Do the Differences in Worldwide Labeling for Some Drugs Correlate with Known Metabolic Variations in Different Races?

by

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Abstract

The purpose of this research paper is to correlate the variation in metabolic enzymes with respect to the drug labeling in various parts of the world. Currently, researchers are focusing on the therapeutic drug response and drug doses in drug development processes. However, this paper explains the importance of drug labeling and metabolism in developing a drug by taking the metoprolol, debrisoquine, and isoniazid drugs as examples. The labeling results for these three drugs were based on the information obtained from regulatory agencies such as US-FDA, UK-MHRA, and Asia (India-CDSCO). All regulatory agencies indicate the different drug doses for the same drugs. Findings from this research project specify that different races in the world show variations in the genes and alleles of various metabolic cytochrome enzymes. As a result of genetic deviation, metabolic enzymes show abnormalities in activating drug molecules. Drug labeling is found to coincide with known drug metabolism of various ethnic groups. Suggestions for future researchers are provided in this paper. Hence, future studies need to be carried out in order to confirm the variations with dose and metabolism.

Key words: Debrisoquine, metoprolol, isoniazid, CYP2D6, N-acetyl transferase, polymorphic nature, drug dose, Food and Drug Administration (FDA), drug metabolizing enzymes, alleles, genetic polymorphisms, cytochrome enzymes.
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<td>4</td>
<td>18</td>
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</tbody>
</table>
Introduction

At present, drug development depends on the respective drug labels across the world. Due to the formation of ICH-GCP guidelines, it became easier to develop the same drug in various parts of world. However, due to the variation in the human genomics it has become difficult to predict the dose of drugs across the world. Temple (2011) questions why the drug labeling in US is different from Canada or Europe. Temple (2011) suggests that this is due to variation of labeled drugs with differences in end-points. Further, a label must indicate the adverse events along with the dose of the drug. However, the drug development becomes daunting task to adjust the dose according to the race.

In clinical trials ethnic factors must be considered before labeling the drug doses. The drug metabolism is influenced by factors such as concomitant medications, food and dietary supplements and genetic variations. Drug labeling indicates dose, adverse events, caution as well as direction of use. The populations in this study include Asian, American, and European. However, the CYP’s class of enzymes are the most important to determine the drug metabolisms (Anderson and Kappas, 1991). The correlation between drug labeling and metabolic variation may lead to the widespread divergence of adverse drug reactions. These adverse reactions may vary from one country to another country.

In the process of drug development, pharmacokinetics of drugs plays a prominent role in adjusting the drug doses. However, the dose may vary from one race to another. The possible reasons may include genetic, environmental and cultural factors and may influence drug metabolism. Horai et al. (1989) stated that differences in the drug metabolism are due to the
variation in the various metabolic enzymes in the different ethnic groups. This is reflected in the labeling of the respective drugs in the regulatory agencies. These agencies include FDA in US, SFDA in CHINA and PMDA in Japan. Bacota (2006) suggests variation in the drug labeling is due to the differences in genetic factors such as metabolic enzyme deficiencies, gene alteration in the genetic deficiencies and inherent metabolic defects. Among African-Americans and European-Americans, 10 percent are considered slow drug metabolizes. In support of Bacota (2006), Burroughs et al. (2002) stated that unequal treatment in health care is due to differences in the race and ethnic groups. However, drug metabolism is mainly highlighted under the polymorphic nature in drug metabolic enzymes which includes, CYP 2D6, CYP2C19. The word genetic polymorphism refers to the naturally occurring variants in the structure of gene. For example, CYP2A6 shows CYP2A6*1A, CYP2A6*1B and CYP2A6*2 type of variants which may differ in its function. Perhaps, this polymorphism is mostly seen in humans and in particular it varies with population to population. Polymorphism may occur in the various classes of drugs such as beta blockers, antidepressants, barbiturates, neuroleptics, opioids, benzodiazepines. Burroughs et al. (2002) explains with an example that drug metabolism may vary with the rapid acetylators or slow acetylators. This example indicates that 62% of whites are slow acetylators compared with 7-34% of Chinese and Japanese.
Background

Drug metabolism in human depends on various factors. These may include biochemical and biological factors. All metabolic enzymes which are related to the metabolism are come under biochemical factors (Oscarson et al. 2002). Race or ethnic, diet and various external factors may also come under the biological factor. Due to the variation in drug metabolism enzymes, concentrations of drugs vary in plasma levels. For people known as poor metabolizers, level of drug concentration in the plasma is small. It is now very important to understand the nature of metabolic enzymes variations in the various races to adjust the doses. On the other hand, understanding the drug labeling for various races in world is also important to indicate metabolic variations. Drug labeling for various regions indicate the variations in drug doses and metabolism due to polymorphic metabolic genes in humans (Zhou, 2000). Drug metabolizing enzymes may cause an increase or decrease of drug metabolism. Drugs undergo the various biotransformation mechanisms to show the variations in the drug reactions. Some of the reactions may include oxidative reactions, hydrolytic reactions and conjugation reactions.

The drug metabolism varies from one population to another. For example, 7-12 % of Japanese are slow acetylators (Horai et al. 1989). According to the Evans et al. (1960), 52-58% of Americans show slow acetylation for the drug Isoniazid. Zhou (2000) stated that there is genetic change within the Chinese population showing the variation the drug metabolism. Further, to indicate metabolic variation, various drug-doses have been studied for drug labeling packages across the world. In the drug labeling, “metabolism” section for the drugs debrisoquine, isoniazid and metoprolol have been discussed. The population from different parts of the world (US, UK and Japan) has been compared for drug metabolism. These populations include
comparison between Orientals and Caucasians (Jurima et al. 1985), metoprolol versus debrisoquine.

A professional drug labeling consists of storage details, warnings, drug dose, batch number expiration, precautions and safety information related to drug. Drug regulatory agencies specify safety information in the labeling package before giving approval to drugs. To understand the metabolism in drug labeling, one must have knowledge on drug metabolic enzymes. Drug molecules may induce or inhibit CYP metabolic enzyme activities. Inhibitors suppress the expression of drugs and inducers may induce the drug metabolism. This expression may vary from one group of population to another group of population (ethnicity).

**Frequency of CYP2A6**

The word frequency in this context refers to the distribution or occurrence of CYP enzyme in a population. To know the polymorphic nature of CYP2A6 enzyme it is important to know CYP enzyme distribution. CYP2A6 is a typical example for polymorphic nature of CYP class of enzymes. According to the Oscarson et al. (1999), the variation in the drug metabolism is due to the polymorphic nature of CYP class of enzymes. The polymorphic nature means a population may contain two or more variants of enzyme on a single locus. According to the available information, Table 1 provides the distribution of various forms of alleles for the enzyme CYP2A6.
Table 1. Distribution of CYP alleles. A table indicating distribution of CYP 2A6 allele in various populations. Data obtained from Oscarson et al. (1999), Nakajima et al (2001).

<table>
<thead>
<tr>
<th>Allele</th>
<th>Spaniards</th>
<th>Japanese</th>
<th>Chinese</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2A6*1A</td>
<td>66.5</td>
<td>42.4</td>
<td>43.2</td>
</tr>
<tr>
<td>CYP2A6*1B</td>
<td>30.0</td>
<td>37.5</td>
<td>40.6</td>
</tr>
<tr>
<td>CYP2A6*2</td>
<td>3.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CYP2A6*3</td>
<td>0</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>CYP2A6*4</td>
<td>0.5</td>
<td>20.1</td>
<td>15.1</td>
</tr>
<tr>
<td>CYP2A6*5</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 1 gives information on different forms of allele subtypes for CYP2A6 and its distribution in different populations such as Japanese, Chinese and Spaniards. All the enzymes are come under same CYP2A6, however variation comes under allelic distribution (Bolt, 1994). Further, the enzyme activity may depend on enzyme inducing or enzyme inhibiting capacity of drugs.

**Inducers & Inhibitors for some drugs**

Drugs were divided into enzyme inducers and inhibitors (Code et al. 1997). According to Code et al. (1997), an enzyme inducer is a type of drug that increases metabolic activity of an enzyme either by binding or by increasing the expression of gene coding. In contrast, an enzyme inhibitor is a molecule which binds to the enzyme and slows down the substrate molecule activity. In humans, enzyme inhibitors/inducers occur naturally and inducers are involved in the regulation of metabolic pathways. Both inhibitors and are inducers involved in the maintenance
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of homeostasis in the body (Code et al 1997). Table 2 indicates examples for the different types of enzymes, inhibitors and inducers.

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>CYP1A2</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>CYP 2E1</th>
<th>CYP3A4</th>
<th>CYP3A5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducers</td>
<td>Omeprazole</td>
<td>Phenobarbital</td>
<td>Rifampin</td>
<td>Isoniazid</td>
<td>Phenytoin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Cimetidine</td>
<td>Flucanazole</td>
<td>Ritinovir</td>
<td>Disulfiram</td>
<td>danazole</td>
<td>Ketoconazole</td>
</tr>
</tbody>
</table>

Table 2. Enzymes inducers and inhibitors. Examples of CYP enzyme inhibitors, inducers for drug metabolism. Data obtained from Code et al (1997).

Human drug metabolism depends on liver microsomal cytochrome enzymes. Inducers and inhibitors have a significant role in CYP enzyme activity in different races (Code et al. 1997). Depending on the inducer/inhibitor nature, the function of cytochrome enzyme activity is altered. For instance, 50mg drug may undergo rapid metabolism instead of slow metabolism due to inducer. Therefore, one must focus on inducer/inhibitor concept.

Factors Affecting Expression of Drug-Metabolizing Enzymes

Several factors may affect drug metabolism. These may include internal and external factors. External factors may consist of nutrients, various plant products, pharmaceutical agents and other chemicals. According to the Bolt (1994), internal factors include steroid hormones and other endogenous substances. A very high protein diet and high carbohydrate diet also influences the activity of CYP enzymes (Anderson and Kappas, 1991). Patients from different ethnic groups have different life styles and may be exposed to the substances which have a strong influence on the drug metabolism. Liu (1991) discusses the importance of herbal medicine in metabolism. Herbal medicines are popular all over the world. However, patients may sometimes combine the
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western medicine along with the herbal. Liu (1991) explains that whenever severe toxic effects occur patients will blame the clinician rather than herbal medicines. Due to the use of the thousands of herbs all over the world, the potential modern drugs and herbals interaction is endless and may cause variations in drug metabolism.

Other important Drug metabolizers (Non CYP 450 enzymes)

Non CYP metabolizers also influence the drug levels in human plasma. Besides the CYP class, some of the non CYP class of enzymes has further discussed. Most of the drugs are metabolized by the CYP class of enzymes (Daly et al. 1996). Other than CYP class include UDP-glucosyltransferases, flavin monooxygenase 3 enzymes, thiopurine methyltransferase, hepatic UDP-glucuronosyltransferase enzyme. According to the Daly et al. (1996), most of non-hepatic enzymes combine with glucoronic acid and forms most hydrophilic nature substances, which may further undergo urinary excretion from the human body. Other conjugation reactions and some cellular factors may result in the metabolism of drugs.

Thiopurine Methytranferase:

There have been four mutant Thiopurine methyltransferases were identified and represented in the Thiopurine methyltransferase enzymes (TPMT). TPMT exists in different forms in various populations. According to the Klemetsdal et al (1992), frequency of this enzyme is as follows

<p>| | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>---------------</td>
<td>10.1%</td>
</tr>
<tr>
<td>South West Asians</td>
<td>---------------</td>
<td>2.0%</td>
</tr>
<tr>
<td>Chinese</td>
<td>---------------</td>
<td>4.2%</td>
</tr>
</tbody>
</table>
Kenyan population  -------------- 10.9%

The deficiency of this enzyme causes the exaggerated accumulation of the nucleotides and may further cause the toxic metabolites in the urine.

**Hepatic UDP-Glucuronosyltransferase & Glucose S tranferase Enzyme**

UDP-Glucuronosyltransferase (UGT) enzyme is the most important enzyme that is helpful in the removal of the lipophilic and phenolic compounds. There have been 24 different UGT genes identified (Mackenzine et al, 2000). From these, 5 showed the polymorphism character. UGT1A1 gene is among one which shows the greater variations in the polymorphism in nature. Genes and frequency of occurrence may vary from one race to another race. On the other hand, Iyer et al. (1999) describes that in people of African origin, alleles show higher number of UGT1A1 than the non-Africans. UGT1A1 is a type of gene from the enzyme UGT. This UGT1A1 is involved in catalyzing the transfer of glucoronic acids to alcohols, carboxylic acids, amines and free sulfhydryl groups of endogenous and exogenous compounds.

Glucose S transferase (GST) is also another example which is wide spread in tissues and catalyze the conjugation of tripeptide and a variety of drugs. The metabolic end products of these enzyme combinations include mercapturic acid and excrete in urine (Arruda et al. 1998). The two forms of GST enzyme include GSTM1 and GSTT1. These may range from 10-60% in various populations in the world. Table 3 indicates the frequency of the GST alleles in selected populations.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Caucasians</th>
<th>African Americans</th>
<th>Chinese</th>
<th>Indians</th>
<th>Koreans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arruda et al., 1998</td>
<td>55%</td>
<td>NA</td>
<td>9%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chen et al, 1996</td>
<td>53.5%</td>
<td>27.6%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>GSTT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arruda et al., 1998</td>
<td>18.5%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chen et al 1996</td>
<td>15%</td>
<td>24.1%</td>
<td>NA</td>
<td>16%</td>
<td>NA</td>
</tr>
<tr>
<td>Nelson et al, 1995</td>
<td>20.4%</td>
<td>21.8%</td>
<td>64.4%</td>
<td>NA</td>
<td>60.2%</td>
</tr>
</tbody>
</table>


Recently, research has confirmed that other cellular factors can affect the metabolism of enzymes. Nuclear receptors are responsible for the release of hormone response elements and may even induce the set of genes. Consequently, several metabolizing enzymes may be produced to metabolize drug molecules (Wei et al. 2000). Hence, along with the CYP metabolic enzymes other metabolic enzymes also have genetic polymorphism in various races.

**Distribution of CYP2D6 & CYP2C19**

The polymorphic nature of the metabolic enzymes shows its impact in the form of unequal drug metabolism. However, there are number of factors to be considered for a drug to be metabolized. According to Burroughs et al. (2002), biological factors, cultural factors and environmental factors show drug response. In these biological factors include age, gender,
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genetics and disease. Cultural factors attitude, beliefs and family influence. Further, the environmental factors include climate, parasite, pollutants and drugs.

Most of the drugs undergo metabolism and thus become inactivated before clearance. Elimination is the process by which drug products are excreted into blood stream by oxidation methylation and acetylation. Some of the enzymes under cytochrome P450 include CYP2C9, CYP2C19, CYP2D6 etc. Table 4 is an example to show the availability of the CYP2D6 and CYP2C19 enzymes according to the populations.

<table>
<thead>
<tr>
<th>Populations</th>
<th>N-population</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>6</td>
<td>3.4</td>
<td>1.8-18.8</td>
</tr>
<tr>
<td>Asian</td>
<td>8</td>
<td>0.5</td>
<td>0-2.1</td>
</tr>
<tr>
<td>Middle East</td>
<td>2</td>
<td>1.5</td>
<td>1.4-1.5</td>
</tr>
<tr>
<td>CYP2C19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>3</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Asian</td>
<td>6</td>
<td>15.7</td>
<td>5.1-23.6</td>
</tr>
<tr>
<td>Middle East</td>
<td>1</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Caucasian</td>
<td>12</td>
<td>2.9</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 4. Distribution of CYP enzymes. Prevalence of CYP2D6 and CYP2C19 poor metabolizers phenotypes in various populations. Data obtained from Burroughs et al (2002).

Table 4 indicates the prevalence of two enzymes CYP2D6 and CYP2C19 in different populations such as African, Asian, Middle eastern and Caucasian. The occurrence of poor metabolizer (PM) for CYP2D6 in Asian shows 0-2.1% and for the Africans indicates about 18.8% and the Middle eastern is about 2%. In contrast the phenotype prevalence of CYP2C19 3.6% and in Asia is about 24%. Therefore, from these data one can understand that prevalence
of the CYP2D6 and CYP2C19 is not the same for all populations. Since, for the drugs such as debrisoquine, metoprolol and isoniazid require CYP2D6 and CYP2C19 for its metabolism, this study supports project hypothesis by indicating differences in occurrence of CYP enzymes on various ethnic groups.

As noted by Burroughs et al. (2002), Lin and Poland (1995) stated genetic polymorphism exist in most of the CYP enzymes. Daly et al (1996) mentioned that CYP2D6 is the most dramatic example, with more than 20 mutations which may lead to the drug activation or inactivation. Finally, from Table 4 it is clear that CYP enzymes will vary genetically and phenotypically in various ethnic groups.

Why debrisoquin, metoprolol and isoniazid?:

Debrisoquine is a drug which depends on hepatic enzyme (debrisoquine hydroxylase, CYP2D6). Moreover, debrisoquine drug metabolizing enzyme (CYP 2D6) has shown differences in xenobiotic in the various populations of the world. Wong et al. (2000) stated that “debrisoquine has been extensively used to study the CYP2D6 function among various ethnic groups”. Hence, in this research project by studying the metabolic characters of debrisoquine on different parts of world will help to predict the drug doses as well as CYP2D6 activity in different populations.

Hypertension and heart disease are common problems in all over the world. Beta-blocker drugs (such as metoprolol) are commonly prescribed by physicians to treat patients (Lee, 2006). CYP2D6 shows polymorphic nature and different drug metabolic rates in various ethnic populations for the antihypertensive drug metoprolol. Therefore, metoprolol is considered is focused in this project.
Isoniazid is an anti-tubercular drug which is used in combination with rifampicin. Evans et al. (1960) states that isoniazid can reduce the CYP450 enzyme activity. It was also reported that N-acetyl transferase can cause difference in drug metabolism (slow acetylation as well as rapid) in various ethnic group. Kubota et al. (2007) stated that 50% of blacks and Caucasians are slow metabolizers and majority of Asians are poor metabolizers for drugs. Due variation in N-acetyl transferase enzyme, isoniazid is included to study drug labeling with respect to metabolic variation.

**Drug studies in US, UK & Asia**

Drug metabolic variations were reported from different parts of world by several researchers. In a view to have understand the ‘Labeling results’ in this paper, drug metabolic studies were presented in the below discussion.

**Drug metabolism in white and black Americans**

Firstly, for metoprolol a study was conducted by Evans et al. (1993) on 468 white and 105 unrelated black Americans. In this study Evans et al. (1993) reported that black Americans have a lower prevalence of CYP2D6 trait for metoprolol metabolism. Black Americans have been less likely affected by the drugs which are activated by enzyme CYP2D6 (example: metoprolol). The activity of CYP enzymes were observed in the population above 30 years of age. Evans et al (1993) reported a study that black Americans have a lower prevalence of CYP2D6 trait for metoprolol metabolism. Black Americans have been less likely affected by the drugs which are activated by enzyme CYP2D6 (Ex: metoprolol). The activity of CYP enzymes were observed in the population above 30 years of age.
Fig 1. Distribution of CYP2D6A & CY2PD6B enzymes. Comparison of white American and black American populations for distribution of CYP enzymes. Data obtained from Evans et al. (1993).

In Fig. 1, the X axis shows the number of subjects and the Y axis represent percentage of genetic distribution of CYP2D6(A) and CYP2D6(B) in black and white Americans. The white Americans in this study showed 90% of the CYP2D6 (B) enzyme which shows mutations. Evans et al (1993) calculated that as a result of these mutations, 85% of the white American population are poor metabolizers for the metoprolol drug. On the other hand, black Americans showed 60% of the CYP2D6 (B) variant and 50% were identified as poor metabolizers. Due to the high frequency of poor metabolizers metoprolol is prescribed (50mg-100mg according to the FDA labeling) for adults in the American population. Minimum ideal adult dose is considered as 50 mg for metoprolol in US. This is due to the presence of poor metabolizers in whites and fewer poor metabolizers in black American population.

Secondly, another study was reported on 130 Nigerian blacks was conducted for debrisoquine phenotype (Larn & Marshall, 1992). It was reported that very low prevalence of the CYP2D6 PM trait in Nigerian population. These Nigerian subjects showed poor metabolism of the given drug debrisoquine. In support of this, Larn & Marshal (1992) state ancestral Nigerians
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also showed the same mutant CYP2D6 alleles. Hence, due to the presence of high frequency of mutant alleles the dose has been fixed to higher for debrisoquine in black Americans.

In a study conducted by the Laun & Marshall (1992) observed differences in metabolizing isoniazid enzyme (N-acetyltransferase enzyme) from 26 families and 53 two generation families. On the basis of the metabolic differences, individuals are divided into rapid metabolizers and slow metabolizers. Rapid and slow metabolizers were known to cause variation of drug in plasma (Laun & Marshall, 1992). Hence, these studies infer that drug metabolism varies from race to race in US population.

Drug Metabolism in Europeans (UK) region

McGourty and Silas (1985) emphasizes that 9% of the British population exhibits the genetic polymorphism in metabolizing debrisoquine. McGourty and Silas (1985) presented a study of 143 hypertensive subjects on both metoprolol and debrisoquine drugs. The results showed that due to the presence of the autosomal recessive trait in CYP enzymes, metabolism of the metoprolol is altered. Fig. 2 indicates the plasma concentration of metoprolol and debrisoquine.
Fig 2. Distribution of metoprolol and debrisoquine in plasma. Comparison of metoprolol distribution and debrisoquine after administration oral dose for 3 hour and shaded area indicates poor metabolizers of debrisoquine. Data obtained from McGourty and Silas (1985).

From Fig. 2, one can draw a conclusion that plasma concentration of metoprolol is higher in clinical trial subjects. After 3 hours of administration of the drug metoprolol showed nearly 220ng per ml in the subjects. Further, the shaded region indicates the poor metabolizers for the debrisoquine drug with concentration around 300ng per ml. In other words, more subjects in the experiment were poor metabolizers (PM) and showed higher concentration of metoprolol and debrisoquine in plasma at a given period of time. However, the “results” section of this paper indicates the lower doses for the metoprolol and debrisoquine. This McGourty and Silas (1985) experiment indirectly tells the dose should be low for the metoprolol and debrisoquine due to the presence of higher number of poor metabolizers in U.K region (80-100mg of metoprolol and 30mg for debrisoquine). Hence due to the presence of PM of CYP enzymes lower dose drugs are suggested.

Nakajima et al. (2001) suggested two types of traits for metabolizing enzymes 1.) Homogenous dominant 2.) Heterogeneous dominant. In addition, Nakajima et al. (2001) also pointed that drug concentration in plasma may vary due to the polymorphic nature of the
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metabolic enzymes. To support this hypothesis Kubota et al (2007) conducted a study for the different doses such as 300mg, 600mg and 900 mg of Isoniazid in Europe. Kubota et al (2007) findings stated that due to the NACP enzyme, N-acetyl transferase-2 (NATT2) enzyme genetic change makes the difference in the form of rapid and slow acetylators for isoniazid. According to this study dose must be increased to 450mg for rapid acetylators and for the slow acetylators dose must be 150mg. Hence, isoniazid will be effective if the dose ranges from 100mg-450mg.

Drug Metabolism in Asians (Indians & Japan)

In the results, data is collected from India which is the 2nd most populous country in Asia. The Indian population mainly shows poor metabolism. For this indication, the working of the CYP2D6*4 allele was considered. The frequency distribution of the allele CYP2D6*4 was higher in Japan and China. Mutation in this allele leads to the defective proteins, and is mainly found in the 25% of the Indians, but rarely identified in other ethnic groups. Thus this mutation is mainly responsible for the high percentage experience of poor metabolizers (PM) (Leathart et al, 1998). All mutations were associated with the lowering of the enzyme activity substrates which may be further responsible for the lowering of the drug doses.

More than 50 alleles were identified for the CYP2D6 gene (Wong et al. 2000). Out of these, 20 alleles were directly related to metabolism of CYP2D6 substrates. According to Wong et al. (2000), these alleles occur with different frequencies. Asians are poor metabolizers (PMs) due to homozygote for deleted or non-functional CYP2D6 gene. Ultra-rapid metabolism (UM) of CYP2D6 substrates is extremely low in Asians (less than 1%) (Bertilsson et al. 1995) and in Indians is 25% (Wong et al., 1999). Therapeutic failure is often observed in the Ultra-rapid metabolizers. Further, most of the Asian has been observed as Ultra-rapid metabolizers
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(Wong et al. 2000). Hence as Asians are rapid and Ultra-rapid metabolizers higher doses were often preferable for isoniazid, debrisoquine and metoprolol.

**Drug metabolism in Japan**

Due to lack of availability of English-language drug labeling information from the regulatory website, it is not possible to correlate the drug metabolism with the drug labeling. However, some interesting aspects of the CYP enzymes were classified. CYPB26 shows the more inter-subject variability regarding in the level of expression, (Code et al 1997). The expression of CYP2B6 is observed in the 30% of the Japanese population. However due to the lack of Japanese labeling, only comparative studies were discussed.

**Comparative Studies**

Comparative studies give more information on genetic variations which further supports and helps in understanding the nature of CYP enzymes in different Asian groups.

**Comparison of debrisoquine metabolism between Japanese and whites**

In a study conducted by Nakamura et al. (1985), debrisoquine metabolism between white population (183) and Japan (100) shown nearly the same mean values. In this study, Nakamura et al. (1985) found that the same 4-hydroxy metabolite of debrisoquine found in the urine. However, Japanese showed slightly increase in the urinary metabolite. Hence, both of these drugs showed same results.

**Drug metabolism of metoprolol for Japanese versus Chinese**

Horai et al. (1989) proposed metoprolol drug metabolism that was compared between Chinese and Japanese populations. The following histograms provide the metabolism of metoprolol. This small study included 200 Japanese subjects and 93 mainland Chinese subjects. The results show that frequency of metabolism of poor metabolizers (PM) in Japan versus Chinese was 0.5% and 0%. Fig. 4 provides data on metoprolol metabolism.

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From Fig. 4, the shaded region indicates poor metabolizers and the remaining region indicate the extensive metabolizers. As per the results, none of the Chinese showed $\log$ metabolic ratio greater than 10. From Fig.4 one can understand that Japanese population contains more poor metabolizers for the drug such as Metoprolol & debrisoquine.

**Research Question**

Based on the background information and discussion, the correlation between drug labeling and rate of drug metabolism was examined.
Methodology

The published literature was searched for topics concerning drug labeling in relation to the drug metabolism in various groups of ethnic populations. The data base for health sciences EBSCOhost® was used for literature research. Key words used for the research are drug labeling, ethnicity, race and metabolism. Information in US, Europe and British regulatory agencies drug information has been helped to identify doses. The research hypothesis is to compare the labeling differences for some known drugs (debrisoquin, metoprolol & isoniazid) across the world (US, Japan, Europe and Asia) and to correlate with the metabolic variations for the drugs. To support the hypothesis, discussion is mainly focused on the two parts 1.) Discuss the nature of CYP enzymes in correlation with the drug metabolism 2.) Discuss the drug doses in each region such as US, UK and Asia. Further, CYP enzymes polymorphic nature also reviewed in various groups of world. So, in the discussion part of this project, to understand the labeling results CYP enzyme nature is also discussed. The remaining part of this discussion part consists of drug doses with experimental studies in each region US, UK and Asia.

After obtaining the drug doses of three regions, results were tabulated and compared with each other. A brief discussion on drug labeling is presented based on the results of drug dose labeling. According to labeling results, ideal drug dose ranges were established with respect to the polymorphic nature of the cytochrome enzymes. The final outcome of this research paper suggests the ideal adult drug doses to physicians during the treatment of various ethnic groups for drugs metoprolol, debrisoquine and isoniazid.
Drug labeling information is collected from the regulatory agencies of US-FDA, UK-MHRA & Asia-CDSCO (India). The doses for debrisoquine, metoprolol and isoniazid were tabulated below. Table 5 indicates that the US and UK therapeutic drug doses are nearly the same. However, due to the presence of poor metabolizers in the US (due to mixed populations of whites and African Americans) drug doses varied with respect to UK population.

<table>
<thead>
<tr>
<th>Drug</th>
<th>US- FDA drug dose</th>
<th>UK- MHRA drug dose</th>
<th>Asia (India) CDSCO drug dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debrisoquine</td>
<td>250 mg</td>
<td>NA</td>
<td>10mg-300mg</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50mg-100mg</td>
<td>50 mg &amp; 100mg</td>
<td>25mg-100mg</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>200mg-300mg</td>
<td>50mg-300mg</td>
<td>5mg-300mg</td>
</tr>
</tbody>
</table>

Table 5. Drug labeling. Labeling information for drugs (isoniazid, metoprolol and debrisoquine). Data obtained from regulatory agencies such as US-FDA, UK-MHRA, Asia (India)-CDSCO.
Labeling and drug metabolism

Discussion

The term labeling refers to the prescribing information for a marketed drug. It includes description of the drug, indications and usage, metabolism, contraindications and adverse reactions. In other words, labeling means information related to the safe use of drug completed before it gets approved for marketing. The hypothesis of this research paper was that drug metabolic differences correlated with drug labeling differences across the various regions of world. This paper mostly focused on “Drug Metabolism” and “Dosage and Administration” parts of labeling information. Hence, the labeling differences for three drugs (debrisoquine, isoniazid and metoprolol) with respect to “metabolism” in each region have been discussed.

United States

Metoprolol: According to US-FDA labeling information, metoprolol for adults should be between 50mg-100mg. Elimination of this drug depends on the CYP2D6 in US populations. At the steady state, in plasma, bioavailability of metoprolol showed plasma peak concentrations for 50mg-400mg tablets in the adult population. FDA emphasizes that the bioavailability of metoprolol will increase with dose. The immediate-release tablets 50mg and 100mg tablets of metoprolol larger peak effect over a 24 hour. However, for the 400mg, 300mg, 200mg showed larger effect of blood pressure suppression over 24 hours when compared to 50mg of dose. Due to these variations in the plasma concentration, FDA labeling for metoprolol recommends in between 50mg-100mg.

Debrisoquine: US-FDA suggests the dose for this antihypertensive should be between 10mg-20mg. Labeling information indicates that debrisoquine acts as substrate for a polymorphic cytochrome P-450 enzyme. In clinical trials, white American subjects shown poor metabolizing enzyme (CYP2D6A isoform of CYP2D6) and black American subjects shown less amount of
poor metabolizing enzyme acting on debrisoquine. Due to presence of poor metabolizers and less poor metabolizers in healthy subjects, FDA recommends a therapeutic drug dose is in between 10mg-20mg. Subjects with certain isoforms (CYP2D6) of this enzyme are unable to properly metabolize debrisoquine. Hence in US, due to presence of both whites and black populations, ideal adult drug dose expected to be 20mg-30mg of dose.

**Isoniazid:** The recommended therapeutic dose for isoniazid is between 200mg-300mg. Isoniazid is metabolized in liver by N-acetylation. US drug labeling specifies that 50% of African Americans are slow acetylators (poor metabolizers). However, slow acetylation may lead to higher blood levels of the isoniazid. As a result, more chances of increase in toxic reactions. FDA highlights that in healthy subjects 60%-70% of the drug excreted in urine due to the presence of poor metabolizers in healthy subjects. Hence, after considering slow acetylation ideal adult drug dose is expected in between 250mg-350mg. Lower doses for the poor metabolizers (African American population) and higher is for normal individuals.

**United Kingdom**

**Metoprolol:** According to the UK-MHRA, metabolism of metoprolol is by CYP2D6 enzymes in Europeans. MHRA states that 95% of an oral dose found in urine. This is due to the presence of the CYP2D6 (poor metabolism) in the liver of European subjects. Further, plasma peak concentration is achieved with the adult dose of 50mg to 100mg in adult European population. Due to the presence of more number of CYP poor metabolizers in European subjects the adult drug dose is expected to be 80mg-100mg.

**Debrisoquine:** The dose for the debrisoquine is suggested as 4mg-8mg in UK adult population by European Medicines Agency. According to the agency, 40%-60% of European clinical trial
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subjects were poor metabolizers for the hydroxyl debrisoquine polymorphisms. However, labeling information for debrisoquine (particularly drug metabolism with respect race) is not available in UK MHRA. According to the available literature review, the ideal adult drug dose expected in between 25mg-30mg (due to 60% of poor metabolizers in white European populations) is higher than US debrisoquine adult drug dose (20-30mg).

**Isoniazid:** UK-MHRA suggests isoniazid therapeutic drug dose must be used in combination with rifampicin, dose ranging from 50mg, 100mg and 300mg. Clinical trial subjects for the isoniazid plasma peak concentration starting from 50mg of dose. For example, MHRA approved for the drug Rifater (combination of isoniazid with rifampicin) for the use of 50mg. Labeling indicates that isoniazid metabolism variation due to the polymorphic nature of the N-acetyl enzyme in the white European clinical trial subjects. So, due to the presence of poor metabolizers in UK population, the ideal drug dose is suggested as 150mg-450mg which is differed from MHRA therapeutic dose (50mg-350mg).

**Asia (India)**

**Metoprolol:** According to the CDSCO regulatory in India, the metoprolol therapeutic suggested dose is 25mg, 50mg, 100mg, or 200mg but may increase to 300mg. Drug labeling for metoprolol indicates higher doses in Asian than Western populations due to low frequency of CYP2D6 poor metabolizer phenotype in Asians. Drug labeling information therapeutic drug doses for the metoprolol is in between 25mg-300mg. However, by considering the literature review the drug dose for Asian is suggested as 80mg-120mg. This range is important for Asians because of the presence of CYP2D6 rapid metabolizers and less poor metabolizers.
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**Debrisoquine:** Labeling by the CDSCO regulatory agency indicates the drug dose range for debrisoquine is in between 10mg and 20mg. The maintenance dose for the drug is mentioned as 20mg-120mg. As the CYP2D6 shows less poor metabolizers for the Indian population, it is suggested that higher doses of debrisoquine may be appropriate when compared to the US & UK (similar to metoprolol) populations. Hence, expected ideal adult dose must be higher, ranging from 20mg-100mg in Indian population. As the CDSCO suggested Indian population have less poor metabolizers, a higher dose in drug labeling suggested.

**Isoniazid:** Labeling for isoniazid recommends 5mg-300mg dose. However, drug metabolism information is not reviewed in Indian regulatory agency (CDSCO). According to the available literature review information ideal adult drug dose expected in between 20mg-350mg. Drug dose reaches to peak plasma concentrations within 1-2hr for 20mg of drug. A higher dose of 350mg for Asian’s is suggested due to presence of rapid activators for the drug. So that most of the inactivated drug eliminated via urine. Hence, an adult dose for isoniazid is expected as higher when compared to the western countries.

**Summary**

The above discussions on drug doses illustrate that regulatory agencies considered therapeutic effect in giving drug doses before labeling. However, CYP metabolic differences with respect to the race have been ignored. In order to minimize the toxic effects of drugs, metabolic differences according to race also need to be reviewed. So, in the big picture of drug development there regulatory agencies need to avoid unwanted toxic effects of drugs by considering genetic variations of metabolic enzymes. This paper suggests possible ways to regulatory agencies to give better labeling. Some of these are as follows.
Labeling and drug metabolism

- Consider genetic variation in drug metabolizing hepatic enzymes (CYP enzymes) before labeling a drug.
- Evaluate the polymorphic nature of metabolizing enzymes in various races.
- Design the drug dose according to poor metabolizers, rapid metabolizers in various races.
- Drugs cause toxic effects in body without proper elimination due to polymorphic nature of hepatic enzymes. In such cases, a separate drug dose must be formulated according to the metabolic enzymes.

Finally, discussion section of this paper supports “research question” and explains “results” with some suggestions to regulatory agencies.

**Dose suggestions for debrisoquine, metoprolol and isoniazid** According to the above discussions and results, the ideal drug doses for the adult population for the three regions are,

<table>
<thead>
<tr>
<th>Region</th>
<th>Drugs</th>
<th>Drug Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Metoprolol</td>
<td>50mg-100mg</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td>250mg-350mg</td>
</tr>
<tr>
<td></td>
<td>Debrisoquine</td>
<td>20mg-30mg</td>
</tr>
<tr>
<td>Asia</td>
<td>Metoprolol</td>
<td>80mg-120mg</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td>20mg-350mg</td>
</tr>
<tr>
<td></td>
<td>Debrisoquine</td>
<td>20mg-100mg</td>
</tr>
<tr>
<td>UK</td>
<td>Metoprolol</td>
<td>80mg-100mg</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td>150mg-450mg</td>
</tr>
<tr>
<td></td>
<td>Debrisoquine</td>
<td>25mg-30mg</td>
</tr>
</tbody>
</table>

Table 6. Ideal adult drug doses. Ideal adult drug doses for isoniazid, metoprolol, debrisoquine based on the discussions.
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From Table 6, some assumptions can be drawn to physicians:

In general, if a physician is treating white population from the US, UK or Europe, due to the high frequency of poor metabolizers, low therapeutic drug doses must be prescribed (slightly higher doses than US drug dose must be prescribed in UK, due to the high frequency of white population than black in UK)

In general, if a physician treating Asians, Chinese or Japanese group of populations slightly higher drug doses than whites must be prescribed due to low prevalence of CYP poor metabolizers (PM)

Lastly, if a physician is treating African population, normal therapeutic drug doses must be prescribed. This is due to the wide variation of the CYP polymorphic enzymes in different parts of Africa.
Labeling and drug metabolism

Conclusion

Based on the discussion of this research paper, regulatory agencies across UK, US and Asian regions doesn’t seem to meet all labeling requirements for debrisoquine, metoprolol and isoniazid. Currently, data collected from different areas specifies regulatory agencies are considering poor metabolizers and slow metabolizers in labeling packages for fixing therapeutic drug doses. However, impact of genomics and polymorphic nature of enzymes on different races have been ignored by the agencies. Further, background information suggests that drug metabolisms will be greatly influenced by diverse nature of CYP genes and alleles. However, polymorphic nature hypothesis is further confirmed by the experimental and comparative studies for US, UK and Asian regions. The final outcome of this project is prescribing ideal adult drug doses (metoprolol, debrisoquine and isoniazid) to physicians when treating different ethnic populations.

These findings are preliminary only and should not be considered as definitive. Further research and consistent mechanisms of drug metabolism on various races are necessary to address this issue accurately.
References


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