Towards personalized management of drug interactions: from drug-drug-interaction to drug-drug-gene-interaction

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chapter ONE

General Introduction

Introduction

An Adverse Drug Reaction (ADR) is still one of the main clinical factors causing excess morbidity and mortality as well as additional economic burden to the healthcare system[1]. According to the WHO, ADR is defined as 'any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy'[2]. In the US, it was reported that ADR led to more than 100,000 deaths in 1994[3]. Additionally, the prevalence of ADR causing hospitalization ranged from below 1% to almost 16%[4]. Importantly, patients in hospitals are also at risk of developing ADR. An epidemiological study of almost 3,700 hospitalized patients in the UK showed that about 15% of them experienced at least one ADR during their treatment and ADR extended the length of hospitalization of almost 27% of patients with ADR[5]. The estimated cost of ADR is about €706 million per year[1]. Another study reported that ADR may cost around €200 to €9000 per hospitalization[6].

There are several main risk factors of ADR related hospitalization such as cognitive impairment, dependent living condition, kidney impairment, non-adherence, multiple comorbidities, and polypharmacy[7]. The latest is commonly defined as the use of five of more drugs daily[8]. The use of multiple medications can trigger the incidence of drug-drug interaction (DDI). The risk of DDI is reported to escalate linearly as the number of drugs consumed increased[9]. Consuming five to seven drugs and ten to fourteen drugs increased the risk of potentially clinically relevant DDI by about 20% to 30% and 40% to 60%, respectively[10]. DDI is one example of ADR which often occurs, about 20% to 30% of ADRs are related to DDI, but it is mostly preventable and avoidable[11].

Drug-Drug Interaction

A DDI occurs when the effect of one drug is interfered with, either enhanced or reduced, the presence of one or more other drugs. The prevalence of potential drug interaction varies widely. A systematic review of nineteen studies on this topic described that the prevalence ranged from 2.2% to 70.3%[12]. The variation in the proportion of reported DDI is caused by the discrepancy in study design, study population, definition of DDI, and method of measurement[12].

The population which is particularly at risk to experience DDI and therefore needs special attention, is the elderly population. Elderly patients are more vulnerable to DDI because of gradual age-related physiologic changes, increased risk for disease associated with aging, and the consequent increase in the number of different medications[13]. The estimated frequency of elderly with four or more drugs was more than 50%[14]. It was also reported that about 46% of elderly patients had at least one potential clinically relevant DDI and the effects of 10% of the DDIs were considered to be severe[15]. This demonstrates the need to increase interventions aimed at reducing these DDIs.

DDIs are divided into pharmacodynamic DDI and pharmacokinetic DDI. A pharmacodynamic DDI occurs when drugs alter the effects of each other directly without changing their blood concentration[16]. This DDI may exhibit synergistic, additive, or antagonistic effects. Meanwhile, pharmacokinetic DDI take places when the absorption, distribution, metabolism, or excretion (ADME) of one drug is altered by another drug, and consequently, its blood concentration is either increased or decreased[16]. There are two possible main outcomes of this particular DDI i.e. serious

adverse effects or treatment failure which depends on the pharmacological properties of the drugs. As far as the pharmacokinetic interactions are concerned, a drug that inhibits or induces the phase I metabolic enzyme cytochrome P450 (CYP450) is commonly involved[17,18].

Phase I metabolic enzyme CYP450

One of the main sources of pharmacokinetic variability of drugs is the family of CYP450 enzymes. These heme-containing enzymes are mostly expressed in the centrilobular area of the liver and located in the membrane of the smooth endoplasmic reticulum[19]. The microsomal enzymes responsible for phase I drug metabolism are a major route of drug biosynthesis and degradation. Based on amino acid sequence similarity, they are divided into 18 families and 44 subfamilies[19,20]. However, there are only several subtypes of CYP450 which are predominantly reported to actively catalyze more than half (70% to 80%) of marketed drugs i.e. CYP1A2, CYP2A6, CYP2B6, CYP2E1, CYP2D6, CYP2C and CYP3A4[20-22]. They accounted for 70% of liver CYP450 enzymes with CYP2C and CYP3A4 as the dominant enzymes with a percentage of 20% and 30%, respectively[21]. CYP450 enzymes have inter-individually differing activity in human drug metabolism and the variation leads to different susceptibility in both pharmacological and adverse reactions of drugs.

An important factor that contributes to the different drug metabolism activity of CYP450 subtype enzymes is genetic polymorphism. It was estimated that genetic aspects are responsible for 20% to 90% of the variation in drug metabolism and response[23]. The genetic polymorphisms can be in the forms of loss of function, decreased or increased function of alleles of CYP genes[20]. This genetic variation could lead to different pharmacokinetic phenotypes of CYP450. For example in the case of CYP2C19, besides normal metabolic function (normal metabolizer/NM), combination of non-functional alleles refers to poor metabolizer (PM), a combination of a non-functional allele or a decreased function allele and a normal function allele refers to intermediate metabolizer (IM), combination of a normal function allele and an increased function allele refers to rapid metabolizer (RM) and combination of two or more increased function alleles refers to ultra-rapid metabolizer (UM) result in no metabolic activity, reduced metabolic activity, faster metabolic activity than NM, and faster metabolic activity than RM, respectively[24]. The clinical consequences of genetic polymorphisms is different among the CYP450 subfamilies with CYP2C9, CYP2C19, and CYP2D6 polymorphisms reported to have the most important clinically relevant implications[20,25,26].

The prevalence of CYP2C9, CYP2C19, and CYP2D6 polymorphisms varies among ethnicities[25]. For example in the Caucasian population, it was reported that the prevalence of people with IM and PM genotypes was 40.5% (40% IM and 0.5% PM), 23% (20% IM and 3% PM), and 50% (40% IM and 10% PM) for CYP2C9, CYP2C19, and CYP2D6, respectively[22]. Since these highly polymorphic enzymes metabolize about 40% of drugs used in daily clinical practice, the interaction between drug and variant CYP2C9, CYP2C19, and CYP2D6 alleles (drug-gene interaction/DGI) is prevalent[27,28]. US based pharmacoepidemiological studies reported that the prevalence of CYP2C9, CYP2C19, and CYP2D6 mediated DGI was about 15% to 25%[28,29]. Some other studies indicated that patients with deviating genotypes had a higher risk of experiencing adverse drug effects than the NM patients[30-32]. The clinical impact of DGI can be substantial ranging from therapeutic failures to death[31,32].

The use of technology and pharmacogenetics to prevent adverse drug effects by DGI is therefore, strongly recommended.

Genetic based therapy guidelines have been provided to deal with DGI in order to generally aid health practitioners to improve drug use and therapy outcomes[33-35]. In these guidelines, clinical interventions have been advised for many drugs. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPGW) are two main leading organizations that actively contribute in updating the guidelines by translating reliable peer-reviewed evidence to actionable recommendations[33,36].

Drug-Drug-Gene-Interaction

To date, the available guidelines have not taken into account the interaction between internal (genetic polymorphisms) and external factors (CYP modulators) on the magnitude of drug interaction[26,33]. The magnitude of CYP-mediated DDIs can vary in patients with different metabolic phenotypes because the functionality of CYP enzymes is central in mediating these DDIs. Some DDIs can be expected to be clinically relevant for patients with normal metabolic phenotype but not clinically relevant for people with deviating phenotypes[26]. In this case, genetic variation of CYP enzymes may alter the impact of the DDIs. Additionally, it was also reported that CYP enzymes with a reduction-of-function allele are more prone to undergo a phenoconversion (discordance between genotype and phenotype) with a co-presence of a CYP inhibitor than those with active alleles[37]. Therefore, the addition of CYP modulator may also modify the clinical impact of DGI.

Furthermore, the genetic polymorphisms may also contribute in impairing the clearance of drugs with multiple metabolic pathways[38]. Combination of the existing non-functional alleles of CYP450 in one pathway and the presence of a CYP inhibitor for another pathway may produce a marked alteration in drug disposition. The interplay condition of DDI and DGI is called drug-drug-gene-interaction (DDGI)[28]. The complex and multimodal interaction of DDGI may produce a greater variability in person-to-person therapeutic drug reactions than bimodal DDI and DGI[26]. An example of DDGI is the interaction between voriconazole (a substrate of CYP2C19 and CYP3A4) and ritonavir (a strong inhibitor of CYP3A4) in a patient with CYP2C19 PM. The Area Under Curve (AUC) of voriconazole in an individual with CYP2C19 PM taking ritonavir was 9-fold, 17-fold, and 26-fold higher than in CYP2C19 PM without ritonavir, CYP2C19 NM with the combination and CYP2C19 NM without the combination, respectively[39]. DDGI is quite prevalent in clinical practice. In the US, it was reported that 19% of about a thousand clinically relevant interactions was deemed as DDGI[28]. Another US based study reported that 22% out of 16,924 severe drug interactions found from more than 20,000 patients was observed as DDGI[29]. Hence, it is important to understand the nature and magnitude of DDGI in order to screen and minimize the severity of this cumulative interaction.

Prevention and Management of DDI

To ensure medication safety, a computerized DDI surveillance system is embedded within most of the electronic prescriptions and health record systems[40]. The tool works as a screening and early warning system to timely identify or detect potential clinically relevant DDIs[41]. When a potentially

harmful medication combination is prescribed or dispensed, an alert will generally pop up to remind the prescriber or pharmacist about the DDI severity and its clinical consequences. The automated medication surveillance system is also usually completed with actionable management recommendations (replacement, dose adjustment, monitoring, etc) to avoid or minimize the detrimental risk of the DDI[40].

Some studies reported that the computerized DDI alerts effectively decrease the ADR related to DDI substantially, and therefore, produce a cost-saving DDI management[42-45]. Furthermore, it was also reported that DDI alerts enhanced the ability of physicians to practice safe prescribing[42]. However, the DDI alert systems are not without limitations. It could produce an 'alert fatigue' problem which leads medical doctors or pharmacists to override the alerts[40,46]. It was reported that 22% of general practitioners using the DDI decision support system frequently overlooked the potential DDI related alerts[47]. The excessive nuisance alerts produced by the safety systems might be due in part to the fact that some DDI decision support systems still alert DDIs with questionable clinical relevance[40,47,48]. The prevalence of actual DDIs is much lower than of potential DDIs[49]. Additionally, another study reported that the safe pharmacotherapy and cost-saving attributed to a DDI alert application is provided by only small parts of the generated alerts[45]. Therefore, it seems that most of the current DDI alerts systems overestimate the impact of some potential DDIs[40].

Moreover, DDI knowledge databases used to support the DDI alerts have different assessment regarding the clinical relevance of specific DDIs[40,50]. Differences in severity ranking and quality of evidence rating systems might produce conflicting conclusions whether to signal a DDI or not[40,50]. Collectively, they can decrease the confidence of health practitioners on the ability of DDI alerts to improve medication safety. However, the decision to ignore the DDI signals may undermine the quality of patient safety and care because it can lead to serious medical consequences[46]. Grizzle at al. reported that 72% of 291,890 overridden DDI alerts in six veterans affairs medical facilities in the US was identified as clinically significant DDIs[51]. Meanwhile, Weingart et al. reported that 89.4% of overridden signals in primary care settings were deemed as alerts for clinically significant DDIs[48].

Therefore, the efforts to provide high quality evidence for DDIs with unclear clinical impact and only supported by weak evidence are critical and should be encouraged in order to improve the consistency, sensitivity and specificity of DDI decision supports. Prescription databases can be used to study the quantity and the clinical relevance of particular omitted DDIs because they can provide real world drug utilization data[52,53]. These prescription repositories have been used as reliable and valid source of data for a wide range of pharmacoepidemiological studies[54-56].

Another limitation is that most of the DDI alerts are only designed to detect binary drug–drug interactions. Multimodal DDIs involving multiple elimination pathways are hardly considered. Moreover, since genotyping is still not part of regular clinical laboratory testing, most of the DDI alerts have also not been upgraded to include detection of gene related interactions such as DGI and DDGI[57]. Most of the current DDI alert systems might not detect more than a third of the potential drug interactions because of the unknown patient genetic status[28,57]. Therefore, there should also be efforts to link patients' genetics data to the DDI alert system and collect evidence especially for DDGI to support more advanced and personalized DDI clinical decision supports.

Thesis objective

The objective of this thesis was to evaluate the burden, management, and impact of DDI as well as to investigate the influence of CYP2D6, CYP2C19, and CYP2C9 polymorphisms in mediating DDGI.

Thesis outline

This thesis consists of two main parts (A and B). Part A focuses on studies with the aim to determine the frequency of CYP2C9, CYP2C19, and CYP2D6 mediated DDIs, as well as to evaluate the concordance between two sources of assessing the burden of DDI i.e. self-reported questionnaire and prescription database (chapter 2). Additionally, this part also includes a study evaluating the burden and management of one of the most frequently ignored potential DDIs in the presence of DDI alerts (chapter 3).

Chapter 4 describes a study which was intended to add evidence regarding the impact of the frequently omitted DDI and then, used this study and other relevant studies to systematically evaluate the potential impact of the DDIs (chapter 5).

Part B depicts the impact of pharmacogenetics on DDIs and DDGIs involving CYP2D6, CYP2C19, and CYP2C9 (chapter 6) and tested the influence of DGIs, DDIs and DDGIs on the prescription profiles of citalopram and escitalopram (chapter 7). Lastly, the main findings and future perspectives in the field of DDI and DDGI were discussed and summarized in Chapter 8.

1

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part A

BURDEN AND MANAGEMENT OF DRUG-DRUG-INTERACTION