Title
Analyzing Potential Intestinal Transporter Drug-Drug Interactions: Reevaluating Ticagrelor Interaction Studies

Authors
Liu, Shuaibing
Sodhi, Jasleen K
Benet, Leslie Z

Peer reviewed

Analyzing Potential Intestinal Transporter Drug-Drug Interactions: Reevaluating Ticagrelor Interaction Studies

Shuaibing Liu[1,2], **Jasleen K. Sodhi**[1,3], **Leslie Z. Benet**[1]

[1]Department of Bioengineering and Therapeutics Sciences, Schools of Pharmacy and Medicine, University of California, San Francisco, San Francisco, CA 94143-0912, USA

[2]Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

[3]Present address: Department of Drug Metabolism and Pharmacokinetics, Plexxikon Inc., South San Francisco, California, USA

Abstract

Purpose—Previous studies evaluating ticagrelor drug-drug interactions have not differentiated intestinal versus systemic mechanisms, which we do here.

Methods—Using recently published methodologies from our laboratory to differentiate metabolic- from transporter-mediated drug-drug interactions, a critical evaluation of five published ticagrelor drug-drug interactions was carried out to investigate the purported clinical significance of enzymes and transporters in ticagrelor disposition.

Results—The suggested CYP3A4 inhibitors, ketoconazole and diltiazem, displayed unchanged mean absorption time (MAT) and time of maximum concentration (T_{max}) values as was expected, i.e., the interactions were mainly mediated by metabolic enzymes. The potential CYP3A4/P-gp inhibitor cyclosporine also showed an unchanged MAT value. Further analysis assuming there was no P-gp effect suggested that the increased AUC and unchanged $t_{1/2}$ for ticagrelor after cyclosporine administration were attributed to the inhibition of intestinal CYP3A4 rather than P-gp. Rifampin, an inducer of CYP3As after multiple dosing, unexpectedly showed decreased MAT and T_{max} values, which cannot be completely explained. In contrast, grapefruit juice, an intestinal CYP3A/P-gp/OATP inhibitor, significantly increased MAT and T_{max} values for ticagrelor, which may be due to activation of P-gp or inhibition of OATPs expressed in intestine.

Conclusions—This study provides new insight into the role of transporter pathways in ticagrelor intestinal absorption by examining potential MAT and T_{max} changes mediated by drug-drug interactions.

Keywords

drug-drug interactions; mean absorption time; ticagrelor

Correspondence should be addressed to: Leslie Z. Benet, leslie.benet@ucsf.edu.

The authors declare no conflict of interest.

INTRODUCTION

Ticagrelor is a widely used antiplatelet agent for patients experiencing acute coronary syndrome. The oral bioavailability of ticagrelor averages only 35% due to marked first pass metabolism [1, 2]. The contribution of hepatic CYP3A4 and CYP3A5 in the metabolism of ticagrelor to its major active metabolite, AR-C124910XX, is well characterized [2, 3]. As a BCS (Biopharmaceutics Classification System) class IV and BDDCS (Biopharmaceutics Drug Disposition and Classification System) class II compound [4, 5], there is a high possibility that transporters could be involved in the pharmacokinetic process. However, little is known about the role of transporters in the uptake and/or efflux of ticagrelor in vivo. Two previous in vitro studies utilizing Caco-2 cells report that ticagrelor is a weak substrate of P-glycoprotein (P-gp) with an efflux ratio of 2.71 [6] and 2.28 [7], and we recently suggested the potential of transporter-enzyme interplay [7]. A genome-wide association study showed that genetic variations in organic anion transport protein 1B1 (OATP1B1) affect the levels of ticagrelor and AR-C124910XX in vivo [8], however, clinical evidence is limited about whether OATP1B1 is responsible for the uptake of ticagrelor. Furthermore, the contribution of OATPs expressed in intestine to the absorption of ticagrelor remains unknown.

Mean absorption time (MAT) is a useful parameter, which can be used to describe the absorption process. Recently, we detailed the necessity of using changes in absorption time to implicate intestinal transporter involvement in oral DDIs [9] and utilized the technique to show that the intestinal efflux transporters P-gp and breast cancer resistance protein (BCRP) are not clinically relevant in apixaban disposition [10], although the FDA approved label states that they are, as well not being clinically relevant in rivaroxaban absorption [11]. Regarding DDIs, important information can be obtained through analyzing MAT and T_{max} changes caused by the perpetrator [9]. For metabolic enzyme-mediated DDIs, inhibition or induction of metabolic enzymes will not change MAT or volume of distribution steady-state (V_{ss}) values [9, 12], whereas MAT and V_{ss} values have the potential to change in transporter-mediated DDIs [9, 13]. More specifically, for P-gp substrates, inhibition of P-gp will decrease MAT values, but induction or activation of P-gp will prolong absorption time and will increase MAT values. For intestinal OATP substrates, inhibition of OATP will prolong absorption time and therefore increase MAT values. For compounds that are CYP3A, P-gp and/or OATP substrates, MAT values may be increased, decreased or unchanged depending on the relative contribution and degree of inhibition of each pathway.

Here we investigated the role of intestinal transporters in ticagrelor absorption based on the analysis of MAT and T_{max} values. This study provides new insights into elucidating the role of transporter pathways in ticagrelor intestinal absorption.

MATERIALS AND METHODS

A thorough literature search was carried out to identify DDI studies between ticagrelor and other drugs/conditions. The analysis procedures were similar to those described for apixaban and rivaroxaban [10, 11]. Pharmacokinetic parameters of interest in this analysis included area under the curve (AUC), area under the moment curve ($AUMC$), MAT, mean residence

time *(MRT)*, T_{max}, terminal half-life ($t_{1/2,z}$), apparent clearance (*CL/F*), and apparent volume of distribution at steady state (V_{ss}/F). Those parameters that were not reported in the original publications were estimated by digitizing and regenerating pharmacokinetic profiles from the original articles and conducting noncompartmental and/or compartmental analysis with WinNonlin® Professional Edition Version 2.1 (Pharsight, Mountain View, CA). As previously described [9], the concentration-time data were fit to a two-compartment model with first order absorption using WinNonlin®, and *MAT* was calculated as the inverse of the first-order absorption rate constant. The mean residence time (*MRT*) was calculated from the ratio of $AUMC_{0-\infty}$ to $AUC_{0-\infty}$ minus *MAT*. The V_{ss}/F value was calculated as the product *CL/F·MRT* [14]. A cutoff value of 25%, calculated as: (regenerated values - reported values)/reported values ·100%, was set to ensure the digitized data were trustworthy. The available reported values and our calculated values for *AUC* and half-life measures (and *CL/F* when reported) was compared and only those values that did not exceed the cutoff value were included in the analysis. Published values were preferentially used in the analysis when available.

RESULTS

We identified five ticagrelor DDI studies that met our criteria, including studies with two CYP3A4 inhibitors (ketoconazole [15] and diltiazem [15]), with ketoconazole purported to also inhibit P-gp, one CYP3A4 and P-gp inducer (rifampicin [16]), one purported CYP3A4/P-gp/OATP inhibitor (cyclosporine [17]) and one CYP3A4 and purported P-gp/OATP inhibitor (grapefruit juice [18]). The results are shown in Table I.

The clinical DDI studies with concomitant oral ketoconazole and diltiazem [15], drugs well-recognized as CYP3A4 inhibitors, resulted in significantly increased *AUC* of ticagrelor and was accompanied by decreased *CL/F* and V_{ss}/F as well as prolonged $t_{1/2,z}$ and *MRT* values. However, *MAT* and T_{max} values remained unchanged. In both cases the decreases in *CL/F* were greater than the decrease in V_{ss}/F, while the changes in $t_{1/2,z}$ and *MRT* for each interaction were comparable. A marked difference between the change in *AUC* vs. C_{max} following these single dose interaction studies is observed for the potent CYP3A4 inhibitor ketoconazole (7.32-fold for *AUC* vs. 2.35-fold for C_{max}), but not for the less potent CYP3A4 inhibitor diltiazem (2.73-fold for *AUC* vs. 1.69-fold for C_{max}). The potential relevance of these differences is presented in the Discussion section.

For the clinical DDI study with concomitant oral rifampicin [16], a CYP3A and P-gp inducer after multiple dosing, *AUC* decreased, *CL/F* and V_{ss}/F increased with the increase in *CL/F* being greater than that for V_{ss}/F, *MRT* and $t_{1/2,z}$ decreased to the same extent, and *MAT* and T_{max} also decreased to same extent. The single dose ticagrelor evaluation following multiple dose rifampin led to an 86% decrease in *AUC* vs. a 73% decrease in C_{max}.

For the clinical DDI study with concomitant orally cyclosporine [17], a purported P-gp/CYP3A/OATP inhibitor, many of the results are similar to that seen for the diltiazem DDI [15], with a fairly comparable increase in *AUC* and decreases in *CL/F* and V_{ss}/F, while no marked increase in *MAT* or T_{max} was observed. The change in C_{max} (2.26-fold) was

comparable to the *AUC* change (2.85-fold) and was somewhat more than the change in C_{max} for diltiazem (1.69-fold). Here, as in our previous work [10, 11], we assumed that ratios falling between 0.77 and 1.30 (± 30% on a logarithmic basis) were not clinically significant changes. However, in contrast to the diltiazem results, with concomitant cyclosporine, $t^{1/2,z}$ and *MRT* did not increase markedly. Unchanged *MAT* and T_{max} values were also observed, indicating that P-gp is not clinically relevant in this DDI. To further explore this observation, we also carried out the analysis assuming there was no P-gp effect following the methodology we recently published to differentiate changes in bioavailability from changes in clearance for metabolized drugs [19]. The analysis was as follows:

$$\frac{\text{CL/F}_{\text{treated}}}{\text{CL/F}_{\text{control}}} = \frac{CL_{treated}}{CL_{control}} \cdot \frac{F_{control}}{F_{treated}} = 0.35 \quad (1)$$

If transporters are not involved in the drug-drug interaction, then V_{ss} is unchanged

$$\frac{V_{ss}/F_{\text{treated}}}{V_{ss}/F_{\text{control}}} = \frac{F_{control}}{F_{treated}} = 0.43 \quad (2)$$

Substituted Eq. 2 into Eq. 1, yields the estimate of the DDI effect on the CL ratio

$$\frac{CL_{treated}}{CL_{control}} = \frac{0.35}{0.43} = 0.81 \quad (3)$$

That is, the cyclosporine DDI effect is estimated to decrease clearance by 19%, but increase bioavailability by 2.3-fold (i.e., 1/0.43).

For the clinical DDI study with concomitant oral grapefruit juice [18], a purported CYP3A/P-gp/OATPs inhibitor, the results are similar to those found for the cyclosporine and diltiazem interactions with the exception that here the T_{max} and *MAT* ratios increase markedly.

DISCUSSION

Although the role of hepatic enzymes CYP3A4 and CYP3A5 in ticagrelor metabolism was well recognized, the contribution of transporters to ticagrelor uptake or efflux remains unknown. This is particularly true when intestinal transporters are considered. In this study, we carried out a comprehensive analysis of published DDIs in humans where orally dosed ticagrelor is the victim. Five different perpetrators (rifampin, ketoconazole, cyclosporine, diltiazem and grapefruit juice) that showed different inhibition/induction potency toward CYP3A4, P-gp or OATPs were examined. As we noted previously [9], average *MAT* or absorption rate values are rarely reported in DDI studies, as was the case for all the ticagrelor DDIs analyzed here. Our reported digitization of published pharmacokinetic profiles are generated from the average drug concentrations in all subjects at each time point, and therefore may result in profiles that do not necessarily represent any single subject within the study and published mean values in the studies would not be expected to coincide

exactly with our calculated values. For this reason, we only included studies where the published mean pharmacokinetic parameters differed by less than 25% from the digitized values.

The results suggested that CYP3A4 inhibitors, i.e., ketoconazole and diltiazem, showed unchanged *MAT* and T_{max} values for ticagrelor, consistent with our findings of the absence of ketoconazole affecting *MAT* for apixaban [10] or rivaroxaban [11]. We believe there is no convincing published evidence of ketoconazole having any clinically significant effect on intestinal transporters for any drug since such analyses would have to evaluate changes in absorption rate as reflected in *MAT* and T_{max} measures, and these results support our repeated cautions that in vitro transporter IC_{50} inhibition values cannot be trusted as the basis for assuming a clinically relevant effect on absorption rate. The comparison of the ketoconazole and diltiazem results in Table I are highly consistent with the greater CYP3A4 enzyme inhibitory effect of ketoconazole with greater increases in *AUC, MRT* and *t½,z* and greater decreases in *CL/F* and V_{ss}/F for ketoconazole compared to diltiazem, and both perpetrators inhibiting both systemic and intestinal enzymes, with greater decreases in *CL/F* compared to V_{ss}/F for both ketoconazole and diltiazem

Of particular interest was the finding that the cyclosporine DDI effect appears to be primarily related to inhibition of intestinal enzymes rather than hepatic enzymes when we assume that volume of distribution is unaffected in metabolic DDIs. Under this condition, we see little change in *MRT* and *t½,z* (and similarly no clinically relevant changes in absorption rate). Then our analysis in Eqs. 1–3 suggests that concomitant cyclosporine only resulted in a 19% change in clearance but a 2.3-fold increase in bioavailability. Although Teng et al. [17] believe that cyclosporine is a weak CYP3A4 inhibitor in vivo, our analysis provides a different perspective, i.e., the inhibitory effect by cyclosporine is important in determining the gut effects mediated by CYP3A, but in agreement with Teng et al. the effect of cyclosporine on CYP3A4 is not clinically relevant systemically. Since we see no meaningful changes in *MAT* or T_{max}, we propose that the cyclosporine DDI is primarily an intestinal CYP3A4 interaction, which is contradictory to the speculation of Teng et al. [17], who suggested that inhibition of intestinal P-gp was the major mechanism responsible for the increased *AUC* values with unchanged $t_{1/2},z$.

The comparison of the changes in *AUC* and C_{max} can be viewed in terms of our previous analysis of such parameters [20]. For low hepatic extraction ratio (*ER*) metabolized drugs such as ticagrelor, single dose interaction studies with a potent hepatic enzyme inhibitor will result in a large change in *AUC*, which is a direct reflection of the changes in clearance. However, as we demonstrated [20], although this large change will be reflected in C_{max} changes at steady-state, this will not be seen in C_{max} following a single dose of victim drug since the change in C_{max} due to hepatic metabolism is a reflection of accumulation with multiple doses. Thus, the difference in changes for *AUC* and C_{max} for the ticagrelor-ketoconazole interaction appear supportive of our belief that there is no intestinal or hepatic transporter interaction occurring. The similarity of the changes for *AUC* and C_{max} with cyclosporine and grapefruit juice, as opposed to that seen with ketoconazole, is consistent with the metabolic interaction being primarily in the intestine in these interactions, since changes in *F* will be immediately observed in both *AUC* and in C_{max}.

Another striking finding in Table I is the observation that the ratios for the potent enzyme inducer multiple dosed rifampicin and the potent enzyme inhibitor ketoconazole are almost exactly the inverse of each other for *AUC*, *CL/F*, V_{ss}/F, *MRT* and *t½,z*. However, where ketoconazole has no clinically significant effects on *MAT* and T_{max}, rifampicin cuts *MAT* and T_{max} in half, suggesting a clinically relevant change in absorption rate. This is a surprising, potentially contradictory result as it is well documented that multiple doses of rifampicin can exhibit an induction effect on P-gp [21, 22], leading to a slower rate of absorption and an increased T_{max} for intestinal P-gp substrates. However, Reitman et al. [22] document rifampicin's additional direct inhibitory effect on P-gp. Since rifampicin and ticagrelor were dosed at the same time on day 15 for this study [16], intestinal concentrations of rifampin may have been sufficient to competitively inhibit P-gp, thus blunting the effect of P-gp induction on the absorption of ticagrelor, or alternatively inhibiting potential intestinal uptake OATP transporters, which would lead to the observed decreased absorption rate. We previously noted the opposing effects of rifampicin increasing enzymatic activity and decreasing hepatic uptake of glyburide [23] but had not considered intestinal OATP uptake inhibition. It is also important to note in Table I the significant 2/3rds decrease in *MRT* and *t½,z* with rifampicin administration, which without any change in absorption rate should lead to a decrease in T_{max}, but not necessarily *MAT*. And we further note that ketoconazole also exhibited a 3-fold change in *t½,z*, but no change in *MAT* or T_{max}. Reviewing the rifampicin interaction studies as summarized [21, 22], there is a paucity of published potential intestinal transporter interactions where *t½,z* and *MRT* are also markedly changed, except for substrates of hepatic OATPs, where significant changes in V_{ss} can lead to counterintuitive elimination half-lives [24]. Therefore, at this time, it appears that rifampicin's effect on intestinal transporters for compounds where metabolism is extensively modified cannot be adequately defined and further studies are needed for such compounds.

As noted by Holmberg et al. [18], grapefruit juice markedly increases the plasma concentrations and antiplatelet effect of ticagrelor, most likely by inhibition of the CYP3A4-mediated first pass metabolism of ticagrelor mainly at the intestinal level. The data in Table I are consistent with this conclusion exhibiting very similar ratios for *CL/F* and V_{ss}/F and no change in *MRT* or *t½,z*. Thus, the increase in *AUC* can be a result of changes in *F* only. It is also instructive to recognize in Table I that except for the *MAT* and T_{max} ratios, the grapefruit juice-ticagrelor interaction is quite similar to that for cyclosporine-ticagrelor, where our analysis in Eqs. 1–3 suggests that the increase in *AUC* is predominantly a gut inhibition effect. The *MAT* and T_{max} changes noted with grapefruit juice are marked but they would not be expected to have an effect on *AUC* unless the CYP3A enzyme in the intestine is saturated at the concentration range of ticagrelor in the intestine. Here, we find that grapefruit juice slows ticagrelor absorption, so lower concentrations of ticagrelor would encounter the enzymes and changes in *F* with changes in absorption rate would only be observed if enzyme saturation was found with the higher control absorption rate. To what may the grapefruit juice effect on ticagrelor be attributed? We believe there are two possibilities. In 1999, our laboratory reported that transporter mediated efflux of drugs that are substrates of P-gp were significantly activated when grapefruit juice was dosed concomitantly [25], which would result in slower absorption. The second possibility is

that the slowing of absorption rate may be due to inhibition of organic anion transporting polypeptide influx transporters OATP1A2 and/or OATP2B1 by grapefruit juice constituents in the intestine [26, 27]. Although there is no human in vivo report indicating OATPs are involved in the uptake of ticagrelor we did observe an effect of rifamycin SV in vitro in a Caco-2 cell line [7], and our previous study conducted in Sprague-Dawley rats showed that prior administration of tea polyphenols for six consecutive days significantly reduced exposure to ticagrelor and its active metabolite as well as the metabolite-parent ratios with oral dosing but had no significant effects with intravenous drug dosing [28]. The inhibition of intestinal absorption mediated by OATPs are believed to be the main mechanism responsible for the interaction, providing preliminary evidence that intestinal OATPs participated in the uptake of ticagrelor in the intestine. Further studies aimed at investigating the role of OATPs expressed in intestine in ticagrelor uptake are underway.

CONCLUSIONS

This study provides new insight into elucidating the role of transporter pathways in ticagrelor intestinal absorption by analyzing MAT and T_{max} changes caused by drug-drug interactions. The ketoconazole and diltiazem DDIs with ticagrelor may be explained based on CYP3A inhibition both on first pass through the intestine and liver and further systemic enzymatic inhibition. No clinically relevant intestinal transporter inhibition is observed. The cyclosporine-ticagrelor DDI can be explained as a result of intestinal enzyme inhibition, with minimal systemic effects and no relevant intestinal transported interaction. The multiple dose rifampicin-ticagrelor DDI appears to be explained by induction of intestinal and hepatic CYP3A enzymes, the latter also affecting systemic concentrations. An unexpected increase in absorption rate is observed that cannot be fully explained at this time. The grapefruit juice-ticagrelor DDI appears to be a result of inhibition of intestinal CYP3A. There is a marked decrease in ticagrelor absorption, but this does not affect AUC. This decreased absorption could be the result of P-gp activation or intestinal OATP inhibition. The analysis here highlights the additional valuable information that can be obtained through analyzing MAT and T_{max} changes, which can aid in explaining the underlying mechanism regarding DDIs. We emphasize that these explanations are specific for ticagrelor and like our previous reviews of the apixaban [10] and rivaroxaban [11] DDIs, this paper presents the general format for evaluating these interactions, not the universality of the explanations.

ACKNOWLEDGEMENTS AND DISCLOSURES

ABBREVIATIONS

AUC   Area under the curve

AUMC	Area under the moment curve
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics classification system
BDDCS	Biopharmaceutics drug disposition classification system
CL/F	Apparent clearance
CYP	Cytochrome P450
DDIs	Drug-drug interactions
ER	Extraction Ratio
F	Oral bioavailability
MAT	Mean absorption time
MRT	Mean residence time
OATP	Organic anion transport protein
P-gp	P-glycoprotein
T_{max}	Time of maximum concentration
$t_{1/2,z}$	Terminal half-life
V_{ss}/F	Apparent volume of distribution steady-state

REFERENCES

1. Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. Drug Metab Dispos 2010;38(9):1514–21. [PubMed: 20551239]

2. Teng R Ticagrelor: Pharmacokinetic, pharmacodynamic and pharmacogenetic profile: An update. Clin Pharmacokinet 2015;54(11):1125–38. [PubMed: 26063049]

3. Zhou D, Andersson TB, Grimm SW. In vitro evaluation of potential drug-drug interactions with ticagrelor: cytochrome P450 reaction phenotyping, inhibition, induction, and differential kinetics. Drug Metab Dispos 2011;39(4):703–10. [PubMed: 21177984]

4. Hosey CM, Chan R, Benet LZ. BDDCS predictions, self-correcting aspects of BDDCS assignments, BDDCS assignment corrections, and classification for more than 175 additional drugs. AAPS J 2016;18(1):251–60. [PubMed: 26589308]

5. FDA. ticagrelor approved pacakage. [cited; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433Orig1s000ChemR.pdf. 2011

6. Marsousi N, Doffey-Lazeyras F, Rudaz S, Desmeules JA, Daali Y. Intestinal permeability and P-glycoprotein-mediated efflux transport of ticagrelor in Caco-2 monolayer cells. Fundam Clin Pharmacol 2016;30(6):577–84. [PubMed: 27416295]

7. Liu S, Wang Z, Hou L, Tian X, Zhang X, Cai W. Predicting the effect of tea polyphenols on ticagrelor by incorporating transporter-enzyme interplay mechanism. Chem Biol Interact 2020;330:109228. [PubMed: 32827518]

8. Varenhorst C, Eriksson N, Johansson A, Barratt BJ, Hagstrom E, Akerblom A, et al. Effect of genetic variations on ticagrelor plasma levels and clinical outcomes. Eur Heart J 2015;36(29):1901–12. [PubMed: 25935875]

9. Sodhi JK, Benet LZ. The necessity of using changes in absorption time to implicate intestinal transporter involvement in oral drug-drug interactions. AAPS J 2020;22:111. [PubMed: 32808084]

10. Sodhi JK, Liu S, Benet LZ. Intestinal efflux transporters P-gp and BCRP are not clinically relevant in apixiban disposition. Pharm Res 2020;37(10):208. [PubMed: 32996065]

11. Kou W, Sodhi JK, Wu X, Benet LZ. Investigating intestinal transporter involvement in rivaroxaban disposition through examination of changes in absorption. Pharm Res 2021;38(5):795–801. [PubMed: 33847849]

12. Sodhi JK, Huang CA, Benet LZ. Volume of distribtuion is unaffected by metabolic drug-drug interactions. Clin Pharmacokinet 2021;60:205–22. [PubMed: 32725383]

13. Grover A, Benet LZ. Effects of drug transporters on volume of distribution. AAPS J 2009;11:250–61. [PubMed: 19399628]

14. Benet LZ, Galeazzi RL. Noncompartmental determination of the steady-state volume of distribution. J Pharm Sci 1979;68:1071–4. [PubMed: 480170]

15. Teng R, Butler K. Effect of the CYP3A inhibitors, diltiazem and ketoconazole, on ticagrelor pharmacokinetics in healthy volunteers. J Drug Assess 2013;2(1):30–9. [PubMed: 27536435]

16. Teng R, Mitchell P, Butler K. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of ticagrelor in healthy subjects. Eur J Clin Pharmacol 2013;69(4):877–83. [PubMed: 23093043]

17. Teng R, Kujacic M, Hsia J. Pharmacokinetic interaction study of ticagrelor and cyclosporine in healthy volunteers. Clin Drug Invest 2014;34(8):529–36.

18. Holmberg MT, Tornio A, Joutsi-Korhonen L, Neuvonen M, Neuvonen PJ, Lassila R, et al. Grapefruit juice markedly increases the plasma concentrations and antiplatelet effects of ticagrelor in healthy subjects. Br J Clin Pharmacol 2013;75(6):1488–96. [PubMed: 23126367]

19. Sodhi JK, Benet LZ. A simple methodology to differentiate changes in bioavailability from changes in clearance following oral dosing of metabolized drugs. Clin Pharmacol Ther 2020;108(2):306–15. [PubMed: 32150643]

20. Benet LZ, Bowman CM, Koleske ML, Rinaldi CL, Sodhi JK. Understanding drug-drug interaction and pharmacogenomic changes in pharmacokinetics for metabolized drugs. J Pharmacokinet Pharmacodynam 2019;46:155–63.

21. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interactions with rifampicin. Clin Pharmacokinet 2003;42(9):819–50. [PubMed: 12882588]

22. Reitman M, Chu X, Cai X, Yabut J, Venkatasubramanian R, Zajic S, et al. Rifampin's acute inhibitory and chronic inductive drug interactions: experimental and model-based approaches to drug–drug interaction trial design. Clin Pharmacol Ther 2011;89(2):234–42. [PubMed: 21191377]

23. Zhang HX, Huang Y, Frassetto LA, Benet LZ. Elucidating rifampin's inducing and inhibiting effects on glyburide pharmacokinetics and blood glucose in healthy volunteers: Unmasking the differential effects of enzyme induction and transporter inhibition for a drug and its primary metabolite. Clin Pharmacol Ther 2009;85:78–85. [PubMed: 18843263]

24. Benet LZ, Bowman CM, Sodhi JK. How transporters have changed basic pharmacokinetic understanding. AAPS J 2019;21:103. [PubMed: 31482335]

25. Soldner A, Christians U, Susanto M, Wacher VJ, Silverman JA, Benet LZ. Grapefruit juice activates P-glycoprotein-mediated drug transport 1999;16(4):478–85.

26. Satoh H, Yamashita F, Tsujimoto M,Murakami H, Koyabu N, Ohtani H, Sawada Y. Citrus juices inhibit the function of human organic anion-transporting polypeptide OATP-B. Drug Metab Dispos 2005; 33:518–23. [PubMed: 15640378]

27. Bailey DG, Dresser GK, Leake BF, Kim RB. Naringin is a major and selective clinical inhibitor of organic anion-transporting polypeptide 1A2 (OATP1A2) in grapefruit juice. Clin Pharmacol Ther 2007; 81:495–502. [PubMed: 17301733]

28. Wang Z-T, Xue Y, Sun H, Zhang Z, Tang Z-J, Liu S-B, Cai W-M. Effect of tea polyphenols on the oral and intravenous pharmacokinetics of ticagrelor in rats and its in vitro metabolism. J Food Sci 2020; 85:1285–91. [PubMed: 32157685]

Table I

Ratios of oral ticagrelor pharmacokinetic DDI parameters (Reported as treated/control)

Perpetrator	Ketoconazole [15]	Diltiazem [15]	Rifampicin [16]	Cyclosporine [17]	Grapefruit juice [18]
$\dfrac{\text{AUC}_{\text{treated}}}{\text{AUC}_{\text{control}}}$	7.32	2.73	0.14	2.85	2.21
$\dfrac{\text{CL/F}_{\text{treated}}}{\text{CL/F}_{\text{control}}}$	0.14	0.37	7.20	0.35	0.45
$\dfrac{\text{V}_{\text{ss}}\text{/F}_{\text{treated}}}{\text{V}_{\text{ss}}\text{/F}_{\text{control}}}$	0.44	0.69	2.33	0.43	0.51
$\dfrac{\text{MRT}_{\text{treated}}}{\text{MRT}_{\text{control}}}$	3.15	1.84	0.34	1.21	1.12
$\dfrac{\text{t}_{1/2,z\ \text{treated}}}{\text{t}_{1/2,z\ \text{control}}}$	3.62	1.96	0.33	0.96	1.07
$\dfrac{\text{C}_{\text{max}_{\text{treated}}}}{\text{C}_{\text{max}_{\text{control}}}}$	2.35	1.69	0.27	2.26	1.65
$\dfrac{\text{T}_{\text{max}_{\text{treated}}}}{\text{T}_{\text{max}_{\text{control}}}}$	1.00	1.00	0.50	1.20	2.00
$\dfrac{\text{MAT}_{\text{treated}}}{\text{MAT}_{\text{control}}}$	1.03	0.93	0.55	1.12	3.03