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Pharmacogenetics of Drug-Drug Interaction (DDI) and Drug-Drug-Gene-Interaction (DDGI): a Systematic Review on CYP2C9, CYP2C19, and CYP2D6

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Acknowledgements

Muh. Akbar Bahar and Didik Setiawan obtained a DIKTI scholarship from the Ministry of Research, Technology and Higher Education of Indonesia. We thanked Karin I. Sijtsma from Centrale Medische Bibliotheek, Universitair Medisch Centrum Groningen (UMCG), for her assistance in building the search strategy used in this review.

ABSTRACT

Currently, most guidelines on drug-drug interaction (DDI) neither consider the potential effect of genetic polymorphism in the strength of the interaction nor do they account for the complex interaction caused by the combination of DDI and drug-gene-interaction (DGI) where there are multiple biotransformation pathways, which is referred to as drug-drug-gene-interaction (DDGI). In this systematic review we report the impact of pharmacogenetics on DDI and DDGI in which three major drug-metabolizing enzymes - CYP2C9, CYP2C19, and CYP2D6 - are central. We observed that several DDI and DDGI are highly gene-dependent, leading to a different magnitude of interaction. Precision drug therapy should take pharmacogenetics into account when drug interactions in clinical practice are expected.

Keywords :

Drug-Drug Interaction (DDI); Drug-Drug-Gene-Interaction (DDGI); Drug-metabolizing enzyme; CYP2C9; CYP2C19; CYP2D6

Background

Drug-Drug Interactions (DDIs) are a leading cause of adverse drug reactions which frequently require hospitalization[1,2]. DDIs occur when the effect of a drug is modified pharmacokinetically or pharmacodynamically by a co-administered drug[3]. With respect to the metabolic interactions, drugs which affect cytochrome P450 (CYP450) isoenzymes are commonly involved and prevalent in clinical practice[4-7]. Importantly, CYP450 isoenzymes are subject to genetic polymorphism[8]. Therefore, since the functionality of CYP450 isoenzymes is crucial to the impact of DDIs, polymorphism can affect their magnitude[9,10].

The pharmacogenetic impact on the interaction between drug and CYP450 isoenzymes (drug-gene interaction) has been incorporated in some guidelines[11-13]. However, these guidelines do not consider any change in the magnitude of the drug-gene interaction (DGI) for different CYP450 isoenzyme genotypes after co-administration of a drug affecting those isoenzymes. Therefore, this interplay is rarely considered in clinical practice, and systematic evidence about such important pharmacogenetic effects on DDIs is lacking.

Furthermore, an even more complicated interaction can develop in drugs metabolized by several CYP450 isoenzymes[14]. There will be a marked alteration in the pharmacokinetics of the drugs if all of their metabolic pathways are blocked by CYP450 isoenzyme inhibitors[15-18]. Polymorphism also plays a role in the metabolism of drugs with multiple metabolic pathways[19]. The genetic polymorphism in their major metabolic pathway and the inhibition of their minor metabolic pathway could result in a significant change to their plasma concentration. This overlapping of DDI and DGI conditions is referred to as drug-drug-gene-interaction (DDGI)[20]. In a retrospective analysis of 1143 genotyped patients in the US, DDGIs were reported to occur in about 19%. DDIs and DGIs accounted for 66% and 15%, respectively[20]. An updated cross-sectional study from the US involving 22,885 patients found that there were about 6,900 drug interactions in which DDGIs, DGIs, and DDIs accounted for 22%, 25%, and 53%, respectively[21]. The complexity of DDGIs results in a greater variability in drug level than DDI and DGI. To the best of our knowledge, no systematic review has compiled all the relevant studies regarding the effect of pharmacogenetics of DDGIs involving CYP450 isoenzymes.

To prevent CYP450-mediated drug interactions, a computerized surveillance tool is incorporated in the majority of health record systems[22]. Since pharmacogenetics testing is not yet part of routine clinical testing, the effect of genetic variations in DDI and DDGI have not been considered in such surveillance system[23,24]. Therefore, the aim of this review is to describe the impact of pharmacogenetics on DDIs and DDGIs involving three major drug-metabolizing enzymes -CYP2C9,

CYP2C19, and CYP2D6. The results may further support the improvement of the quality of computerized surveillance systems and enhance precision drug therapy.

Method

The systematic review was structured according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[25] (www.bmj.com). (www.bmj.com) Studies published before November 2015 from the Pubmed and Embase databases were reviewed systematically. Keyword combinations such as CYP2D6, CYP2C19, CYP2C9, substrate, inhibitor, inducer, drug interaction and polymorphism (extensive metabolizer, intermediate metabolizer, poor metabolizer, and ultra-rapid metabolizer) were used as search terms (for the complete search strategy, see Supplement 1). Clinical, observational or case studies involving CYP2D6/CYP2C9/CYP2C19 mediated drug interaction published in English in the peer-reviewed literature were eligible. The DDI group included articles comparing the effect of DDIs in different genotypes and/or phenotypes. The DDGI group consisted of articles presenting data about DDIs mediated at least by two enzymes, one of which (CYP2D6/CYP2C19/CYP2C9) had a deviating genotype and/or phenotype, while the activity of another enzyme was influenced by an effector drug. We also performed a reference tracking process to include eligible studies which were not retrieved in our systematic search.

Data Abstraction

The extracted papers were screened by two independent reviewers (MAB and DS) based on the eligibility criteria. Conflicting results were discussed by MAB and DS. A third reviewer (BW) was involved if no consensus was reached. The review process was performed by screening the title and abstract. The results were then evaluated by full-text screening. The relevant information such as pharmacokinetics and/or pharmacodynamics data; study type; name, drug type and dose; number and type of patients; and genotype and/or phenotype data were collected. The strength of the evidence (0 to 4) was also evaluated independently by MAB and DS using the previously published criteria by Van Roon et al. and Swen et al. (Supplement 1)[11,24]. The differences in the scoring of evidence level were resolved by consensus involving BW. The clinical impact of interactions was estimated based on changes in pharmacokinetic values using the criteria provided by Verbeurgt et al. and Polasek et al. (Supplement 1)[4,20]. The availability of the pharmacodynamics data could change the categorization of the interaction. If the substrate had a narrow therapeutic index, the level of the interactions was upgraded to a level above their categories based on their pharmacokinetic value assessments[20]. The categorization of the interaction was structured based on its impact and whether an action should be taken to manage it as suggested by Van Roon et al.: Interaction:

Yes/Action: Yes, Interaction: Yes/Action: No and Interaction: No/Action: No[24]. If there was at least one genotype with a major (contraindicated interaction) or substantial (needing monitoring or dose adjustment) interaction, we categorized it as Interaction: Yes/Action: Yes. If the maximum clinical impact of the interactions in the genotype subset was moderate (possible interaction/no action required), we categorized it as Interaction: Yes/Action: No. Lastly, if the genotype subset only had a minimal (not clinically significant) interaction, we categorized it as Interaction: No/Action: No. Some aspects should be considered in this clinical assessment. Firstly, using data from one study with only few patients or healthy volunteers constrained offering a comprehensive judgement about the clinical interpretation of interactions. Secondly, some interactions were between effector drugs and probe substrates, therefore, the assessment could be viewed as an estimate of the potency of effector drugs as inhibitors or inducers.

Included articles

The scheme of the review was illustrated in a PRISMA chart (Figure 1). The search strategy retrieved 2,428 articles from Pubmed and 3,587 articles from Embase, and 1,907 duplicates were found. After title and abstract screening, 243 of 4,108 articles were included for full paper screening. After removing the irrelevant articles (144 articles) and adding eligible articles from the reference tracking (6 articles), 66 and 39 articles reporting evidence for DDIs and DDGIs, respectively, were chosen for data abstraction. The main reasons for exclusion included: only reporting on DGI, no genotype comparisons, no interaction and that the interactions between genotypes were hardly differentiated.

Genotype data

The genotypes were grouped with the phenotypes based on the 'Royal Dutch Association for the Advancement of Pharmacy' (KNMP) categorization and adjusted in concordance to the standardized terms provided by the Clinical Pharmacogenetics Implementation Consortium i.e. Normal Metabolizer (NM), Intermediate Metabolizer (IM), Poor Metabolizer (PM), Rapid Metabolizer (RM) and Ultrarapid Metabolizer (UM)[26,27]. NM of CYP2C9 included CYP2C9*1/*1. IM of CYP2C9 included CYP2C9*1/*2; CYP2C9*1/*3. PM of CYP2C9 included CYP2C9*2/*2; CYP2C9*2/*3; CYP2C9*3/*3. NM of CYP2C19 included CYP2C19*1/*1. IM of CYP2C19 included CYP2C19*1/*2; CYP2C19*1/*3. PM of CYP2C19 included CYP2C19*2/*2; CYP2C19*2/*3; CYP2C19*3/*3. RM of CYP2C19 included CYP2C19*1/*17. UM of CYP2C19 included CYP2C19*17/*17. NM of CYP2D6 included CYP2D6*1/*1; CYP2D6*1/*2; CYP2D6*2/*2; CYP2D6*1/*10; CYP2D6*1/*41; CYP2D6*2/*10; CYP2D6*2/*41. IM of CYP2D6 included CYP2D6*1/*3; CYP2D6*1/*4; CYP2D6*1/*5; CYP2D6*1/*6; CYP2D6*1/*21; CYP2D6*2/*3; CYP2D6*2/*4; CYP2D6*2/*5; CYP2D6*10/*41; CYP2D6*10/*10; CYP2D6*3/*41; CYP2D6*4/*41; CYP2D6*5/*10; CYP2D6*6/*10; CYP2D6*6/*41;

CYP2D6*10/*21; CYP2D6*10/*30. PM of CYP2D6 included CYP2D6*3/*4; CYP2D6*4/*4; CYP2D6*4/*5; CYP2D6*4/*6; CYP2D6*5/*5; CYP2D6*5/*16; CYP2D6*7/*7. (open.library.ubc.ca) UM of CYP2D6 included CYP2D6*1/*1xN; CYP2D6*1/*2xN; CYP2D6*1/*4xN; CYP2D6*1/*41xN; CYP2D6*2/*2xN.

Pharmacogenetics of Drug-Drug Interaction (DDI)

CYP2C9

Interaction: Yes/Action: Yes

There were five scenarios of CYP2C9 mediated DDI producing clinically significant interactions (Table 1). First, co-administration of CYP2C9 substrates in patients with CYP2C9 variant alleles produced a competitive inhibition, as shown for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and coumarin interactions. Since both of them are CYP2C9 substrates, NSAIDs appeared to further decrease coumarin metabolism in patients with decreased CYP2C9 activities. Therefore, NSAIDs elevated the risk of over-anticoagulation in coumarin-treated CYP2C9*1/*2 and CYP2C9*1/*3 patients[28,29].

Second, a CYP2C9*3 selective inhibition aggravated the metabolic interference due to genetic polymorphism as presented in warfarin and simvastatin interaction. Warfarin was less metabolized by CYP2C9*3, and simvastatin specifically inhibiting CYP2C9*3 by simvastatin caused an even larger impairment of warfarin metabolism. Consequently, patients with CYP2C9*3 needed a higher dose reduction of warfarin compared to non-carriers[30]. It was also reported that CYP2C9*2 played no role in this interaction.

Third, the magnitude of interaction depended on the CYP2C9 activity as observed in fluconazole and flurbiprofen interactions[31]. Fluconazole inhibited flurbiprofen metabolism more profoundly in normal metabolizers (NMs) and intermediate metabolizers (IMs) than in poor metabolizers (PMs) of CYP2C9. The increase of the dose of fluconazole from 200 mg to 400 mg enhanced its inhibitory capacity, indicated by a twofold increase of the AUC (Area Under Curve) value in NMs and IMs but not in PMs. The reduced function of CYP2C9*3 caused insusceptibility towards the inhibition in PMs. However, there was still an inhibition of fluconazole in PMs because fluconazole (at a dose ≥200 mg) may inhibit the remaining metabolic pathways of flurbiprofen (CYP3A4/2C19)[32].

Fourth, the capacity of a CYP2C9 inhibitor, which was also a substrate of the enzyme, to impair the metabolism of a CYP2C9 substrate was correlated with its plasma concentration in different genotypes. It was considered in valproic acid and losartan interaction[33]. Patients with CYP2C9*3 had a higher plasma concentration of valproic acid compared to those with other genotypes.

Consequently, valproic acid produced a greater magnitude of inhibition in losartan metabolism in this group.

Fifth, the greatest increase in CYP2C9 activity after administration of an inducer was in CYP2C9*3/*3 as demonstrated in rifampicin and tolbutamide combinations[34]. There was a six-fold difference in the baseline activity of CYP2C9*1/*1 and CYP2C9*3/*3 in metabolizing tolbutamide. It, therefore, seems that the greater the CYP2C9 activity, the smaller the induction magnitude produced by rifampicin. The underlying mechanism of this negative correlation should be investigated further. Additionally, rifampicin showed a comparable induction capacity to other genotypes. This could be due to the involvement of the P-glycoprotein (P-gp) transport system, since rifampicin is an inducer of this transporter. But there was no evidence for this speculation reported in the study.

Interaction: Yes/Action: No

The only study in this group was a gene-dependent interaction between phenytoin and losartan[35]. Phenytoin moderately inhibited losartan metabolism in CYP2C9*1/*1 but not in CYP2C9*1/*2. However, this result was hardly justified since there were only two CYP2C9*1/*2 subjects in the study.

CYP2C19

Interaction: Yes/Action: Yes

CYP2C19-mediated DDIs engage a different magnitude of interaction in different genotypes as demonstrated by various interaction scenarios (Table 1). The first scenario was a competitive inhibition between two CYP2C19 substrates due to segregation of a metabolic pathway in normal but not in slow CYP2C19 metabolizers. Polymorphism in the IMs and PMs diminished the metabolic function of CYP2C19. Competitive binding to this isoenzyme was thus hardly emerged. It was observed in the combination of Proton Pump Inhibitors (PPIs) and clopidogrel. Omeprazole and rabeprazole, but not lansoprazole, (link.springer.com) significantly affected clopidogrel efficacy in NMs but not in IMs and PMs[36,37]. Lansoprazole did not have a comparable gene-dependent interaction because it has a lower affinity to CYP2C19 compared to omeprazole. Therefore, it produced a lesser inhibitory potency to clopidogrel bioconversion. Interestingly, rabeprazole, which also has a low affinity to CYP2C19, had a comparable potency as omeprazole. This could be because rabeprazole was metabolized by CYP2C19 along with its non-enzymatic metabolite, rabeprazole thioether, rabeprazole thus generated a stronger competitive inhibition than lansoprazole to clopidogrel[37].

Further, PPIs attenuated the clopidogrel effect more profoundly in CYP2C19*17 than CYP2C19*2, and CYP2C19*1 homozygotes carriers[38]. Since CYP2C19*17 is related to the increased activity, it appeared that the larger contribution of CYP2C19 in the bio-conversion of clopidogrel, the bigger alteration was produced by PPIs.

A competitive inhibitory mechanism was also found in the PPI-warfarin interaction. Patients with CYP2C19 IM using lansoprazole and warfarin concomitantly had a greater incidence of haemorrhagic complications than NMs and PMs[39]. The combination of polymorphism and inhibition by lansoprazole yielded a reduction of warfarin metabolism causing an increased risk of bleeding. In addition, Uno et al. reported that omeprazole inhibited R-warfarin metabolism, but not S-warfarin (CYP2C9 substrate) metabolism, only in NMs[40]. Therefore, CYP2C19 is one of the factors determining the effectiveness of warfarin.

The second scenario was phenoconversion of the CYP2C19 NM genotype to the PM phenotype as presented by ticlopidine and omeprazole interaction[42]. Ticlopidine strongly inhibited omeprazole metabolism in NMs and IMs producing pharmacokinetic values to the level of PMs (Supplement 3). However, PMs were not affected. The gene-dependent interaction was also shown by moclobemide and omeprazole, which produced a substantial interaction in NMs but not in PMs[43]. Moreover, CYP2C19 inhibition by moclobemide produced an increase of omeprazole sulphone concentration (omeprazole metabolite via CYP3A4) indicating the metabolic shifting of omeprazole from CYP2C19 to CYP3A4. The affinity of omeprazole to CYP2C19 is ten times greater than to CYP3A4[14]. The latter contributes 13 to 22% to omeprazole metabolism[44]. However, when CYP2C19 is inhibited, CYP3A4 will have a greater metabolic contribution.

The third scenario was an inhibitor and substrate of multi CYP450 isoenzyme interaction as illustrated by fluvoxamine (CYP2C9/2C8/1A2/2C19/3A4 inhibitor) and PPIs combination[14,41,45-47]. The highest influence of fluvoxamine on PPIs metabolism was observed in NMs, followed by IMs and then PMs. Omeprazole and lansoprazole produced a greater magnitude of interactions with fluvoxamine than rabeprazole for all genotypes, because rabeprazole only involves CYP2C19 in its metabolism while omeprazole and lansoprazole involve CYP2C19/3A4. Fluvoxamine thus had a greater impact on omeprazole and lansoprazole than rabeprazole since their bimodal metabolic pathways were affected. It seems that if the effector drug can inhibit several of the CYP isoenzymes responsible for drug metabolism, it will produce a greater magnitude interaction[14].

The fourth scenario was that CYP2C19 inhibition involved NMs predominantly, but with less pronounced CYP2C19 isoenzymes with increased activities, as indicated by oral contraceptives (OC) and omeprazole interaction[48]. OC impaired the omeprazole metabolism by substantially increasing

the metabolic ratio (MR) of omeprazole/5-hydroxyomeprazole in CYP2C19*1/*1 but not in CYP2C19*1/*17 and CYP2C19*17/*17. It was speculated that CYP2C19*17 offered protection against the inhibitory effect of OC[48].

The fifth scenario was that a CYP2C19 inhibitor did not interact with the parent compound of a drug but with its metabolite. It was demonstrated by the interaction between sulthiame and an active metabolite of clobazam (mainly by CYP3A4), N-desmethyl-clobazam (DMCLB)[49]. DMCLB was metabolized by CYP2C19, and co-administration of sulthiame enhanced the concentration/dose (C/D) ratio of DMCLB substantially in NMs and IMs. Although the anti-seizure effect of DMCLB was less than clobazam, the significant increase of its concentration after sulthiame administration, may increase its efficacy as well as its side-effects[49].

The last scenario was the interaction of a CYP2C19 inducer and substrate as observed in rifampicin and mephenytoin combination[50]. The largest increase of 4-hydroxymephenytoin excretion, a product of mephenytoin hydroxylation by CYP2C19, was in NMs. However, rifampicin produced comparable induction in IMs and PMs, probably because of non-CYP2C19 hydroxylase induction[50].

Interaction: Yes/Action: No

The first scenario was a competitive inhibition between two CYP2C19 substrates as presented by clopidogrel and omeprazole interaction[51]. In this interaction, clopidogrel became an inhibitor distinct from the previously explained major interaction where clopidogrel acted as a substrate. Clopidogrel moderately inhibited omeprazole metabolism in NMs but not in PMs. There was an increase of omeprazole sulfone concentration in NMs after clopidogrel treatment indicating the CYP3A4 buffer mechanism. However, after clopidogrel co-administration, the amount of omeprazole sulfone remained at the same level meaning that clopidogrel did not inhibit CYP3A4.

Comparable cases were observed when the inhibitory effect of omeprazole was examined against moclobemide and diazepam. Omeprazole competitively inhibited the metabolism of moclobemide via CYP2C19 and diazepam via CYP2C19/3A4 to produce moderate impact in NMs but not in PMs[52-54]. Diazepam is also metabolized by CYP2B6. The CYP2C19/3A4 inhibition may shift diazepam metabolism to CYP2B6[14]. Consequently, the interaction only produced a moderate impact since diazepam still had a metabolic pathway remaining. The final scenario was the gene-dependent interaction between a CYP2C19 inhibitor and a substrate as observed in fluvoxamine and chloroguanide combination[55]. Fluvoxamine moderately inhibited the biotransformation of chloroguanide to cycloguanil and 4-chlorphenylbiguanide in NMs, and minimally in PMs.

CYP2D6

Interaction: Yes/Action: Yes

CYP2D6 with polymorphism are perturbed to different DDI magnitudes than with normal metabolic activity, as implied in several interaction scenarios (Table 1). First, the interaction between CYP2D6 inhibitors and substrates only involved patients with functional CYP2D6, as presented in dextromethorphan and CYP2D6 inhibitors (terbinafine, perhexiline, and quinidine) interactions (Figure 2)[56-59]. CYP2D6 inhibitors increased the MR of dextromethorphan/dextrorphan significantly in NMs and IMs but not PMs, similarly to the effect of genetic impairment[56,58]. They phenoconverted NM and IM genotype to a PM phenotype at a higher rate in individuals with one functional allele compared to those with at least two functional alleles[57]. The gene-selective inhibition by quinidine was also found in combination with propafenone, venlafaxine, mexiletine, brofaromine, methoxyphenamine, encainide, procainamide, and flecainide[60-66,66-70]. Quinidine significantly changed the pharmacokinetic parameters of these substrates in NMs and IMs, but not in PMs. The pharmacodynamic parameters of this gene-dependent interaction showed comparable results. Quinidine abolished the differences between NMs and PMs in encainide-induced QRS and PR prolongation. The strong inhibitory potency of quinidine can be corroborated by its ability to inhibit the P-gp transporter[58].

Paroxetine and quetiapine also inhibit the CYP2D6 and P-gp transporter[14]. Paroxetine produced a significant inhibition of flecainide, desipramine, aripiprazole and R-methadone metabolism more profoundly in individuals with two active alleles than those with decreased or dysfunctional alleles[71-75]. Similarly, quetiapine gene-dependently affected the R-methadone metabolism[76]. These interactions generated pharmacodynamic effects in a comparable manner. Paroxetine significantly changed the QT interval of flecainide-treated NMs but not IMs[72]. However, amiodarone and flecainide interaction produced different results[77]. Amiodarone inhibited flecainide metabolism both in NMs and PMs. This could be because amiodarone was not a CYP2D6-specific inhibitor and might therefore, inhibit the other metabolic pathway of flecainide[77].

Other genetically determined DDIs were produced by metoprolol and some CYP2D6 inhibitors. Diphenhydramine and dronedarone impaired metoprolol metabolism greatly in NMs and IMs but not in PMs[78-80]. Therefore, they only significantly affected heart rate profile and systolic blood pressure of metoprolol-treated NMs and IMs[79-81]. Additionally, amiodarone and celecoxib in their interactions with metoprolol indicated that NMs are more profoundly affected by the DDIs than IMs[82,83]. Furthermore, diphenhydramine and other CP2D6 inhibitors, thioridazine and

propafenone, also respectively obstructed venlafaxine, mianserin and mexiletine metabolism to a greater extent in CYP2D6 with fully functional alleles than with reduced or dysfunctional alleles[84-86].

Second, the variability of pharmacokinetic values produced by CYP2D6 inhibition and polymorphism did not cause different clinical activities because the substrate and its metabolite had comparable clinical effects. The total concentration of active moiety compensated for the pronounced kinetic differences, as presented by fluoxetine and risperidone or tolterodine interactions[87,88]. Fluoxetine significantly inhibited risperidone metabolism in NMs and tolterodine metabolism both in NMs and IMs. The genetic polymorphism in PMs produced the same metabolic inhibition with minimal effect of fluoxetine. Nevertheless, despite the increased plasma concentration in NMs and PMs, their clinical effect seemed not to be influenced substantially. In the case of risperidone, the incidence of extrapyramidal symptoms was not augmented after fluoxetine co-administration since the 9-hydroxy metabolite of risperidone has a similar potency as risperidone. Interestingly, fluoxetine still impeded risperidone disposition in PMs moderately, probably by the effect of its metabolite (norfluoxetine), which altered the secondary metabolic pathway of risperidone (CYP3A4)[87].

A comparable effect was found in the quinidine and propafenone interaction. Quinidine did not alter the effects of propafenone in NMs, despite a significant decrease in its oral clearance, because the 5-hydroxy propafenone has a comparable QRS interval prolongation action to propafenone[63]. Further, Morike et al. reported that propafenone and 5-hydroxy propafenone were equipotent in blocking sodium channels but not in their beta-blockade effects. Quinidine thus significantly increased propafenone-induced beta blockade in NMs to the level of PMs[62]. Quinidine abolished the differences in the pharmacodynamic effects of propafenone between NMs and PMs. These cases showed that the counterbalance effect of the clinical activity of the main metabolite reduced the potential impact of kinetic variability caused by polymorphisms.

Third, CYP2D6 inhibitors impaired the bioconversion of prodrugs to a greater extent in individuals with two normal function alleles than one. This was shown by the interaction between CYP2D6 inhibitors (paroxetine, amiodarone, cimetidine, and ranitidine) and tramadol, and between levomepromazine and codein[89,90]. CYP2D6 inhibitors substantially decreased the production of the active metabolite of tramadol, (+)O-desmethyl tramadol (DMT), in Ultrarapid Metabolizers (UMs), NMs, and IMs. A greater reduction of (+)DMT concentration was found in NMs than IMs. This indicated that the more the active alleles, the greater the inhibition. However, the results in UMs did not support this thesis. This was probably because there were only two UMs involved in the study.

Additionally, the second interaction showed comparable results. Levomepromazine inhibited the O-demethylation of codeine from generating morphine significantly in NMs but not in IMs.

Interaction: Yes/Action: No

CYP2D6-mediated moderate DDIs were shown by gene-dependent interactions between imatinib or hydroxychloroquine with metoprolol, pazopanib or methadone with dextromethorphan and propafenone with lidocaine[91-95]. NMs were affected more profoundly than IMs and PMs. Therefore, these DDIs could produce clinically significant interactions in NMs, but this was less likely in IMs and PMs.

Pharmacogenetics of Drug-Drug-Gene Interaction (DDGI)

CYP2C9

Interaction: Yes/Action: Yes

CYP2C9-mediated DDGI was found in a CYP2C19 IM patient treated with cotrimoxazole (CYP2C9 inhibitor) and venlafaxine (Table 2)[96]. The latter was metabolized through multiple CYP450 isoenzymes, O-demethylation by CYP2D6 and N-demethylation by CYP2C9/2C19/3A4. There was thus a reduction of venlafaxine metabolism because of polymorphism in CYP2C19 and CYP2C9 inhibition. Consequently, the serum concentration of venlafaxine was elevated about 30%, leading to toxicity.

CYP2C19

Interaction: Yes/Action: Yes

The first scenario in CYP2C19-mediated DDGI was that polymorphism in CYP2C19 made the secondary metabolic enzyme compensate for metabolic failure. However, if an inhibitor further blunted this minor pathway, the substrate plasma concentration greatly increased (Figure 2). It was observed in the co-administration of itraconazole (CYP3A4 inhibitor) in CYP2C19 IM tacrolimus-(CYP2C19/3A4 substrate) treated patients[97]. The reduced capacity of CYP2C19 and CYP3A4 inhibition caused a 200% increase in tacrolimus exposure. Tacrolimus drug concentration was doubled after switching itraconazole to voriconazole (CYP2C19/3A4 inhibitor and substrate). Voriconazole metabolism was impaired because of polymorphism in CYP2C19 causing a high voriconazole concentration. Voriconazole subsequently produced a self-metabolic inhibition in CYP2C19/3A4. At the same time, both tacrolimus metabolic pathways were also severely inhibited.

Mochizuki et al. reported a comparable scenario where voriconazole and tacrolimus were co-administrated in CYP2C19 PMs. The non-functional CYP2C19 led to a more severe increase in

tacrolimus exposure (1500%) than the previous case[98]. This DDGI magnitude depended on the number of CYP2C19 functional alleles (lowest in NMs and highest in PMs)[99]. CYP3A4 was less inhibited by voriconazole in NMs because voriconazole was metabolized by CYP2C19. Moreover, the inhibition of CYP3A4 metabolic pathway of tacrolimus could induce the metabolic compensation by CYP2C19. Since the voriconazole AUC was significantly higher in CYP2C19 PMs and IMs than in NMs, the tacrolimus AUC was also higher in PMs and IMs than NMs.

Voriconazole was also a substrate of CYP2C19-mediated DDGI. Ritonavir and erythromycin impacted the voriconazole metabolism gene-dependently[100,101]. A greater extent of AUC changes was found in patients with variant CYP2C19 alleles because both voriconazole metabolic pathways were altered profoundly by polymorphism in CYP2C19 and by inhibitors in CYPP3A4 (Supplement 3).

The second scenario involved voriconazole combination with CYP2C19 and CYP3A4 inhibitors (voriconazole and atazanavir) in a patient with CYP2C19*17[102]. CYP3A4-inhibition caused CYP2C19 to be the only metabolic pathway for voriconazole. The increased CYP2C19 activity which caused voriconazole trough concentration was below the expected range. Substitution therapy was then started by co-administration of esomeprazole (CYP2C19 inhibitor) and ritonavir (CYP3A4 inhibitor). The co-inhibition of bimodal voriconazole metabolic pathways generated a four-fold increase of voriconazole concentration which reached therapeutic levels.

The third scenario was co-administration of multiple CYP450 isoenzyme substrates which induced competitive inhibitions in all of their metabolic pathways, evident in PPI and tacrolimus (CYP2C19/3A4 substrates) interaction[103-109]. The strength of inhibition was determined by the affinity of PPIs to CYP2C19 and the CYP2C19 genotypes. Since omeprazole has a higher affinity to CYP2C19 than lansoprazole and rabeprazole, it produced the largest increase in tacrolimus concentration. The CYP2C19 polymorphism interfered with the PPI metabolism. Therefore, CYP2C19 PMs had the highest concentration of PPIs, greatly impairing tacrolimus metabolism via CYP3A4 in this group. Another key determinant was the CYP3A5 genotype. Miura et al. reported that lansoprazole and rabeprazole profoundly impaired tacrolimus metabolism in CYP2C19 PM with CYP3A5*3/*3 but not with CYP3A5*1/*1-*1/*3[106].

A case reported by Marusic et al. showed a comparable mechanism[110]. Along with other risk factors, SLCO1B1 c.521C and ABCB1 c.3435T homozygotes, the presence of CYP2C19 PM in the interaction between pantoprazole and atorvastatin (CYP3A4 substrate) caused a rhabdomyolysis incidence due to the high concentration of atorvastatin.

The fourth scenario was CYP3A4 inhibitors and PPI interaction. Clarithromycin produced a marked increase in the pharmacokinetic parameters of PPI regardless of the CYP2C19 genotypes[111-115]. Two reasons possibly underlay these results. Firstly, the hepatic and intestinal CYP3A4 inhibition contributed to the increase of PPI concentrations in all genotypes. It was also the possible mechanism generating weak inhibition of omeprazole metabolism by troleandomycin[116]. Secondly, changes in the pharmacokinetic values were not solely related to the metabolic failure but also to P-gp transporter inhibition since clarithromycin could affect the P-gp transporter[113,117]. Ketoconazole, also a CYP3A4 and P-gp inhibitor, generated comparable results by significantly inhibiting omeprazole metabolism in NMs and PMs[118]. However, because CYP3A4 played a more important role in CYP2C19 PMs than in NMs, a greater extent of interaction was produced by CYP3A4 inhibitors in PMs than NMs. Overall, taking the effect of polymorphism into account, the total impact of metabolic impairment was greatest in PMs, less in IMs and least in NMs (Supplement 3). These effects were different in fluvoxamine administration[114]. Fluvoxamine had a gene-dependent interaction with lansoprazole. It produced a major and substantial interaction with lansoprazole in NMs and IMs (CYP2C19/3A4 inhibition), respectively, and a minimal interaction in PMs resulting from the weak inhibitory capacity of fluvoxamine in CYP3A4.

The fifth scenario was the combination of inducer and substrate of CYP3A4 and CYP2C19, as illustrated by efavirenz and omeprazole gene-dependent interaction[119]. Since efavirenz induced CYP3A4/2C19, it increased the AUC of omeprazole moderately in all CYP2C19 genotypes, but with a greater magnitude in individuals with at least one CYP2C19 active allele than in PMs[120]. This was to be expected since efavirenz only induced CYP3A4, as a minor metabolic pathway for omeprazole, in CYP2C19 PMs.

The sixth scenario was the interaction between CYP3A4 inducer and CYP3A4/2C19/2B6 substrate as observed in clobazam and CYP3A4 inducers (phenytoin and carbamazepine) combination[121]. CYP3A4 inducers decreased clobazam and increased DMCLB concentrations markedly in NMs and IMs. However, although the clobazam concentration was reduced substantially, there was no significant change in DMCLB concentration in PMs. This might be because of the shift in the clobazam metabolic pathway in this group[121].

The last scenario was the involvement of CYP2C19/2B6 inducers in DDGI as demonstrated by S-mephenytoin and artemisinin combination[122]. S-mephenytoin is mainly metabolized by CYP2C19 to S-4-OH-mephenytoin and secondarily by CYP2C9/2B6 to S-nirvanol. Artemisinin induced S-mephenytoin metabolism to a different extent among CYP2C19 genotypes. Artemisinin increased the conversion of S-mephenytoin to S-nirvanol at a higher rate in PMs than in NMs. It was plausible

because the reduced function of CYP2C19 in PMs caused CYP2C9/2B6 became a more substantial metabolic pathway.

Interaction: Yes/ Action: No

The first CYP2C19-mediated moderate DDGI scenario was a CYP3A4 inducer and a CYP3A4/2C19 substrate interaction, as demonstrated in the glycyrrhizin and omeprazole combination[123]. Because glycyrrhizin induced CYP3A4 only without significant effects on CYP2C19, it reduced the plasma concentration of omeprazole significantly, regardless of CYP2C19 genotypes. The second scenario was a CYP3A4 inhibitor and a CYP2C19/3A4/2B6 substrate combination, as shown in diltiazem (CYP3A4 inhibitor) and diazepam interaction[124]. Since the role of CYP3A4 in metabolizing diazepam was greater in CYP2C19 PMs than NMs, the magnitude of interaction was greater in PMs than NMs. The CYP2C19/3A4 impairment in diltiazem-treated PMs could cause CYP2B6 to be the main metabolic pathway for diazepam.

Interaction: No/Action: No

The DDGI which caused the least impact in all CYP2C19 genotypes was cilostazol and clopidogrel interaction[125]. The study showed that there were no significant changes in the clopidogrel efficacy after cilostazol co-administration. It was because cilostazol only minimally decreased the active metabolite of clopidogrel in CYP2C19 genotypes.

CYP2D6

Interaction: Yes/Action: Yes

CYP2D6-mediated DDGI involved several scenarios which yielded clinically significant interactions. First, the concomitant impact of CYP2D6 and CYP3A4 inhibitors with polymorphism affected the CYP2D6 substrate exposures profoundly, demonstrated by co-administration of clarithromycin and paroxetine (CYP3A4 and CYP2D6 inhibitor, respectively) with venlafaxine (CYP2D6/3A4 substrate) in NMs and IMs[126]. When administered sequentially, clarithromycin caused minimal interaction with venlafaxine in NMs but moderate interaction in IMs. Because the main metabolic pathway of venlafaxine (CYP2D6) was unaffected in NMs, CYP3A4 inhibition might not produce a marked alteration. Moreover, the paroxetine addition caused a substantial increase of venlafaxine concentration in NMs since both metabolic pathways were blocked. The role of CYP3A4 became more important in CYP2D6 IMs because of the reduced activity, therefore, clarithromycin yielded a greater impact than in NMs. But, paroxetine did not produce an equal inhibitory potency as it

produced in NMs. However, the higher baseline plasma level of venlafaxine in IMs led to more prominent inhibitory effects. Compared to NMs, paroxetine and clarithromycin co-medication in IMs doubled the incremental effect on venlafaxine concentration (Supplement 3). The simultaneous impairment of CYP2D6 and CYP3A4 was found to induce opioid toxicity in a child with CYP2D6*41 (decreased function allele) co-medicated with hydrocodone and clarithromycin[127]. The impairment of hydrocodone metabolism due to CYP3A4 inhibition and polymorphism yielded a toxic level of hydrocodone.

The second scenario was co-administration of CYP3A4 inhibitors and a prodrug (bio-activated by CYP2D6/3A4) in patients with increased CYP2D6 activity. This was demonstrated by clarithromycin and voriconazole combination in a codeine-treated CYP2D6 UM patient[128]. CYP3A4 inhibition directed the metabolic pathway of codeine to CYP2D6, causing the amount of codeine transformed to morphine by UMs to be remarkably high. Moreover, the patient's condition was corroborated by acute renal failure which decreased the excretion of morphine metabolites. Consequently, opioid intoxication resulted.

The third scenario was the co-administration of a CYP3A4 and P-gp transporter inhibitor with CYP2D6 substrates, as seen in itraconazole and haloperidol or risperidone combination[129,130]. The interaction produced substantial impacts in all CYP2D6 genotypes. In addition, since polymorphism also increased the pharmacokinetic parameters of the drugs in IMs, the total impact of the metabolic inhibition was greater in IMs than NMs (Supplement 3). This DDGI was confirmed by the side-effects assessment using the Barnes Akathisia Rating Scale (BARS)[129]. The BARS score was not significantly different in haloperidol-treated NMs co-administered with placebo or itraconazole. In contrast, the BARS score was higher in the itraconazole-treated group in IMs than in NMs.

Another CYP3A4 and P-gp inhibitor, ketoconazole, also generated comparable effects in its interaction with fesoterodine[131]. It produced substantial interaction with fesoterodine regardless of CYP2D6 genotype. Fesoterodine is a prodrug and converted to 5-hydroxymethyl tolterodine (5-HMT) which is metabolized by CYP2D6 and CYP3A4. An equivalent increase in 5-HMT exposure was shown when CYP3A4 was inhibited by ketoconazole or when CYP2D6 was genetically impaired (Supplement 3). The contribution of CYP2D6 and CYP3A4 in the 5-HMT elimination is seemingly comparable.

The fourth scenario was the involvement of CYP3A4 inducers in DDGI. Rifampicin produced substantial interactions with fesoterodine among CYP2D6 genotypes[131]. Because of the equal contribution of CYP2D6 and CYP3A4 in 5-HMT disposition, rifampicin induced the 5-HMT degradation comparably in NMs and PMs. In addition, rifampicin also increased propafenone (CYP2D6/3A4/1A2

substrate) metabolism significantly in a similar fashion, as can be observed by the substantial decrease of the AUC value of propafenone and maximum QRS prolongation in all CYP2D6 genotypes. Since CYP2D6 is not an inducible enzyme, the interaction is fully mediated by CYP3A4/1A2. It was also reported that rifampicin induced the phase II metabolic pathways of propafenone because propafenone glucuronide was increased in both genotypes. Moreover, rifampicin is also an inducer of the P-gp transporter. The induction of non-CYP2D6 metabolic pathways of propafenone was responsible for the interaction.

Another CYP3A4 inducer, phenytoin, altered gefetinib clearance more profoundly in CYP2D6 with decreased activity or dysfunctional alleles, since CYP3A4 played a more prominent role in these groups. Moreover, this interaction was attributed more to intestinal than hepatic CYP3A4, because the result of an erythromycin breath test, a probe of hepatic CYP3A4 activity, was not associated with the interaction[132].

The fifth scenario was the involvement of CYP1A2 in DDGI, as observed in propafenone (CYP2D6/3A4/1A2 substrate) and caffeine (CYP1A2 substrate) interaction[133]. In CYP2D6 PMs, the contribution of CYP1A2 to propafenone metabolism is greater than in NMs. Therefore, it triggered the competitive inhibition with caffeine in CYP1A2. Consequently, the decrease in caffeine clearance was greater in CYP2D6 PMs than NMs. Thus, propafenone and caffeine interaction produced a greater clinical impact in PMs than in NMs.

Interaction: Yes/Action: No

CYP2D6-mediated DDGIs producing moderate impacts involved CYP3A4 and P-gp transporter inhibitors with CYP2D6 substrates combination. It was demonstrated by ketoconazole-venlafaxine combination and itraconazole-aripiprazole co-adminsitration. They produced weak interactions in all CYP2D6 genotypes[134,135]. Nonetheless, since IMs and PMs have reduced metabolic capacities, overall metabolic impairment was higher in these groups than in NMs (Supplement 3).

Conclusion and Future Perspectives

The impact of DDIs concerning metabolizing pathways involving CYP2C9, CYP2C19 and CYP2D6 is heavily dependent on the genotype of patients. The larger the contribution of the gene to the drug metabolism, the stronger the disruption produced by perpetrator drugs. Generally, the distortion of the interaction is largest in NMs, less in IMs and least in PMs. PMs have absent/decreased metabolic activities, and are therefore, not significantly impacted by an effector drug. In this group, the key determinant of the interaction is the gene itself. Hence, the generalization of the application of DDI guidelines to these individuals may mislead pharmacotherapy management. Moreover, DDIs can impact only a specific genotype. The interaction between simvastatin and warfarin is mediated exclusively by CYP2C9*3. Therefore, only patients with this specific genotype need special treatment.

Further, the combination effect of polymorphism and the effector drug on the impact of a DDI is shown in the NSAID and coumarin interaction. NSAIDs or decreased CYP2C9 activity do not individually increase the risk of bleeding in coumarin-treated patients. However, NSAID and coumarin co-administration in patients with less active CYP2C9 profoundly increases the haemorrhagic risk. Hence, genotyping is urgently needed to manage the DDI.

The other consideration in DDI is the clinical effect of metabolites. If the influence of parent drug and its metabolite is comparable, despite the pharmacokinetic changes, the addition of an inhibitor will not affect the pharmacodynamic effect of the drug significantly in NMs and PMs. The concentration of active moiety compensates for the variability in pharmacokinetic values due to the effect of the interacting drug and polymorphisms.

Polymorphism also plays a pivotal role in substrates metabolized by multiple pathways resulting DDGIs. The impairment of the primary metabolic pathway of substrates because of polymorphism increases the importance of the secondary pathway. Therefore, the subsequent impediment of the secondary metabolic pathway yields a considerable increase in the plasma concentration of the substrates. Nevertheless, the deprivation of the secondary pathway sequentially without alteration of the main pathway causes a less potent metabolic impairment. Additionally, drug transporter might be involved in the drug interaction. In the clarithromycin and PPI interaction, the interaction has been found to occur in all genotypes. The possible underlying reason is that the interaction involves not only the alteration of hepatic and intestinal CYP3A4 but also the P-gp transporter. However, since the baseline concentration of PPIs is genotype dependent, the net drug exposure of the substrate after the addition of inhibitor is also gene dependent. The magnitude of DDGI depends on the number of functional CYP alleles. PMs produce a greater extent of DDGI than IMs and NMs.

These complex interactions may escape the attention of clinical practitioners because the drug interaction guidelines have mostly not considered the significance of the interactions yet. Meanwhile, most of the DDI alerts have no capability to recognize, or if capable, lack the ability to provide a recommendation to manage these complicated interactions. Moreover, genotyping has not become a clinical standard, despite polymorphism being an important determinant in DDI and DDGI. We therefore assume that pharmacogenetics in DDI and DDGI will be considered thoroughly in the coming years.

Financial and competing interest disclosure

We declare no conflict of interests in this study. There was no writing assistance used in the creation of this manuscript.

Executive summary

- Genetic predisposition has a pronounced role in determining the magnitude of DDIs and DDGIs.
- DDIs and DDGIs occur in a genotype-dependent manner.
- The scenario of DDI and DDGI is highly dependent on the properties of perpetrator and object drugs, and the type and function of the enzymes affected.
- The impact of the addition of an effector drug to the context of a DDI is greatest in NM, less in IM and least in PM. Polymorphism has an impact in the reverse order.

- The effect of DDIs and polymorphism are not apparent in drugs which have a comparable clinical effect with to their metabolites.
- For substrates of multiple CYP-enzymes, the impairment of the main metabolic pathway of the drugs shifts the elimination pathway to the minor metabolic pathway.
- Perturbation of the minor metabolic pathway leads to a weak or moderate increase in the pharmacokinetic values of the concerned drugs in normal metabolizer patients.
- The obstruction of the metabolic pathways by both polymorphism and drug inhibitor yields a considerable inhibition in the elimination of the substrate. Therefore, DDGIs produce a more severe interaction than DDIs.
- The DDGIs occur in a greater extent in PMs than in IMs and NMs.
- Disruption of a drug transporter can affect the nature and magnitude of drug interactions.
- Generalization in drug interaction management can lead to inappropriate administration.

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