Research Article

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Reviewing drug package inserts available in United Arab Emirates for USFDA recommended pharmacogenomic information

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Abstract

Pharmacogenomics aims to characterize the contribution of genetic polymorphisms to variability in therapeutic response and toxicity. The USFDA has issued a list of drugs which exhibit polymorphism and relevant sections in the package inserts for providing pharmacogenomic information and their biomarkers to reduce the risk of drug toxicity. A total of 67 Package inserts of 41 drugs in 5 therapeutic areas, available in UAE under various brand names, were thoroughly reviewed for direct and indirect pharmacogenomic information and compared with FDA recommendations. It was observed that only 26 package inserts of 17 drugs (41%) prescribed provided direct genetic evidence and information on the type of polymorphism influencing drug efficacy and toxicity. Indirect indicators describing genetic variation in metabolizing enzyme activity was present in 20 inserts (30%)., It was concluded that incorporating the necessary pharmacogenomic information, as recommended by the USFDA, in the package inserts of drugs available in UAE will help in enhancing drug efficacy, safety and awareness among the physicians, pharmacists and patients.

Keywords: Drug inserts, Pharmacogenomic information, Biomarkers

Abbreviations:
USFDA: United states Food and Drugs Administration
UAE: United Arab Emirates

Introduction

Inter-individual variability in drug response has been one of the primary concerns resulting in therapeutic failure or adverse drug reactions [1, 2]. The discipline of Pharmacogenomics has emerged as a branch of Pharmacology to identify genetic variants from candidate genes related to drug metabolism, transport or molecular targets/pathways1 that lead to variation in drug response and forms the basis of personalized medicine. The pharmacogenomic biomarker information has been incorporated in package inserts for improving the drug's benefit-risk ratio as they serve as good source of necessary information for health professionals [3].

The US-FDA has recommended Pharmacogenomic information in package-inserts for more than 120 drugs with the relationship established to nearly 50 genes. Most of these therapeutic agents either have a narrow therapeutic index and/or high potential for serious and life-threatening adverse effects which significantly affect the clinical outcome supporting the concept of individualized medicine. Information on genetic polymorphism of these listed drugs can play an important role in identifying responders and non-responders to treatment, optimizing dose requirement as well as avoiding adverse events [4]. According to FDA requirements, drug labels should contain relevant information on genetic biomarkers to describe the various aspects of drug response such as drug exposure and clinical response variability, the risk for adverse events, genotype-specific dosing, mechanisms of drug action, polymorphic drug target and disposition genes [5].

The above information in the package inserts can help the clinician to undertake necessary investigations before prescribing and will also help the pharmacists to counsel the patients regarding proper use of the drug, response variability, expected side effects and early reporting. It will also serve to create awareness among the patients regarding diagnostic needs and understand the treatment being given. Despite the requirement by US-FDA, the pharmacogenomic biomarker information is often lacking / incomplete or presented in different sections of the package inserts which may go unnoticed by the health professionals [6]. Thus, it is necessary to review the package inserts for the availability of pharmacogenetic-based prescribing information which is helpful to the clinician, pharmacist and the patient.

Since, no study has been undertaken in UAE in this direction, it would be worthwhile to review the package inserts of the available drugs that exhibit genetic polymorphism and provide recommendations based on the results for enhanced efficacy and safety of drugs.

Materials and Methods

The methodology for reviewing the drug package inserts involved following steps:

1. The US-FDA Table of 'Pharmacogenomic Biomarkers in drug labels' was obtained.
2. The drugs listed in different therapeutic categories were checked for their availability in the different pharmacies.
3. The different brands of the drugs of interest were identified and the package inserts were obtained.
4. All package inserts were reviewed for Pharmacogenetic and drug interaction information/biomarkers in different sections.
5. The drug labels were selected for analysis if there was a mention of the following terms in any section: a. Specific gene (full name or symbol) or b. Genetic terms such as inherited, gene, genotype, carrier, homozygous, heterozygous, chromosome, deletion, duplication, or translocation.
6. Drug labels were excluded if they only contain contraindications regarding drugs or foods that share metabolic pathways, or are associated with genetic polymorphism different from the one listed in the FDA table.
7. In addition, drugs that include warning for patients with other genetic conditions (e.g. phenylketonuria) or risk of developing a new condition due to genetic predisposition were also omitted.
8. The leaflets were also reviewed for indirect indicators of Pharmacogenetic variability with respect to altered efficacy or safety.
9. The information in the package inserts was compared against the FDA recommendations on drug labeling.

Results

A total of 67 package inserts of 41 drugs belonging to 5 therapeutic categories (Anticancer, cardiovascular, blood, gastrointestinal and Central nervous system) were obtained and reviewed for pharmacogenomic information. The package inserts included single brand of 35 drugs and multiple brands of six drugs (6 brands of Atorvastatin, 4 brands of omeprazole, 3 brands of Clopidogrel and 2 brands each of Tamoxifen, esomeprazole and Lansoprazole).

Table1: Drug package inserts with and without pharmacogenomic (PGx) information

Cardio-vascular	Anticancer	GIT	CNS	Blood
Drug inserts with PGx information				
Carvedilol	Capecitabine	Omeprazole (4)	Carbamazepine	Nil
Metoprolol	Imatinib	Esomeprazole (2)	Phenytoin	
Propranolol	Nilotinib		Aripiprazole	
Atorvastatin (6)	Thioguanine		Diazepam	
	Dasatinib		Celecoxib	
Drug inserts without PGx informationn nbnn				
Pravastatin	Everolimus	Lansoprazole (2)	Risperidone	Warfarin
Isosorbide	Tretinoin	Rabeprazole	Citalopram	Clopidogrel (3)
hydralazine	Lenalidomide	Pantoprazole	Valproic acid	Ticagrelor
	Tamoxifen (2)		Fluoxetine	
	Mercaptopurine		Amitriptyline	
	Exemestane		Paroxetine	
	Erlotinib		Venlafaxine	
	Lapatinib			
(No. of brands)	Letrozole			

The direct genetic information was present in the various sections of the package inserts of 41% drugs which were comparable with (followed) the FDA recommendations. The most common biomarkers were metabolizing enzymes followed by pharmacological target and transporter (for Atorvastatin). Single nucleotide polymorphism was responsible for variation in drug responses for all drugs except anticancer tyrosine kinase inhibitor drugs (Imatinib, Nilotinib and Dasatinib) where polymorphism was insertion/deletion type. The type of biomarker, polymorphism type, FDA compliance with respect to labeling section and drug interaction of each drug have been presented in Tables 2-4.

Table 2: Cardiovascular and Gastrointestinal drug inserts with pharmacogenomic information

Drug	Biomarker	Type of biomarker	Variation Type	Role of biomarker	Labeling section	FDA compliance	Drug-Drug interaction & Mgt
Cardio-vascular drugs							
Carvedilol Propranolol Metoprolol	CYP2D6	Metabolizing enzyme	SNP	Efficacy	ADR, DI, clinical pharmacology	Yes	No - Carvedilol Propranolol Yes – Metoprolol (Caution with CYP2D6 inhibitors)
Atorvastatin		Transporter	SNP	Safety	-Do-	Yes	Yes Rifampicin inhibits OATP Atorvastatin levels
Gastrointestinal drugs							
Omeprazole		Metabolizing					
Esomeprazole		enzyme	SNP	Efficacy	-Do-	Yes	No

Table 3: CNS drug inserts with pharmacogenomic information

Drug	Biomarker	Type of biomarker	Variation Type	Role of biomarker	Labeling section	FDA compliance	Drug-Drug interaction & Mgt
Carbamazepine	HLAB*1502	Pharmacological target	SNP	Safety	Warning & precautions	Yes	No
Phenytoin	HLAB*1502	Pharmacological target	SNP	Safety	ADR, DI, clinical pharmacology	No	No
Aripiprazole	CYP2D6	Metabolizing enzyme	SNP	Efficacy Safety	Indications, Dosage adm. ADR, DI	Yes	Dosage halved with CYP3A4 / CYP2D6 inhibitors;Dose doubled with CYP3A4 inducers
Diazepam	CYP2C19	Metabolizing enzyme	SNP	Efficacy	NA	No	Yes Mgt: No
Celecoxib	CYP2C9	Metabolizing enzyme	SNP	Safety	W & P Indications, Dosage adm. ADR, DI	Yes	Co-adm. With Warfarin, Li, Aspirin ACEI, Fluconazole Furosemide & MTx cautioned

Table 4: Anticancer drug inserts with pharmacogenomic information

Drug	Biomarker	Type of biomarker	Variation Type	Role of biomarker	Labeling section	FDA compliance	Drug-Drug interaction & Mgt
Capecitabine	DPYD	Metabolizing enzyme	SNP	Safety	Warning precautions ADR, DI, clinical pharmacology	Yes	Yes 4w between DPYD inhibitors (Brivudine/Sorivudine) and Capecitab.
Imatinib Nilotinib Dasatinib	FIP1L1-PDGFRA BCR-ABL BCR-ABL	Pharmacological target	Ins/Del	Efficacy	Indications & usage, dosage, adm	Yes	No
Thioguanine	TPMT	Metabolizing enzyme	SNP	Safety	Warning precautions	Yes	Yes Increased ADR with TPMT inhibitors (Olsalazine, sulphasalazine; mesalazine)

Indirect information referring to variation in drug response as consequence of genetic variation in metabolizing enzymes was present in 30% of the package inserts. Most package inserts were revised more than 3 years ago and had poor readability.

Discussion

The package insert is a fundamental document which provides all drug related information to the health professionals. It is obligatory to read the given information and decide the treatment plan. These inserts are periodically updated based on pharmacovigilance data as a part of the regulatory requirement. The study helps to recognize the deficiencies, if any, in package inserts regarding Pharmacogenomic and drug-interaction information for drugs that exhibit variable response due to genetic polymorphism.

Only 41% of the reviewed package inserts described pharmacogenetic information explaining therapeutic failure/ increased risk in patients with the variant. The biomarkers for the pharmacogenetic interaction have been described in few inserts explaining the cause and consequences of the inter-individual variation in drug response. However, for all drugs, the reported/ suspected adverse reactions had been mentioned along with warnings and contraindications, but without any special reference to a genetic cause. The drug-drug interaction also becomes unpredictable because of polymorphism. This poses a potential risk while using the drugs in recommended doses or with other drugs. Though, the genetic information was missing in many leaflets, the risk of adverse drug reaction may be high only for certain drugs leading to life-threatening consequences. Genotyping may not be important for many drugs due to multiple metabolic pathways, active metabolites, ill-defined concentration-effect relationship or poor clinical implication.

A similar study of pharmacogenomic information in drug labels had been undertaken in the US using the electronic version of the Physician's Desk Reference for screening packet inserts for pharmacogenomic-related information [7]. Moreover, the drug labels in the US have been compared with those in Japan to identify the similarities, differences, factors influencing the contents and the description of the drug labels in various therapeutic drug groups [8].

Including the pharmacogenetic information in patient-targeted sections, such as Patient counseling information section or medication guides, will empower the patient in health care decision-making resulting in an improved outcome [9]. In the case of non-compliance, necessary action must be taken to improve drug efficacy and safety. Moreover, it will help to increase awareness among the physicians, pharmacists and patients about the inconsistent response of selective drugs and may require therapeutic monitoring [10]. The present study showed that the pharmacogenetic information was lacking in 59% of the studied package inserts. This reflects a need to include FDA recommended pharmacogenomic information in the package inserts to enhance patient safety and awareness.

References

1. Evans WE, Relling MV (1999) Pharmacogenomics: Translating functional genomics into rational therapeutics. 286: 487-491.
2. Mayer UA (2000) Pharmacogenetics and adverse drug reactions. Lancet 2000; 356: 1667-1671.
3. Frueh FW, Amur S, Mummaneni P, Epstein RS, Aubert RE et al. (2008) Pharmacogenomic biomarker information in drug labels approved by the United States food and drug administration: Prevalence of related drug use. Pharmacotherapy 28: 992-998.
4. Qiang Ma and Anthony Y. H. Lu (2011) Pharmacogenetics, Pharmacogenomics, and Individualized Medicine. Pharmacol Rev 63: 437-459.
5. US Food and Drug Administration (2015) Table of Pharmacogenomic Biomarkers in Drug Labels.
6. Zineh I, Pebanco GD, Aquilante CL, Gerhard T, Beitelshees AL et al. (2006) Discordance between availability of pharmacogenetics studies and pharmacogenetics-based prescribing information for the top 200 drugs. Ann Pharmacotherapy 40: 639-644.
7. Zineh I, Gerhard T, Aquilante CL, Beitelshees AL, Beasley BN et al. (2004) Availability of pharmacogenomics-based prescribing information in drug package inserts for currently approved drugs. Pharmacogenomics J. 4: 354-358.
8. Otsubo Y, Asahina Y, Noguchi A, Sato Y, Ando Y et al. (2012) Similarities and differences between US and Japan as to pharmacogenomic biomarker information in drug labels. Drug Metab Pharmacokinet 27: 142-149
9. Weiner SJ, Schwartz A, Sharma G, Binns-Calvey A, Ashley N et al. (2013) Patient-centered decision making and health care outcomes: an observational study. Ann Intern Med 158: 573-579.
10. Gardiner SJ, Begg EJ (2006) Pharmacogenetics, Drug-metabolizing enzymes, and Clinical Practice. Pharmacological Reviews 58: 521-590.