Review of Grapefruit Juice Mediated Drug-Drug Interactions – Trends from a Chirality Perspective

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Abstract: Prolific literature data exists on the drug-drug interaction (DDI) potential of many important xenobiotics including racemic drugs with concomitant intake of grapefruit juice (GFJ). Since recently reports have appeared that suggested that GFJ has the potential to inhibit enzymes in a stereoselective fashion, this review examines the impact of DDI studies with GFJ using examples of several racemic drugs with an emphasis on stereoselectivity in the pharmacokinetic disposition. Also, all reported mechanisms have been collated to comprehend the interaction dynamics with GFJ. Overall, the disposition of the xenobiotics regardless of chirality considerations is governed by dual interplay of cytochrome P450 and transporters in humans. Hence, the interpretation of DDI data with GFJ of chiral substrates needs to be made with caution as there is a potential for the change in the eudismic ratio due to the interaction potential. Moreover, extrapolation of either in vitro findings or preclinical data for human prediction of GFJ interactions may sometimes be misleading.

Keywords: Grapefruit juice, chirality, drug-drug interaction, stereoselective, pharmacokinetics, CYP, CYP3A4, transporters, esterases.

1. INTRODUCTION

Grapefruit juice (GFJ) has been extensively studied in the last several decades with scores of xenobiotics in several pharmacokinetic drug-drug interaction (DDI) studies [1-9]. Especially in certain population such as patients with liver cirrhosis, the importance of DDI with GFJ attains much significance since these patients are solely dependent on intestinal CYP3A4 for biotransformation of the ingested drugs because the hepatic CYP3A4 activity is greatly reduced or non-existent due to the hepatic insult [10]. The effects of GFJ has been generally shown to increase the bioavailability of orally administered compounds that have a pre-systemic metabolism component and hence, orally administered co-substrates with GFJ have a tendency to show much more dramatic effect as opposed to intravenously administered substrates. GFJ exerts its effect merely after a single dose intake and the effect has been shown to be influenced by the dose size of GFJ and time of dosing of GFJ [11, 12]. Using simvastatin as a model substrate, duration of the effect of CYP3A4 inhibition was shown to be dependent on both the dose size and treatment period; CYP3A4 enzyme continued to be inhibited to a mild to moderate degree for a number of days post GFJ stoppage as evidenced by increased exposure of simvastatin [13]. Similar findings observed for simvastatin have been confirmed for nisoldipine in healthy subjects [14]. The effect of GFJ is not merely restricted to inhibition of gut metabolism - a recent update provides an overwhelming effect of GFJ, relative to other fruit juices, to block the uptake transport of several compounds including fexofenadine, acebutolol, talinolol, L-thyroxine etc [15]. Also, GFJ has been shown to block efflux transporters mediated via P-glycoprotein (Pgp) to increase exposure of substrates such as digoxin [16]. In vitro, GFJ has been shown to induce Pgp expression and promote reverse transport (i.e., efflux phenomenon). Hence, the overall effects of GFJ with the co-administered drug in a DDI study may be difficult to predict as it may involve complex phenomena especially if the co-administered drug is not just a substrate for CYP3A4 but its disposition is governed by multiple transporter play (efflux and/or uptake transporters).

2. SCOPE

It is well documented that racemic drug administration in many instances may pose challenges in the clinic with respect to pharmacokinetics and/or pharmacodynamics of the two enantiomers, if the racemic drug exhibits stereoselectivity during absorption, metabolism, distribution, and/or elimination process [17-23]. Hence if GFJ can further influence the stereoselectivity of the disposition of such racemic substrates, due to the occurrence of DDI at a specific enzyme, transporter and/or process level, it may add to the complexity of understanding the drug kinetics/exposure to ensure safety and efficacy of the therapy is not compromised. The intent of this review is to provide case studies of several racemic substrates where a formal DDI study has been carried out with the
co-administration of GFJ. While highlighting the pharmacokinetic interaction (or lack of it as the case may be), the review attempts to provide mechanistic basis to understand the interaction dynamics of GFJ. In addition, notes are provided on various topics such as challenges with GFJ studies, transporter related interactions, translatability of preclinical findings to humans, and data interpretation in patient population to provide some perspectives on this important topic as poly-pharmacy has become a common practice in today’s disease management.

3. METHODS

Literature data were collected on number of racemic drugs where DDI study with GFJ has been carried out. Additional literature work relating to in vitro studies, interesting mechanistic studies involving GFJ, reports on preclinical to clinical translatability of GFJ interactions, and select clinical DDI studies of GFJ carried out with non-chiral drug substrates were also collected for incorporation in this review article. Additional, relevant literature information involving racemic substrate or non-chiral substrate with suitable CYP3A4 and/or transporter inhibitor(s) were also collected and reviewed.

4. RACEMIC SUBSTRATES AND GFJ - DRUG-DRUG INTERACTION CASE STUDIES

Table 1 provides a tabulation of several racemic drug substrates that have been evaluated for drug-drug interaction liability with GFJ. Out of the 8 case studies presented [24-31], the inhibition of GFJ resulted in a marginal to moderate change in the stereoselective pharmacokinetics of 3 (nicardipine, methadone and manidipine) out of 8 racemic substrates (<50%) as compared to the pharmacokinetic data obtained by a concomitant water (placebo) treatment. It appeared that stereoselectivity was not a common phenomenon with all studies and was substrate dependent. However, if the entire pharmacological activity of racemic drug was residing in just one enantiomer, then probably the substantial increase in the exposure of the eutomer relative to distomer in presence of GFJ, may translate into clinically relevant safety issues as a result of shift in its therapeutic index. However, from the present regulatory context, it is highly improbable to develop and market a racemic drug. Since today’s knowhow in technology provides a basis for synthesis of individual enantiomers and/or separation of a racemate, the development of single enantiomer is both rational and justified. In order to provide a comprehensive summary of DDI of racemic drugs with GFJ, tabulation includes summary of key results and critical remarks (Table 1).

In the studies reported in Table 1, there were both qualitative and quantitative differences with the use of the perpetrator, GFJ. Some notable ones included: a) use of different brands; b) intake of fresh fruit juice versus frozen concentrate; c) volume of beverage ranging from 200 mL to 300 mL, d) single-dose beverage intake versus repeated-dose beverage intake; e) double strength juice vs regular strength juice. It should be appreciated that the above factors when considered individually may each have consequences on the total inhibition of the gut CYP3A4/transporters and also may have influenced the extent of time duration for the physiological/enzymatic process to get to normalcy (i.e., baseline). To underscore this view, Paine et al. have unequivocally confirmed that active furanocoumarins of GFJs have different on set time for gut CYP3A4 inhibition and hence, can potentially work in an overlapping fashion for a prolonged inhibition resulting in the altered disposition of the xenobiotic [32].

In spite of such differences in the commercial sources of GFJ, experimental conditions, and design of individual clinical studies, the data consistently provided some key observations, such as: 1) the large acute effect of the GFJ mediated interaction; 2) time and dose dependency (quantum of GFJ intake) of the observed interaction; 3) reversible nature of the interaction.

Since most of the studies used an acute GFJ treatment and/or repeated daily dosing of GFJ (not exceeding two glasses of GFJ per day), it is not expected that the GFJ would have a larger impact on the liver CYP enzymes for any of the compounds presented in Table 1. While it may have been possible with substantially larger intake of GFJ per day (3 or 4 glasses of double strength and/or 6 to 8 glasses of regular strength) and/or continuous daily intake of a few glasses of GFJ for a number of days may lead to a possible inhibition of liver CYP3A4 enzymes as suggested for triazolam and midazolam [33, 34]. Hence in the examples provided in Table 1, although GFJ enhanced oral bioavailability, either in a stereoselective or non-stereoselective fashion as the case may be, it did not appear to alter elimination half-life values (GFJ versus placebo) suggesting that liver hepatic CYP3A4 was not inhibited.
### Table 1: Summary of Drug-Drug Interaction Studies of Racemic Substrates with GFJ

<table>
<thead>
<tr>
<th>Reference</th>
<th>Substrate</th>
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| Uno et al.      | Nicardipine | Does gut metabolism play a role in low bioavailability? Site of stereoselective metabolism (gut vs liver)? To what extent GFJ alters stereoselective disposition? | N=6 males; non-blind, non-randomized 4-way crossover with 4-week washout between treatment phases.  
Phase 1: Oral-40 mg drug+water  
Phase 2: Oral-40 mg drug+GFJ (300 mL)  
Phase 3: IV-2 mg drug without GFJ  
Phase 4: IV-2 mg drug with oral GFJ | 1) Gut first-pass effects was responsible for lower bioavailability (BA); 2) BA was 2-fold greater for (+)-nicardipine; 3) No profound selectivity in PK after IV with or without GFJ; 4) Gut site contributed for the stereoselective PK differences.  
GFJ further enhanced the bioavailability of (-)-nicardipine. | 1) Involvement of gut site for stereoselective metabolism was confirmed; 2) Since first-pass inhibition by GFJ favored (-)-nicardipine, could it lead to therapeutic index changes in some patients?  
3) Should there be a recommendation for the timing of GFJ intake in patients taking nicardipine? |
| Soons et al.    | Nitrendipine | Contribution of GFJ for stereoselective first pass metabolism? Contribution of cimetidine for stereoselective first pass metabolism? | N=9 males; double-blind (only for cimetidine), placebo controlled randomized 3-way crossover with a 1-week washout between treatments.  
Treatment 1: 20 mg nitrendipine + cimetidine (total of 5 doses in 24 h – total dose: 1200 mg)  
Treatment 2: 20 mg nitrendipine + g placebo tablets matching cimetidine, administered in identical fashion over 24 h  
Treatment 3: 20 mg nitrendipine + GFJ (150 mL) | 1) Inhibition of gut metabolism by GFJ increased BA of both enantiomers by approximately 2.2-fold – the S/R ratio was not altered as compared to placebo; there was a faster absorption of both enantiomers relative to placebo; 2) cimetidine inhibited gut metabolism and increased BA of both enantiomers favoring S-cimetidine with S/R ratio of 2.25 as compared to ratio of 1.89 for placebo; appeared to slow down rate of absorption for both enantiomers relative to placebo. | 1) Confirmation that the effect of a single drink of a beverage can be as powerful as that of a known CYP inhibitor, cimetidine; 2) While pretreatment and continuous doses of cimetidine were needed for the inhibition of gut CYP, a mere co-administration of GFJ caused similar effect; 3) Steroselectivity was not observed for GFJ, it may be speculated that faster absorption rate may have circumvented this effect. |
| Vincent et al.  | Amlodipine | To determine extent of DDI between amlodipine and GFJ after oral and IV treatments? Is there a stereoselective play in the purported DDI? | N=20; open label, 4-way placebo (water) controlled, randomized crossover study with at least 2-weeks of washout in between treatment phases.  
Treatment 1: IV 10 mg amlodipine + GFJ (200 mL)  
Treatment 2: IV 10 mg amlodipine + water (200 mL)  
Treatment 3: Oral 10 mg amlodipine + water (200 mL)  
Treatment 4: Oral 10 mg amlodipine + GFJ (200 mL) | 1) High oral BA of amlodipine was not altered by GFJ; 2) GFJ had no effect on the IV PK parameters of amlodipine; 3) The PK parameters appeared to be largely similar between (S) and (R)-enantiomers of amlodipine regardless of route of administration. | 1) Due to intrinsic low first-pass effect, amlodipine behaved differently from other substrates in the class; 2) the observed very slight stereoselectivity in amlodipine PK after oral may be an experimental artifact as opposed to stereoselective first pass inhibition. |
| Desta et al.    | Cisapride | Whether or not the clinical PK of cisapride is stereoselective? Degree/extent of inhibition of GFJ on the PK of cisapride enantiomers? | N = 10; two-period, open label, 2-way randomized crossover study with 2-week intervals between successive treatments.  
As it was a repeated GFJ DDI study, the treatments were as follows:  
Treatment 1: days 1/2: 3 times daily GFJ intake (200 mL) and on day 3: GFJ(200 mL) intake 2 times – post 0.5 h and 1.5 h after 10 mg oral dose of cisapride  
Treatment 2: days 1/2: 3 times daily water intake (200 mL) and on day 3: water intake (200 mL) 2 times – post 0.5 h and 1.5 h after 10 mg oral dose of cisapride | 1) Cisapride exhibits stereoselective PK disposition in humans; the relative oral BA of (-)-enantiomer is about 3 times greater than that of (+)-enantiomer; no differences in the elimination half-life of the two enantiomers; 2) co-administration of GFJ caused significant inhibition of first-pass metabolism; the effect was found to be identical for the two enantiomers (approximately 2.5 fold greater exposure); an increase in the elimination half-life of both enantiomers was observed with GFJ. | 1) The observed effect of GFJ on the inhibition of presystemic metabolism of cisapride is consistent with the reported intermediary range of oral absorption of cisapride (approximately 40 -50%); 2) Lack of stereoselective effects in the PK of cisapride in spite of significant inhibition of gut metabolism suggests that GFJ effects cannot be consistently predicted across various substrates. |
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<td>Ho et al. (2000) [28]</td>
<td>Verapamil</td>
<td>Extent of effect of GFJ on stereoselective PK/PD of verapamil?</td>
<td>N=9; two-period, open label, randomized crossover study with a 4-week washout period between the treatments. It was a multiple dose study of both GFJ and verapamil. Treatment 1: days 1 – 5, twice daily administration of GFJ (200 mL); days 3-5 daily administration of 120 mg sustained release (SR) verapamil. On day 6, 120 mg SR verapamil was taken with GFJ (200 mL). Treatment 2: Treatment 1: days 1 – 5, twice daily administration of orange juice (OJ – 200 mL); days 3-5 daily administration of 120 mg SR verapamil. On day 6, 120 mg SR verapamil was taken with OJ (200 mL).</td>
<td>Verapamil exhibits stereoselective metabolism which was further inhibited by GFJ such that the relative BA of both enantiomers were increased approximately by 3.5-fold. 2) GFJ appeared to have little effect on the clearance of both verapamil enantiomers; 3) The decreased exposure of metabolite in this study confirmed the significant inhibition produced by GFJ and the stereoselectivity PK of metabolite was not affected by GFJ relative to OJ treatment</td>
<td>1) Given the extensive presystemic metabolism of verapamil (oral BA of 20%), the GFJ effect in the present was not found to be profound. Additionally, stereoselectivity play in GFJ’s inhibition was muted. 2) Since verapamil disposition is governed by both CYP metabolism and transporter interplay, it could be speculated that GFJ may have blocked the efflux transport leading to a greater absorption of verapamil in spite of blocking its gut metabolism.</td>
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<td>Benmabarek et al. (2004) [29]</td>
<td>Methadone</td>
<td>To assess the steady state PK of methadone enantiomers with co-administered GFJ? Whether a correlation could be obtained between variabilities of PK of methadone and measured CYP3A4 activities?</td>
<td>N=8; since the patients were on continuous methadone therapy, individual doses were different. Prior to the study, the unchanged patients’ methadone dose for 2 weeks was kept as the study dose. Study dose range was 63 to 150 mg/d. Treatment 1: Lasted for 2 weeks. Days 1-4, patients got GFJ daily (200 mL) 30 min prior to methadone. On day 5, patients were treated with twice the amount of GFJ (2 X 200 mL), followed by methadone dose. From day 5 till end of 2 weeks, they were on methadone dose. Treatment 2: Lasted for 2 weeks. Days 1-4, patients got control administration (water – 200 mL) 30 min prior to methadone. On day 5, patients were given a control (water – 2 X 200 mL) treatment, followed by methadone dose. From day 5 till end of 2 weeks, they were on methadone dose.</td>
<td>1) The GFJ intake caused a modest increase in the relative BA of methadone enantiomers. 2) The methadone enantiomers showed slight stereoselectivity favoring R-methadone as compared to S-methadone; however, GFJ did not alter the observed stereoselective disposition of methadone and it increased the relative BA of both enantiomers to a similar extent; 3) Based on the overlapping of midazolam data along with methadone data with GFJ to draw inference on CYP3A4, it was found that patients had increased CYP3A4 expression level showed a higher change in the relative BA of methadone</td>
<td>1) As oral bioavailability of methadone is relatively high, it was not expected that GFJ will have a large impact in boosting the bioavailability of methadone. Hence a marginal increase of 17-20% was observed in the study in presence of GFJ; 2) The possible contribution of GFJ on Pgp efflux mechanism was not evaluated, it is unlikely if methadone PK was altered as a result of Pgp transporter in this study.</td>
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<td>Uno et al. (2006) [30]</td>
<td>Manidipine</td>
<td>Qualitative and quantitative determination of GFJ interaction with manidipine enantiomers</td>
<td>N=7; 2-way randomized, 2-treatment crossover study with a washout interval lasting at least 2 weeks between treatment phases. Treatment 1: 40 mg manidipine- single glass 250 mL GFJ Treatment 2: 40 mg manidipine- single glass 250 mL water</td>
<td>1) Administration of GFJ produced increased relative BA of both manidipine enantiomers relative to control; 2) Stereoselectivity was evident in the interaction with GFJ – more profound change in exposure was noted for R-manidipine (approximately 3.4 fold) as compared to S-manidipine (about 2.4 fold); 3) other parameters such as time to peak concentration or elimination half-life were unchanged between the two treatments and also, were not stereoselective</td>
<td>1) Confirmation that GFJ can stereoselectively inhibit the metabolism of R-manidipine more than that of S-manidipine; 2) since manidipine is not a substrate for Pgp transporter, the explanation for the observed effect was attributed to the inhibition of the pre-systemic CYP3A4 enzyme; 3) Because the pharmacological activity resides in S-manidipine, the observed interaction of GFJ with R-manidipine should have no clinical bearing.</td>
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5. DISCUSSION

The various mechanisms purported to be involved in the interaction of scores of drugs with GFJ has been understood. As represented in Figure 1, multiple mechanisms (enzymatic/non-enzymatic) may come into play depending on the experimental conditions and/or the intrinsic attributes of the drug(s) involved. Some perspectives are provided in this section to address challenges encountered in the interpretation of the DDI data.

5.1. Transporter Related Activity – Understanding and Solving the Complexity

Number of studies has indicated that there is a tendency for GFJ to also inhibit the transporters that are responsible for efflux mechanisms. For instance, Dahan and Amidon have reported that GFJ and its important constituents such as naringin, naringinin, and 6’-7’-dihydroxybergamottin are responsible for an increased absorption of colchicines [7]. While 10% GFJ caused a substantial increase in the intestinal rat in-situ permeability and also increased jejunal permeability, the other ingredients of GFJ caused concentration dependent alterations in the inhibition of the efflux transporter responsible for colchicines transport from basal to apical surface [8]. Previously, Wang et al. have shown that components of GFJ caused a dose dependent inhibition of the Pgp transport of a test substrate [35]. Also, it was observed that the transporter inhibition effect of GFJ was as powerful as that of CYP3A4 inactivation and was reported that the concentration required for both interactions (i.e., CYP3A4 inactivation and Pgp blockade) was similar [35]. Although, reports have not appeared that substantiate the effect of GFJ in the inhibition of transporters, indirect evidence suggested that GFJ may have the propensity to mediate such interactions. For instance, GFJ caused modest changes in the exposure of digoxin (approximately 9% increase as compared to control group) in a clinical study [36]. Since digoxin is a relevant substrate for Pgp efflux mechanism, lack of effect of GFJ was considered to signify modest or no role of GFJ to cause clinically significant drug-drug interaction via this route [36]. Perhaps, as a result of CYP3A4 inhibition taking precedence, the effect on transporter, if any, may not appear noticeable. Although stereoselective aspects of racemates have not been delineated via a transporter related clinical DDI study with GFJ, it may be important to consider a situation for fexofenadine. Recently, Akamine et al. have reported the influence of drug transporter (with respect to OATP, Pgp and MRP2) polymorphisms on the pharmacokinetic disposition of fexofenadine enantiomers in a clinical pharmacokinetic study [37]. Interestingly, the study suggested that multiple transporters may be involved in tangent to determine the pharmacokinetic disposition of fexofenadine.

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<td>Fuhr et al. (2002)[31]</td>
<td>Verapamil</td>
<td>Assessment on the effects of GFJ on steady state PK of verapamil enantiomers. To understand effect of smoking on the PK of verapamil. To establish/postulate a relationship between GFJ and its active ingredient (naringenin).</td>
<td>N=24 (12 non-smokers and 12 smokers); an open-label, randomized 2-way crossover with two treatments. No washout period was provided in the study. Treatment 1: A prolonged release 120 mg verapamil was administered twice daily for 7 days. On days 5-7, GFJ (250 mL) was given 4 times daily. Treatment 2: A prolonged release 120 mg verapamil was administered twice daily for 7 days. On days 5-7, water (250 mL) was given 4 times daily. Steady state PK of verapamil was gathered on day 7 for both treatments.</td>
<td>1) A substantial increase in the exposure was observed after GFJ intake in both steady state verapamil and norverapamil plasma levels; 2) Smoking led to a significant exposure loss for both verapamil and norverapamil in both control and GFJ groups.</td>
<td>1) While increase in the exposure of steady state verapamil occurred with GFJ – appeared stereoselectivity was not compromised as a result of GFJ co-administration. 2) Increase in norverapamil exposure in presence of GFJ was speculated due to blockade of CYP3A4 which may have further contributed to the metabolism of norverapamil; 3) higher change in relative bioavailability of verapamil was attributed to a significant higher quantity of GFJ used in the study as compared to a previous study reported by Ho et al. (2000); 4) the effect of smoking on increased metabolism of both verapamil and norverapamil may have clinical relevance and was in accordance with an increased activity of CYP1A2 in smokers.</td>
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### Table 1. Continued.
Grapefruit Juice – Mechanisms for DDI

**Oral Ingestion**
- Altered pH
- Physical incompatibility

**GI Tract**
- CYP3A4 inhibition (Time / Dose dependent)
- Transporters blockade – Efflux and Uptake
- Induction of Pgp – in vitro
- Inhibition of esterases

**Intestine**
- Potential for stereo-selective CYP inhibition
- Blockade of transporters

**Liver**

Figure 1: Different mechanisms in the purported DDI of a substrate with co-ingested grapefruit juice.

enantiomers [37]. In another clinical study, Sakugawa et al. have confirmed that verapamil effectively alters the pharmacokinetic disposition of fexofenadine in a stereoselective manner [38]. The co-administration of verapamil impacted the overall exposure of both enantiomers of fexofenadine; however, it selectively increased the exposure of S-fexofenadine rather than R-fexofenadine [38]. Similar findings have been reported for fexofenadine enantiomers when itraconazole (a dual Pgp and CYP3A4 inhibitor) was co-administered with fexofenadine in a well conducted clinical study [39]. In this study, the fold increase of both enantiomers of fexofenadine and observed stereoselectivity (S-fexofenadine > R-fexofenadine) after itraconazole co-administration was relatively higher [39] as compared to a previous study that involved verapamil as a Pgp inhibitor [38]. In this context, GFJ has been shown to decrease the exposure of fexofenadine to a clinically relevant significance in two separate clinical studies [40, 41]. Unlike the interaction between verapamil and fexofenadine where Pgp efflux transporter was involved, the interaction between GFJ and fexofenadine was suggestive of the inhibition/blockade of uptake transporters such as OATP, which has been documented to occur for several compounds when co-administered with GFJ [15]. Hence, it will be interesting to delineate if GFJ has the potential to alter the pharmacokinetics of fexofenadine in a stereoselective manner or any other drug racemate whose pharmacokinetics is governed by multiple drug transporters. Such studies would provide a basis to confirm stereoselective contribution, if any, by GFJ on the transport of racemic substrates. However, one needs to be cautious in data interpretation of such interaction study as multiple mechanisms may be involved. For instance, Lilja et al. have reported that itraconazole and GFJ produced different effects on the plasma concentrations of celiprolol in a clinical study [42]. It was postulated that celiprolol was a substrate for transporter and hence co-administration of itraconazole and GFJ effectively blocked the Pgp efflux mechanism which in turn lead to an increased plasma concentrations of celiprolol [42]. On the contrary,
although GFJ can potentially inhibit the transporter(s), it did not result in increased celiprolol concentrations upon co-administration – it resulted in a decreased exposure of celiprolol [42]. In order to explain these discrepant results, it was postulated that there was a possible interference in the absorption of celiprolol with GFJ and/or physical incompatibility of celiprolol in presence of GFJ [42]. Furthermore, it was shown that a greater inhibition of the absorption of celiprolol also occurred when co-administered with orange juice confirming the interaction with GFJ may be mediated by intestinal pH and/or physical incompatibility [43]. To unequivocally support these observations, recently, it was shown that celiprolol’s disposition was governed by both influx and efflux transporters [44]. Another example of dilemma in data interpretation is presented by talinolol, a known substrate for Pgp efflux transporter [45]. The decreased exposure of talinolol in the presence of GFJ suggested the possible involvement of other mechanism via blockade of OATP or other uptake transporter [45].

5.2. Applicability of Preclinical DDI Findings to Humans

Extrapolation of data from preclinical species to humans should factor the likely species differences in both stereoselective metabolism via Cytochrome P450 isoenzymes as well as on the transporters for both tissue uptake and excretion. While stereoselective metabolism was largely attributed to CYPs such as CYP2D6, CYP2C9, CYP219 but not to CYP3A4, a recent publication noted that CYP3A4 may also be involved in stereoselective biotransformations [46]. The conversion of the thioether metabolite of rabeprazole back to the parent moiety rabeprazole involving CYP3A4 isozyme, has been shown to be stereoselective favoring the formation of the S-rabeprazole [46]. Hence scrutiny of the drug disposition data needs to be considered with respect to both CYP3A4 expression/levels and the applicable transporters [46]. Shirasaka et al. have shown extensive differences between humans and rats for certain transporters such as OATP/Oatp and /MDR1/Mdr1 [47]. Hence, caution needs to be exercised for not only inter-species data interpretation but also for subsequent dose projections.

5.3. DDI as a Potential Surrogate to Assess Extent of Intestinal Availability of Oral Drugs: Potential Pitfalls for Racemate Drugs

Gertz et al. have explored the applicability of GFJ to estimate intestinal bioavailability in lieu of the traditional approach of oral and intravenous administration of the agent [48]. In this interesting work, it was reported that drugs that are substrates for uptake transporters/efflux pumps are prone to provide erroneous estimates and higher variability in presence of grapefruit juice [48]. In contrast, if drugs were predominantly metabolized in the gut without any involvement of transporters/efflux pumps, the estimates were predicted closer to the oral/intravenous approach [48].

In the above context, if racemic drugs undergo stereoselective disposition, it may pose challenges in the application of the above concept if GFJ additionally can modify the ‘native’ pharmacokinetic differences between the two enantiomers. If GFJ does not influence the stereoselectivity and the ‘native’ enantiomeric ratios are preserved, it is likely that this concept may work for racemic drugs for the estimation of oral bioavailability.

5.4. Formulation/Dose Modifications to Avoid DDI with GFJ - Considerations

It is possible to avoid drug absorption in the upper intestine when the drug is co-ingested with GFJ. However, it requires two important considerations: a) formulation manipulation from immediate release to delayed release to avoid drug dissolution in the upper GI tract; b) intrinsic property of the drug to show absorption from other regions of intestine especially lower intestine and colon. Although not many case studies have been reported on the aspect of formulation modifications to avoid potential DDI with GFJ, the reported data on budesonide are not very encouraging [49]. In an elegant clinical study, repeated daily ingestion of 3 glasses of GFJ for 4 consecutive days was shown to affect the pharmacokinetics of budesonide orally ingested on the fourth day with regard to immediate release or delayed release formulation [49]. In both instances, the interaction with GFJ resulted in doubling of the exposure of budesonide [49]. Although the design of delayed release budesonide considered drug absorption to occur at ileum region and/or proximal colon region where the activities of gut enzymes are low as compared to upper small intestine, it did not appear to translate under in vivo conditions as evidenced by the data [49]. In a previous work, with the use of ketoconazole as a probe, it was demonstrated that local administration of budesonide in humans was most affected in upper small intestine as compared to lower small intestine/proximal colon and therefore, it appeared that
delayed-release formulation may have released the drug faster than anticipated [50].

5.5. Challenges of DDI Study in Patients on Chronic Medication with Substrate(s) that can Modulate CYP3A4/Transporter - a Dilemma

The DDI case study of methadone - GFJ (Table 1) was somewhat complicated when compared to others as it involved the patient population that need to be on continuous methadone therapy for the management of opioid dependency [29]. In this particular study, almost 50% of the patients were on other co-medications. While a number of these co-medications were not expected to impact with the planned DDI assessment of methadone with GFJ, still it represented a tricky situation since any one of them or its metabolite(s) had the potential to interfere in an unsuspected manner with the known mechanisms of GFJ (interference with intestinal/ hepatic metabolism and/or Pgp efflux/Uptake transporters). The inclusion of midazolam probe was an important consideration in this study design to pin point the likely area of DDI as midazolam oxidative pathway is a well-established route to confirm CYP3A4 activity [29]. In spite of such heterogeneity, it was indeed intriguing that the study results provided useful data on the stereoselective methadone pharmacokinetics in the intended patient population [29]. The authors also speculated if methadone itself had an opportunity to induce CYP3A4 based on other literature evidence [51] and thereby may have produced an imbalance given the fact that the daily maintenance doses were different among the patients. It need to be emphasized that in spite of performing DDI study under less than ideal conditions the study provided data that could be correlated with other studies which did not pose such a challenge in terms of its conduct [29].

In some instances, the substrate itself may have a tendency to be a moderate/potent inhibitor of CYP3A4 and/or Pgp transporter such as verapamil. Hence, on repeated doses with such substrate(s) if one attempts a DDI study with GFJ, it may make it difficult to interpret the study findings as to which was the most pronounced perpetrator (GFJ versus the substrate). Therefore, it is important that study design, planning and execution phases consider all of the possible overlapping mechanisms, interferences and/or confounding factors to ensure that data interpretation is made without any bias.

6. CONCLUSIONS

On the basis of evaluation of pharmacokinetics of published racemic substrates the DDI caused by GFJ does not appear to overwhelmingly affect the stereoselectivity in the disposition. In some instances the impact was mild to moderate and it merely augmented the stereoselectivity observed for drug alone treatment (i.e., naturally observed distorted R/S ratio was further increased). However, since reported studies in the literature have been done under varied experimental conditions pertaining to the size and duration of GFJ, one may need to be cautious of the interpretation of the data. Hence, in some instances of aggressive GFJ intake, the substantial increase in the exposure of eutomer with GFJ may change the therapeutic index and may warrant close patient monitoring if deemed necessary. Since drug development paradigm has now shifted and development of racemic drugs has been now replaced by a single enantiomer, this would not represent a major hurdle in drug development. However, there are a number of previously approved racemic drugs generically available where distinction of eutomer/distomer still exists and eudismic ratio plays a role in the respective therapeutic index. Therefore, aggressive GFJ intake while taking certain racemic drugs especially the ones deemed problematic for a potential DDI should be avoided. Interestingly, the recent finding that GFJ has the potential to inhibit gut esterases [52] opens up another venue for DDI with racemic drugs that are ester derivatives most notably methylphenidate, esmolol, oxazepam, propranolol/ ibuprofen/flurbiprofen prodrug derivatives [53-58].

The interpretation of DDI data with GFJ regardless of type of substrate (chiral or achiral) needs to be made with caution especially if the disposition of drug or drug class has been shown to be governed by both CYP3A4 and transporters. As evident by literature examples, since the transporters may participate either in uptake or efflux phenomenon, the GFJ effect can go either way. To underscore this view, the recent report of Lu et al. unequivocally demonstrated stereoselective differences in the CYP inhibition properties of naringenin, the active component of GFJ – it was noted that the inhibition of CYP2C19 was 2-fold greater with (S)-naringenin as compared to (R)-naringenin, whereas the potency for (R)-naringenin was 2-fold greater for the inhibition of CYP2C9 and CYP3A as compared to (S)-naringenin [59]. Also, other mechanisms such as change in local pH environment, physical incompatibility of the drug with GFJ and/or subtle
changes in gastric emptying/gastric motility may also influence the drug absorption when co-administered with GFJ. More importantly, extrapolation of either in vitro results or preclinical findings to humans involving GFJ interactions may sometimes be flawed and discretion needs to be exercised in making drug development decisions.

CONFLICTS OF INTEREST

Author has no conflicts of interest to report.

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Review of Grapefruit Juice Mediated Drug-Drug Interactions


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