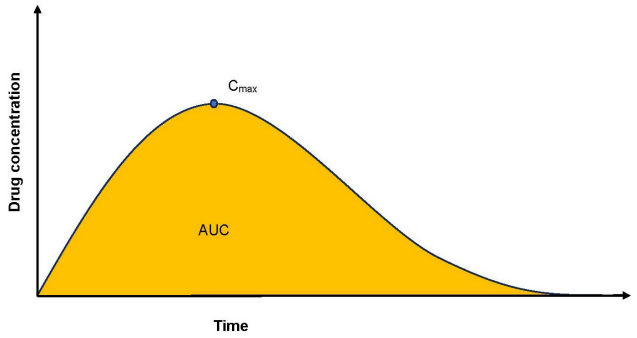

Figure 1. A graph illustrating the AUC and C_{max} in a pharmacokinetic concentration time curve. AUC is a measure of the average drug concentration in a given period of time. C_{max} is the maximum drug concentration after drug administration.

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and C_{max} than those with a <45% decrease or no change. The present study demonstrated that (1) no difference was noted in the evaluation of drug interactions between drugs with pH-dependent solubility and those with pH-independent solubility, which is not in line with the hypothesis, (2) a decrease in AUC and C_{max} was observed more in drugs with pH-dependent solubility that sharply decreased at pH 3-5, and (3) dose adjustment was recommended more for drugs with a ≥45% decrease in AUC and C_{max}, which are both in line with the hypotheses. Our findings may help identify drugs with a higher risk of drug interactions with ARAs and assess the need for comprehensive evaluation of drug interactions and dose adjustment.

RESULTS

We collected the data from the package inserts or FDA reviews of 30 oral cancer drugs (8-50). We investigated 23 drugs with pH-dependent solubility (**Table 1**) and seven drugs with pH-independent solubility (**Table 2**). They were indicated for hematologic cancers (e.g., lymphoma, leukemia, and myelofibrosis) and non-hematologic cancers (e.g., thyroid cancer, lung cancer, ovarian cancer, breast cancer, and bile duct cancer). When ARAs (mostly PPIs) were co-administered, the pharmacokinetic changes of the cancer drugs included a decrease, increase or no change in AUC and C_{max}.

Based on the patterns of solubility we observed, we divided the drugs with pH-dependent solubility into three sub-categories: drugs that were soluble or highly soluble across the physiological pH range (sub-category 1), drugs with adequate to low solubility at pH 1 and sharply decreasing solubility at pH 3-5 (sub-category 2) and drugs with low solubility or were practically insoluble across the physiological pH range (sub-category 3). Among the 23 drugs with pH-dependent solubility, five were in sub-category 1, twelve in sub-category 2, and six in sub-category 3 (**Figure 2**). All seven drugs with pH-independent solubility had low solubility or were practically insoluble across the physiological pH range (**Table 3**).

Drug interactions with ARAs were evaluated for 19 (83%) of the 23 drugs with pH-dependent solubility, including one in sub-category 1, all twelve in sub-category 2, all six in sub-category 3, and in three (43%) of the seven drugs with pH-independent solubility (**Figure 3**). No data were available for the remaining eight drugs. No significant difference was noted in the proportions of drugs for which drug interactions were evaluated between drugs with pH-dependent solubility and those with pH-independent solubility (83% vs. 43%; Fisher's exact test; p=0.06).

Among the 19 drugs with pH-dependent solubility where drug interactions were evaluated, six (32%) had a decrease in AUC and C_{max} deemed clinically meaningful by drug manufacturers or the FDA. No decreases in AUC and C_{max} were noted in the three drugs with pH-independent solubility (**Table 3**). No difference in the proportions of drugs with a decrease in AUC and C_{max} was noted between drugs with pH-dependent versus pH-independent solubility (32% vs. 0%; Fisher's exact test; p=0.54).

Of the 12 drugs with pH-dependent solubility that sharply decreased at pH 3-5, six (50%) had a decrease in AUC and C_{max}, whereas none of the seven drugs in sub-categories 1 and 3 had a decrease (**Table 3**). A decrease in AUC and C_{max} was observed more consistently in drugs with pH-dependent solubility that sharply decreased at pH 3-5, than those without this property (50% vs. 0%; Fisher's exact test; p=0.04). That is, drugs with pH-dependent solubility presenting as adequate to low solubility at pH 1 and sharply decreasing solubility at pH 3-5 had the most reduced AUC and C_{max}.

Among the 22 drugs for which drug interactions were evaluated, six had a decrease in AUC and C_{max}, 14 had no change, and two had an increase (**Table 3**). Based on the review of the decreases in AUC and C_{max}, the six drugs were further divided into three drugs with a ≥45% decrease and three drugs with a <45% decrease in AUC and C_{max}.

Dose adjustment was recommended, by drug manufacturers or the FDA, for all three drugs with a ≥45% decrease in AUC and C_{max} but was not recommended for the three drugs with a <45% decrease and the eleven drugs with no change (**Table 4**). The three drugs with a ≥45% decrease in AUC and C_{max} were (1) gefitinib with a decrease of 47% in AUC and decrease of 70% in C_{max}, (2) selpercatinib with a decrease of 69% in AUC and decrease of 88% in C_{max}, and (3) infigratinib with a decrease of 45% in AUC and decrease of 49% in C_{max} (**Table 1**). Dose adjustment was recommended

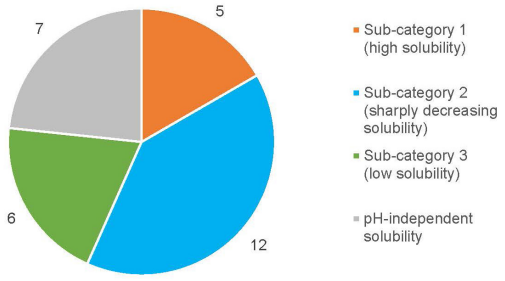

Figure 2: Drugs in different solubility categories. The 30 drugs were divided into 23 drugs with pH-dependent solubility and 7 drugs with pH-independent solubility. The 23 drugs with pH-dependent solubility were further divided into 3 sub-categories: 5 drugs that were soluble or highly soluble across the physiological pH range (sub-category 1), 12 drugs with adequate to low solubility at pH 1 and sharply decreasing solubility at pH 3-5 (sub-category 2), and 6 drugs with low solubility or were practically insoluble across the physiological pH range (sub-category 3).

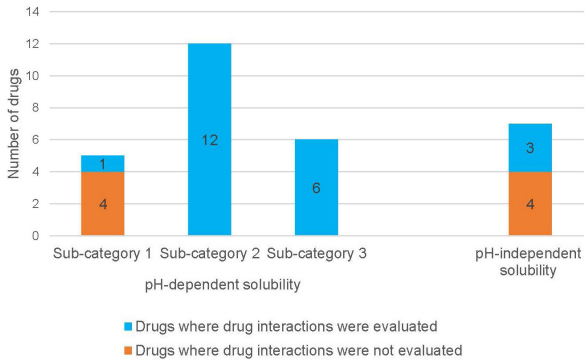

Figure 3: Evaluation of drug interactions in each solubility category. Drug interactions were evaluated in 1 of the 5 drugs in sub-category 1, all 12 drugs in sub-category 2, all 6 drugs in sub-category 3, and 3 of the 7 drugs with pH-independent solubility.

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Drug	Indication(s)	Solubility	PK change when ARAs were co-administered	Ref
gefitinib	lung cancer	sparingly soluble at pH 1, solubility sharply decreasing between pH 4 and 6	47% decrease in AUC 70% decrease in C_{max} (sodium bicarbonate)	8, 9
zanubrutinib	lymphoma	0.3 mg/ml at pH 1.2, 0.07 mg/ml at pH 4.5, 0.05 mg/ml at pH 6.8	no change (ARA)	10
adagrasib	lung cancer	>262 mg/ml at pH 1.2, <0.01 mg/ml at pH 7.4	32% decrease in AUC 38% decrease in C_{max} (pantoprazole)	11, 12
futibatinib	bile duct cancer	0.7 mg/ml at pH 1.2, 0.004 mg/ml at pH 4.5, 0.003 mg/ml at pH 6.8	no change (lansoprazole)	13, 14
selpercatinib	lung cancer	sparingly soluble at low pH to practically insoluble at neutral pH	69% decrease in AUC 88% decrease in C_{max} (omeprazole)	15
pemigatinib	bile duct cancer	>0.7 mg/ml at pH 1.2, 0.03 mg/ml at pH 4.3, <0.001 mg/ml at pH 6.5	no change (esomeprazole)	16, 17
capmatinib	lung cancer	4.2 mg/ml at pH 1, <13.6 mcg/ml at pH 4 and 6.8	25% decrease in AUC 38% decrease in C_{max} (rabeprazole)	18, 19
crizotinib	lung cancer lymphoma	>10 mg/ml at pH 1.6, <0.1 mg/ml at pH 8.2	no change (esomeprazole)	20
dabrafenib	lung cancer thyroid cancer melanoma	43 mcg/ml at pH 1.2, 6.8 mcg/ml at pH 4.9, 6.2 mcg/ml at pH 6.3	no change (rabeprazole)	21, 22
abemaciclib	breast cancer	63.2 mg/ml at pH 1, 1.6 mg/ml at pH 6.8 (highly soluble across PPHR)	-	23
ruxolitinib	myelofibrosis	soluble across PPHR	-	24
mobocertinib	lung cancer	152 mg/ml at pH 1.0, >17.6 mg/ml at pH 6.8 (highly soluble across PPHR)	-	25
avapritinib	GI stromal tumor	3.6 mg/ml at pH 1, 0.07 mg/ml at pH 4, < 0.001 mg/ml at pH 7	no change (PPI)	26
infigratinib	bile duct cancer	<1 mg/ml at pH 1, <0.5 mcg/ml at pH 6.8 (adequate solubility at pH 1, insoluble at pH 6.8)	45% decrease in AUC 49% decrease in C_{max} (lansoprazole)	27, 28
lorlatinib	lung cancer	32.4 mg/ml at pH 2.6, 0.4 mg/ml at pH 4.6, 0.1 mg/ml at pH 6.8	no change (rabeprazole)	29, 30
umbralisib	lymphoma	0.03 mg/ml at pH 1.2, 0.002 mg/ml at pH 4.5	no change (ARA)	31, 32
pralsetinib	lung cancer thyroid cancer	0.9 mg/ml at pH 2, <0.001 mg/ml at pH 7.6	15% decrease in AUC 25% decrease in C_{max} (esomeprazole)	33
venetoclax	leukemia	<0.004 mcg/ml at pH 4 and 7.4 (practically insoluble across PPHR)	no change (ARA)	34
azacitidine	leukemia	260 mg/ml at pH 1, 26 mg/ml at pH 3-7	18% increase in AUC 13% increase in C_{max} (omeprazole)	35, 36
tazemetostat	lymphoma	7.3 mg/ml at pH 1, 7.0 mg/ml at pH 4, 0.03 mg/ml at pH 6.8	26% increase in AUC 25% increase in C_{max} (omeprazole)	37, 38
brigatinib	lung cancer	highly soluble from pH 1.2-6.8	-	39
ripretinib	GI stromal tumor	1.6 mcg/ml at pH 2, <1 mcg/ml at pH 6.5 (insoluble across PPHR)	no change (pantoprazole)	40, 41
encorafenib	colon cancer melanoma	slightly soluble at pH 1, insoluble at pH 3 or higher	no change (rabeprazole)	42

Table 1: Indications, solubility, and pharmacokinetic (PK) changes of the 23 cancer drugs with pH-dependent solubility when ARAs were co-administered. Drugs in parentheses in the column of "PK change when ARAs were co-administered" were ARAs used to study the PK changes. If specific ARAs were not reported, only "ARA" or "PPI" was shown. Abbreviations: AUC=area-under-the-concentration curve; C_{max}=maximum drug concentration; GI=gastrointestinal; PPHR=the physiological pH range. –: data not reported.

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Drug	Indication	Solubility	PK change when ARAs were co-administered	Ref
pirtobrutinib	lymphoma	insoluble across PPHR	no change (omeprazole)	43
olutasidenib	leukemia	0.4 mcg/ml at pH 1.9, 0.3 mcg/ml at pH 7 (insoluble across PPHR)	-	44
ivosidenib	leukemia bile duct cancer	practically insoluble across PPHR	no change (ARA)	45
olaparib	ovarian cancer breast cancer pancreatic cancer prostate cancer	approximately 0.1 mg/ml at pH 1, 4.5 and 6.8 (low solubility across PPHR)	-	46
cabozantinib	kidney cancer liver cancer thyroid cancer	approximately 0.01 mg/ml at pH 1 and 4.5, 0 at pH 6.8 (insoluble across PPHR)	no change (esomeprazole)	47, 48
rucaparib	ovarian cancer	low solubility across PPHR	-	49
niraparib	ovarian cancer	1.1 mg/ml at pH 1, 1.0 mg/ml at pH 6.8 (low solubility across PPHR)	-	50

Table 2: Indications, solubility, and pharmacokinetic (PK) changes of the 7 cancer drugs with pH-independent solubility when ARAs were co-administered. Drugs in parentheses in the column of "PK change when ARAs were co-administered" were ARAs used to study the PK changes. If specific ARAs were not reported, only "ARA" was shown. Abbreviation: PPHR=the physiological pH range. –: data not reported.

more for drugs with a ≥45% decrease in AUC and C_{max} than those with a <45% decrease or no change (100% vs. 0%; Fisher's exact test; p=0.002).

The recommended dose adjustment was to separate the administration of cancer drugs and ARAs with a longer interval (12 hours) for PPIs and shorter interval (2 to 10 hours) for H_2 receptor antagonists or antacids (**Table 5**).

DISCUSSION

According to FDA guidance, the potential for an interaction with ARAs can be assessed in a stepwise manner: if the drug has pH-dependent solubility, it is possible that the drug may have drug interactions with ARAs, and therefore, that drug interaction studies may be needed. If the drug has pH-independent solubility, it is unlikely that they will have *in vivo* drug interactions with ARAs (5). To assess drug interactions in cancer drugs, we conducted the present study with the hypothesis that drug interactions were evaluated more for drugs with pH-dependent solubility than those with pH-independent solubility. We did not observe a difference in the proportions of drugs for which drug interactions were evaluated between drugs with pH-dependent solubility and those with pH-independent solubility. This finding appears to be inconsistent with the guidelines. This may be because drug manufacturers may still conservatively conduct drug interaction studies to evaluate the risk of drug interactions with ARAs, even when the drugs have pH-independent solubility. The reason for not evaluating drug interactions for the four drugs with pH-dependent solubility was less obvious. It could be because they have high solubility across the physiological pH range and thus, that the higher pH associated with ARAs may not reduce the solubility significantly enough to affect drug absorption.

Solubility	Change in AUC and C_{max}				Drug interactions not evaluated	Total
	decrease		no change	increase		
	≥45%	<45%				
Drugs with pH-dependent solubility	n=23					
soluble or highly soluble across the physiological pH range (sub-category 1)	0	0	0	1	4	5
adequate to low solubility at pH 1 with sharply decreasing solubility at pH 3-5 (sub-category 2)	3	3	5	1	0	12
low solubility or practically insoluble across the physiological pH range (sub-category 3)	0	0	6	0	0	6
Drugs with pH-independent solubility	n=7					
low solubility or practically insoluble across the physiological pH range	0	0	3	0	4	7

Table 3: The numbers of drugs with different pharmacokinetic (PK) changes in each solubility category. The 5 drugs in sub-category 1 were abemaciclib, ruxolitinib, mobocertinib, azacitidine, and brigatinib. The 12 drugs in sub-category 2 were gefitinib, adagrasib, selpercatinib, pemigatinib, capmatinib, crizotinib, avapritinib, infigratinib, lorlatinib, pralsetinib, tazemetostat, and encorafenib. The 6 drugs in sub-category 3 were zanubrutinib, futibatinib, dabrafenib, umbralisib, venetoclax, and ripretinib.

Among the 23 drugs with pH-dependent solubility, six drugs (gefitinib, adagrasib, selpercatinib, capmatinib, infigratinib, and pralsetinib) had a decrease in AUC and C_{max}. All six drugs were in sub-category 2 (adequate to low solubility at pH 1 and sharply decreasing solubility at pH 3-5), supporting the hypothesis that *in vivo* drug interactions occur more in drugs with pH-dependent solubility that sharply decreases at higher pH. If the drugs were highly soluble across the physiological pH range (sub-category 1) or practically insoluble across the physiological pH range (sub-category 3), or if the solubility was pH-independent, the solubility would not be significantly changed by the increased gastric pH; therefore, *in vivo* drug interactions were not noted. The reason why six drugs in sub-category 2 did not have a decrease in AUC and C_{max} may be because factors other than solubility, like drug stability, permeability, and particle size, also determined the extent of drug absorption (51).

As noted in the results, the recommendations for the three drugs with dose adjustments were similar, namely separating the administration of cancer drugs and ARAs. The intervals were slightly different, depending on the types of ARAs used according to patients' need and cancer drug dosing regimens: 12 hours for PPIs and 2–10 hours for H_2 receptor antagonists or antacids. The difference may be due to longer duration (> 24 hours) of suppression of gastric acid secretion associated with PPIs compared to other ARAs, like antacids, that neutralize gastric acid for approximately two hours (5, 51).

Our study had some limitations. The sample size in the present study (30 drugs) was not very large. The drugs included were all FDA-approved drugs and the analyses only included data reported in the package inserts or FDA reviews of the drugs. Both these factors limited the generalization of our research findings. In addition, findings reported in pharmacokinetic studies not conducted for regulatory approval were not included. Since ARAs had different mechanisms of action, interpreting the analyses may need to take inter-drug variability into consideration, especially when different ARAs

Solubility and PK change	All drugs	Drugs with dose adjustment recommended
Drugs with pH-dependent solubility	19	
≥45% decrease in AUC and C_{max}	3	3
<45% decrease in AUC and C_{max}	3	0
no change in AUC and C_{max}	11	0
increase in AUC and C_{max}	2	0
Drugs with pH-independent solubility	3	
≥45% decrease in AUC and C_{max}	0	0
<45% decrease in AUC and C_{max}	0	0
no change in AUC and C_{max}	3	0
increase in AUC and C_{max}	0	0

Table 4: Dose adjustment of cancer drugs by solubility and pharmacokinetic (PK) change. The numbers in the column of "All drugs" represented the numbers of drugs in the solubility categories with the specific PK change.

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Drug	Dose adjustment	Ref
gefitinib	take gefitinib 12 hours after the last dose or 12 hours before the next dose of a PPI; take gefitinib 6 hours after or 6 hours before an H_2 receptor antagonist or an antacid.	8
selpercatinib	take selpercatinib with food when coadministered with a PPI; take selpercatinib 2 hours before or 10 hours after administration of an H_2 receptor antagonist; take selpercatinib 2 hours before or 2 hours after administration of a locally-acting antacid.	15
infigratinib	separate administration of infigratinib by 2 hours before or 10 hours after an H_2 receptor antagonist; separate administration of infigratinib by 2 hours before or after a locally-acting antacid.	27

Table 5: Dose adjustment recommended for gefitinib, selpercatinib, and infigratinib when ARAs are concurrently used. The intervals between the administration of cancer drugs and ARAs depend on the types of ARAs used.

were used to study the PK changes that they may not be directly comparable. In addition, the ≥45% decrease in AUC and C_{max} was chosen based on the data from six drugs only. The value has not been reported in other studies as a value indicating a need for dose adjustment.

In this study, we have shown that a majority of cancer drugs examined had pH-dependent solubility (23 out of 30 drugs). Drugs with pH-dependent solubility that sharply decreased at pH 3-5 are more likely to have reduced AUC and C_{max}, as compared to drugs in other categories, and drugs with a ≥45% decrease in AUC and C_{max} are more likely to have dose adjustment recommendation when they are concurrently used with ARAs. These findings may help drug manufacturers and the FDA identify drugs with a higher risk of significant drug interactions with ARAs, which may require dose adjustments. Evaluating drug interactions with ARAs based on the mechanism of action of cancer drugs and acid reducing agents, and the effectiveness of dose adjustment in decreasing AUC and C_{max} to a lesser degree may be important topics for future work.

MATERIALS AND METHODS

Cancer drugs, including new indications, approved from April 2020 to January 2023 that were posted on the FDA "Approval Notifications" website were reviewed to collect eligible drugs for the study (7). Only oral cancer drugs were included because all new oral cancer drugs were listed chronologically on the dedicated FDA website. In addition, only drugs approved recently were included because they had more data required by the FDA guidance, which was needed for analysis in the present study. Oral drugs with adequate data on solubility across the physiological pH range, i.e., pH 1.0 to 6.8, and a clear description of the solubility as pH-dependent or pH-independent in the package inserts or FDA reviews of the drugs were included. Intravenous, topical, and other non-oral drugs were excluded from our analysis.

Information on indication, solubility across the physiological range, and classification of the solubility as pH-dependent or -independent was collected from the package inserts or FDA reviews of the 30 shortlisted drugs. In addition, pharmacokinetic changes (i.e., changes in AUC and C_{max}) of cancer drugs when they were concurrently used with ARAs, the ARAs used to study the PK changes, and the recommended dose adjustment were also collected. The clinical pharmacology and biopharmaceutical review, multi-discipline review and product quality review were included in the FDA reviews.

The drugs were divided into two categories: drugs with pH-dependent solubility and those with pH-independent solubility. Solubility of pH-dependence or not was used to categorize the drugs because it is an important solubility property frequently studied and reported in pharmacokinetic studies (10, 13, 17). Based on the patterns of solubility observed, drugs with pH-dependent solubility were further divided into three sub-categories: drugs that were soluble or highly soluble across the physiological pH range (sub-category 1), drugs with adequate to low solubility at pH 1 and sharply decreasing solubility at pH 3-5 (sub-category 2) and drugs with low solubility or were practically insoluble across the physiological pH range (sub-category 3). The changes in AUC and C_{max} were categorized as one of the three categories: decrease, increase, and no change. A value determined from the review of the decreases in AUC and C_{max} was used to categorize these decreases.

The differences in the proportions of drugs where drug interactions were evaluated and of drugs with a decrease in AUC and C_{max} between different categories were analyzed using Fisher's exact test, a statistical method for testing the difference between two categorical variables in a small sample size.

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