Ethnicity And Its Relation To Pharmacokinetics And Pharmacodynamics

Ethnicity is one factor that may represent the recognized differences in both pharmacokinetics (PK) and pharmacodynamics (PD) of medications, resulting in variability in response to drug therapy. Given that the appropriateness of clinical examination results to the treatment of an individual patient is a basic consideration in a doctor's decision of drug treatment, drug development should be focused and looked into to ensure that a clinical pharmacologic evaluation includes a population that is representative of the target therapeutic population. Ethnic diversity in drug response with respect to safety and efficacy and the resulting differences in recommended doses have been well described for some drugs. Some of these differential responses may be related to the pharmacogenomics of a particular drug. Pharmacogenomic techniques have recently enjoyed widespread use in studies of drug exposure and response

In this review, we'll be discussing about some drugs which are warfarin, omeprazole, and methadone. Each of the drugs mentioned have different pharmacokinetics variability among ethnicities and have different effects.

Warfarin is probably the best known and most widely used oral anticoagulant. It is a non-habit forming medication used to limit the size of existing blood clots and to prevent formation of new blood clots in high-risk patients. Methadone is a synthetic, long-acting opioid with pharmacologic actions qualitatively similar to morphine and is active by oral and parenteral routes of administration. It is primarily a ?-receptor agonist and may mimic endogenous opioids, enkephalins, and endorphins and affect the release of other neurotransmitters—acetylcholine, norepinephrine, substance P, and dopamine. Omeprazole, like other PPIs, inhibits gastric acid production by binding to and inactivating the H+/K+-ATPase of gastric parietal cells, causing inhibition of the proton pump that transports H+ into the gastric lumen, the common final step in gastric acid production.

Warfarin

Warfarin is one of the anticoagulants that is commonly used today. Sometimes, people used to call it as blood thinner or blood thinning agent. It is a prescription drug that we usually consume for preventing blood clots to form in our blood vessels. The advantages of blood clots which is to stop bleeding to avoid blood loss, but the disadvantages of blood clots which are heart attack, deep vein thrombosis, pulmonary embolism and stroke. Hence, warfarin is usually taken by people with an irregular heartbeat, prosthetic heart valves, and people who have suffered a heart attack. Warfarin is also used to treat or prevent venous thrombosis and pulmonary embolism.

The liver will synthesis different types of clotting factors such as clotting factors II, VII, IX, and X. Vitamin K is an essential cofactor for the synthesis of all of these clotting factors. Therefore, we used to call them as vitamin K-dependent clotting factors.

The mechanism of action of warfarin is that it will competitively inhibit the VKORC1 also known as vitamin K epoxide reductase complex 1. This enzyme's function is to activate the vitamin K so that the amount of activated vitamin K will increase in the body. Hence, warfarin can stop vitamin K activating process by inhibiting this enzyme. Therefore, it reduce the synthesis of active clotting factors via this mechanism.

However, the dose-response of warfarin is variable among the patients and depends on specific factors of the patients. Some patient-specific factors such as drug metabolism, patient's diet, genetics, vitamin K-dependent clotting factors, disease states, binding proteins, drug interactions, and medication adherence should be assessed before using warfarin.

For this part of the assignment, we are going to discuss about the variation of the enzyme in different ethnic group which may affect the pharmacokinetics of warfarin.

Pharmacokinetic of Warfarin

Absorption

According to warfarin chemistry structure, it is a racemic mixture of a right-handed and a left-handed stereoisomer. Hence, it used to be called as R and S isomer. According to research, this racemic mixture half-life is approximately 36 to 42 hours. The S isomer is five times more potent as a vitamin K antagonist than the R-isomer. Studies have proved that absorption of warfarin is rapidly and complete.

Distribution

After absorption in the gastrointestinal tract, warfarin is highly bound to protein which is about 97%. Studies had shown that warfarin is primarily bound to protein albumin. Besides that, only the unbound warfarin is pharmacologically active. Therefore, when the serum albumin level is low, the free fraction of warfarin is increased, followed by increased in plasma clearance.

Metabolism

According to Andrew Blann et al., the Asians and Afro-Caribbeans may have different levels of the various enzymes that regulate vitamin K metabolism when compared to the Caucasians. This shows that there are enzymes that play an important role in metabolized warfarin specifically.

The enzyme involves in warfarin metabolism is CYP2C9. The wild type is CYP2C9*1 and scientist has found that two variant forms with reduced activity which are CYP2C9*2 and CYP2C9*3. Research has shown that patients with at least one of the two genetic variants could have serious bleeding incident. In clinical studies, individuals heterozygous for CYP2C9*1/*2 required a 20% lower mean maintenance dose of warfarin to sustain therapeutic anticoagulation than the wild type homozygotes. The CYP2C9*3 variant has been found to have a pronounced reduction in catalytic activity across all CYP2C9 substrates. A decreased metabolic clearance of S-warfarin was found in individuals heterozygous for CYP2C9*3.

Recently, there are three more CYP2C9 variants have been identified which are *4, *5 and *6.

But the metabolic consequences of individuals carrying those alleles remain to be evaluated.

After that, researchers have found that that carrier of the CYP2C9*5 allele, which is expressed among African Americans, would eliminate CYP2C9 substrates at slower rate relative to individuals expressing the wild type protein. They suggested that screening for CYP2C9 variants may allow clinicians to develop dosing protocols and surveillance techniques to reduce the risk of adverse drug reactions in patients receiving warfarin.

Another study shown that patients with either CYP2C9*2 or CYP2C9*3 variant alleles require a lower warfarin dose. The risk of bleeding in patients with CYP2C9*2 and CYP2C9*3 alleles is approximately double during initiation of warfarin treatment as compared to wild type genotype carriers CYP2C9*1/*1. The frequencies of these variant alleles vary from race to race. Hence, they found that these variant allele increased in Caucasians as compared to African-Americans, Africans and Asians.

In another studies, researcher has found that genetic factors accounted for a larger proportion of the dose variability for European American patients whereas clinical factors accounted for a larger dose variability in African Americans. They noted that the gene variants may have a different effect on dose across race groups. For example, European Americans with a variant of CYP2C9*2 required less of the drug according to race-specific dosing models whereas African Americans did not.

Excretion

Primarily, the metabolites of warfarin is eliminated by glomerular filtration in the kidney. If calculated by percentage, it is 92% eliminated from kidney.

Researchers has reported that patients with heterozygous or homozygous CYP2C9*3 mutations exhibited 63 to 66% and 90% reductions in the clearance for S-warfarin compared with those with homozygous CYP2C9*1 (wild-type). In addition, they found that the clearance to (S)-7-hydroxywarfarin in these groups of patients was reduced to a similar extent as the clearance for (S)-warfarin.

Besides that, some researchers also reported that patients with the CYP2C9*1/*2, CYP2C9*2/*2, CYP2C9*1/*3 or CYP2A6*1/*2 genotypes required on average 15 to 30% lower maintenance dosages of racemic warfarin than those with the CYP2C9*1/*1 genotype. These could imply that the CYP2C9*2 variant may be associated with reduced in vivo elimination of (S)-warfarin, although to a lesser extent than that elicited by the CYP2C9*3 variant. At present, it remains unclear whether patients with homozygous CYP2C9*2 variant which is CYP2C9*2/*2, or with combined heterozygous variants of CYP2C9*2 and CYP2C9*3 which is CYP2C9*2/*3, have a significantly altered elimination of (S)-warfarin compared with those having the homozygous wild-type CYP2C9.

Methadone

Methadone is a synthetic opioid agonist which is very effective to treat opiate addiction. Morbidity and mortality associated with opiate addiction can be reduced when methadone maintenance therapy was given to patient. Methadone is also a racemic mixture of R- and S-

enantiomers. R-enantiomer can provide therapeutic effect at mu-opioid receptors while both R- and S- enantiomers are known to have weak affinity towards N-methyl-D-aspartate (NMDA) receptor antagonists. When concentration of R- and S-methadone is above the therapeutic level, detrimental side effect will occur. Elevated R-methadone will depress ventilation which induce respiratory depression as the excess R-methadone will act on the respiratory centers in brainstem. However, excess S-methadone will block the voltage-gated potassium channel of the human ether-a-go-go related gene (hERG), which will prolong QT intervals of ECG leading to torsades de pointes. This will results in cardiotoxicity.Most of the studies about methadone pharmacokinetics only evaluated based on total methadone levels. However, there are also variability exists in pharmacokinetics within and between enantiomers. Although methadone is effective in opiate overdose therapy, it is considered difficult to use with its highly variable pharmacokinetics.

Pharmacokinetics of Methadone

Metabolism

Methadone is primarily metabolized by cytochrome P450(CYP) enzymes that present in the liver. This metabolism is predominantly done by CYP2B6 and followed by CYP3A4,2C19 and 2D6. CYP2B6 is the predominant determinant which involved in the N-demethylation of methadone and clearance. This enzyme also display stereoselectivity towards S-methadone.3 Single nucleotide polymorphisms(SNPs) which is located in CYPs may play an important role in altering the metabolism of methadone. When there is several SNPs occur in the CYP enzymes which are important in the metabolism, increased methadone plasma concentrations, decreased N-demethylation and decreased methadone clearance will be observed. African Americans will have significantly lower methadone metabolism and clearance due to the larger proportion of CYP2B6*6 carrier. Hence, they will have a greater risk of experiencing those detrimental adverse effect. It is said so as the diminished in metabolism and clearance will increase methadone plasma concentration which may lead to methadone toxicity. On the other hand, those population with more CYP2B6*4 allele will have increased methadone clearance which resulted in diminish of plasma concentration. Generally, CYP2B6 variant will have greater influence on the metabolism of S- enantiomers rather than R-enantiomers and oral than intravenous methadone.

CYP2D6 is another enzyme which is mainly expressed in liver and is not inducible also involved in methadone metabolism. It also subjected to genetic polymorphism, SNPs. According to research, prevalence of poor metabolism phenotype is higher in Europe with a mean value of 7.4% and lower in Orientals with mean value of 1%. For the rapid metabolizer, the prevalence will be 1% in German population, 7% in Spanish and about 2 to 5% in Black population.

Elimination/Clearance

Metabolites produced in the metabolism will be eliminated in the urine. Renal excretion of methadone is related to the urinary pH, however, manipulation of urinary pH will not impact the treatment of methadone toxicity as overall elimination of methadone in urine is small. Methadone also eliminated in feces mostly as metabolite with less than 5% as methadone. This methadone systemic clearance included both metabolic clearance and renal clearance with more dependence on metabolic clearance which can be evidenced by the significant correlation between methadone metabolism and apparent oral clearance. As mentioned in the section

above, metabolism is greater in CYP2B6*4 than CYP2B6*6. Hence, clearance of CYP2B6*4 is greater than CYP2B6*6. African American with greater number of CYP2B6*6 and/or absence of CYP2B6*4 have lower clearance.

Among are a minor ethnicity from the mountains of Laos which historically and linguistically linked to Southern China. Hmong still remain a non-admixed ethic minority which their ethnicity can serve as surrogate maker for the genetic influence on the methadone pharmacokinetics. Microsatellite maker studies performed in other minorities from same geographical region is used to support unique background of Hmong. According to research, it is found out that these Hmong ethnicity is associated with the reduced clearance. This reduced clearance in Hmong is consistent with the findings that lower methadone dose is required for Hmong patient to reach stabilization. These findings indicate that this population have their own unique pharmacogenetic or plasma protein binding influences on methadone. Findings revealed that the CYP2B6 516>T (rs3745274) minor allele will decrease clearance of S-methadone. According to the study, researcher found a significant difference in treatment retentions between Hmong and non-Hmong patients which enrolled in methadone maintenance program. Hence, the Hmong required significantly lower dose of methadone as they have a significantly greater retention time than non-Hmong. This greater retention time is somehow associated with the decreased clearance in Hmong population. There was a significant association between methadone dose and retention. However, Hmong are still less likely than non-Hmong to stop the treatment even after the dose adjustments of methadone.

Omeprazole

Omeprazole is one of the types of gastric medications which are used commonly to reduce gastric acid secretion. It is used to treat gastrointestinal conditions such as gastroesophageal reflux disease (GERD), excessive acidity in stomach, stomach or peptic ulcer, hypersecretory conditions such as Zollinger-Ellison syndrome and etc. Besides that, this medication is also used to some types of stomach problems which are caused by a type of bacteria known as Helicobacter pylori (H.pylori) together with several types of medications including antibiotics.

Omeprazole is a selective and irreversible proton pump inhibitor in which it works by suppressing stomach acid secretion by specific inhibition of the H+/K+-ATPase found at the secretory surface of gastric parietal cells. Due to the inhibition of this enzyme pumping system, final step of acid production is inhibited. When administration of omeprazole is stopped, baseline stomach acid secretory activity will eventually return after 3 to 5 days and plateau on the inhibitory effect of omeprazole on acid secretion will occur after 4 days of repeated daily dosing.

Generalization is always a conflicting point when it comes to drug dosing whether should it be applied or not especially among different ethnicities (Asians and Caucasians) in which genetic variation plays an important role in determining metabolizing enzyme constitution or should we apply customized therapy accordingly and this will be discussed more in the pharmacokinetic process part III and IV below. This is a concern as metabolizing enzymes are essential in the pharmacokinetic process of drugs in the body especially metabolism and excretion of drugs which will greatly affect the drug plasma concentration level which will further link to toxicity.

Pharmacokinetics of Omeprazole

Absorption

Omeprazole is acid labile and therefore absorption of omeprazole takes place in the small intestine. This process usually occurs rapidly and can be done on an average of 3 to 6 hours. The bioavailability of this drug is about 40% due to instability in gastric acid as well as a substantial first-pass effect. However, it can be increased slightly by altering the dosage regimen such as by giving repeated dosing.

Distribution

Omeprazole has a volume of distribution of 0.4 L/kg and a high plasma protein binding of almost 95%. In contrast to the long duration of antisecretory action, omeprazole is rapidly eliminated from plasma. The half-life is less than 1 hour, and omeprazole is almost entirely cleared from plasma within 3-4 hours.

Metabolism

Omeprazole undergoes significant hepatic first-pass metabolism and is completely metabolized in the liver by the polymorphic CYP 2C19 enzyme (S-mephenytoin hydroxylase), thus, kinetic differences between racial groups can be observed. Omeprazole is a prodrug and has to be activated prior its action to be exerted and the two major plasma metabolites are the omeprazole sulphone and hydroxy omeprazole.

Genetic variation of CYP 2C19 can be explained by a limited number of single-nucleotide polymorphisms, namely, in which includes allele CYP 2C19* 2, CYP 2C19*3, CYP 2C19*4 and CYP 2C19*5. However, it is almost explained for 100% that of for Asian and 85% for white that are poor metabolizers (PM) is due to the mutations of alleles which are the CYP 2C19* 2 and CYP 2C19*3 respectively which is related to inactive enzyme production. This then brings to a marked ethnic variability in S- mephenytoin hydroxylation, with 2% to 5% PMs in white populations and 13% to 23% PMs in Asian populations in which these two alleles are higher in Chinese compared to Caucasians. Clinical measurements are done and area under the curve (AUC) is used as an indicator as systemic exposure to proton pump inhibitor and it is observed that the concentration is 5-12-times folds in poor metabolizers than in extensive metabolizers (EM).

This in turn supports several studies that the AUCs of omeprazole were significantly higher in the Chinese EMs than in the Caucasian EMs possibly due to the higher proportion of heterozygotes in the former than in the latter group. Therefore, the initial genotyping was done for this enzyme and a much higher dosage must be given to an extensive metabolizer to improve the therapeutic effect of proton pump inhibitors for ideal gastric acid suppression. In another way, poor metabolizers experience superior acid suppression than the rest of the population due to higher blood concentrations of omeprazole which leads to the decrease of dose administered which will then decrease side effects of this drugs.

Early identification of ethnic sensitivity is needed for different dosing regimens in a specific ethnic group for substrates of CYP2C19 for omeprazole metabolism in this case for maximum therapeutic effect and minimize drug toxicity and side effects.

Excretion

Omeprazole is mainly excreted by the kidneys and the plasma half-life normally between 1/2 to 1 hour and the interesting part about this drug is their effects may persist for days. The elimination half-life observed and obtained in the Chinese PMs and EMs was 2.4 +/- 0.2 and 0.8 +/- 0.2 h--similar to the observations in the Caucasian subjects However, elimination half-life of the hydroxy metabolite observed to be longer in PMs than in EMs in both of this two populations which was being studied.

Conclusion

Review of the current literature on racial differences in pharmacokinetics of drugs supports the premise that only pharmacokinetic processes which are biologically or biochemically mediated have the potential to exhibit differences between racial or ethnic groups. Thus, the pharmacokinetic factors which can be expected to potentially exhibit racial differences are for example, bioavailability for drugs which undergo gut or hepatic first-pass metabolism, protein binding, volume of distribution, hepatic metabolism, and renal tubular secretion.

Absorption (unless active), filtration at the glomerulus, and passive tubular reabsorption would not be expected to exhibit racial differences. As is evident from this review, there are relatively few drugs for which there is information on ethnic or racial differences in pharmacokinetics. Thus it is often necessary to try to predict whether such differences might exist. Taking into consideration the above factors and evaluation of the pharmacokinetic characteristics of the drug, it should be possible to identify those drugs most likely to exhibit differences in their pharmacokinetics. For example, a drug which is eliminated entirely by the kidneys through filtration and reabsorption and is not highly bound to plasma proteins (or is bound to albumin) is highly unlikely to exhibit racial differences in its kinetics. Conversely, a drug which undergoes significant gut and/or hepatic first-pass metabolism and is highly bound to AGP is much more likely to exhibit kinetic differences between racial groups. A discussion of the impact of racial differences in kinetics on drug response or racial differences in drug efficacy, toxicity, or pharmacodynamics (concentration-response relationship) is beyond the scope of this review