A Physiologic Approach to the Pharmacogenomics of Hypertension

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Hypertension is a multifactorial condition with diverse physiological systems contributing to its pathogenesis. Individuals exhibit significant variation in their response to antihypertensive agents. Traditional markers, such as age, gender, diet, plasma renin level, and ethnicity, aid in drug selection. However, this review explores the contribution of genetics to facilitate antihypertensive agent selection and predict treatment efficacy. The findings, reproducibility, and limitations of published studies are examined, with emphasis placed on candidate genetic variants affecting drug metabolism, the renin-angiotensin system, adrenergic signalling, and renal sodium reabsorption. Single-nucleotide polymorphisms identified and replicated in unbiased genome-wide association studies of hypertension treatment are reviewed to illustrate the evolving understanding of the disease's complex and polygenic pathophysiology. Implementation efforts at academic centers seek to overcome barriers to the broad adoption of pharmacogenomics in the treatment of hypertension. The level of evidence required to support the implementation of pharmacogenomics in clinical practice is considered.

Key Words: Antihypertensive, Pharmacogenomics, Implementation, Cytochrome P450

INTRODUCTION

Essential hypertension affects over 40 million Americans and is associated with significant morbidity and mortality. Blood pressure (BP) response to specific antihypertensive agents is highly variable with the mean BP response typically similar to the standard deviation of the response measured. Although physiologic pathways are known to regulate BP and BP response to specific classes of antihypertensive agents, the management of patients with essential hypertension has suffered from a "hit or miss" approach, and BP control rates remain low, at approximately 40% in the general population. Demographic characteristics including age, gender, and ethnicity are informative regarding the selection of class of antihypertensive agent; however, other variables (including genotype) that predict BP response are lacking. In part, measures of relative activation of the renin-angiotensin-aldosterone system (RAAS) including plasma renin (REN) activity, plasma REN activity/aldosterone ratios, and plasma REN activity indexed for sodium intake have helped to guide selection choice of antihypertensive agent (typically diuretic vs no diuretic), but significant variation in response to antihypertensive agents exists, even when these characteristics are included while using a specific class of antihypertensive agent.

Hypertension is a multifactorial disease with convergent and divergent physiologic-regulating systems contributing to its presence, severity, and pathways involved in pharmacologically mediated reduction in BP levels. Counter-regulatory systems play a significant role in the development of hypertension and response to therapy, and establishing genetic predictors of antihypertensive response has been less than ideal. Although candidate gene approaches and genome-wide association studies (GWAS) are beginning to demonstrate validated genetic predictors of BP response to antihypertensive therapy, it is most likely that yet-to-be identified significant genetic predictors exist in the form of rare (<1% allele frequency) variants, copy number variation, intronic flanking polymorphisms, RNA variation, and finally that there is a high likelihood that BP response to a given antihypertensive agent is due to polygenic causes. In this review, we have elected to review in a physiologically guided manner, the pharmacogenomics of hypertension and provide a review of available and published studies, including their findings, reproducibility and their limitations (Table 1).

METABOLISM POLYMORPHISMS

Polymorphisms in genes encoding the enzymes responsible for phase I and phase II biotransformation contribute to interindividual differences in antihypertensive drug pharmacokinetics. The cytochrome P450 enzymes are part of a microsomal metabolism system in the smooth endoplasmic reticulum that resides predominantly in hepatocytes and in other cells. These enzymes catalyze phase I nonsynthetic metabolism of xenobiotics through oxidation, reduction, and hydrolysis. In contrast, phase II synthetic biotransformation enzymes catalyze the conjugation of drugs through glucuronidation, acetylation, sulfation, and methylation. The phase I and phase II metabolism of antihypertensive drugs often leads to their activation or deactivation.

Functional polymorphisms may modify either expression or function of metabolic enzymes that will ultimately influence the parent drug and metabolite concentrations. These concentration changes manifest as alterations in the phenotypic response (BP response to a drug) and in pharmacokinetic parameters such as drug clearance, area under the curve, or maximum concentration (C_{max}). During drug development, the US Food and Drug Administration (FDA) provides regulatory guidance to

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pharmaceutical companies regarding both *in vitro* and *in vivo* drug metabolism and drug interaction studies. As a result, a drug's metabolic enzymes are often known and have received great attention in candidate gene analyses to explore relevant genotype–drug interactions.

Metoprolol is predominantly metabolized by CYP2D6. At least 74 variant alleles of *CYP2D6* have been described, including nonfunctional and loss of or reduced function alleles.[137] Individuals who are homozygous for the nonfunctional alleles are defined as poor metabolizers with a resultant extended half-life of metoprolol. Intermediate metabolizers are heterozygous for nonfunctional alleles or homozygous for reduced function alleles, whereas extensive (normal) metabolizers are homozygous or heterozygous for reference functional alleles. The functional allele frequency for Caucasians is 71%, and for those of African and Asian ancestry, it is closer to 50%.[138] The FDA label of metoprolol succinate cautions that the CYP2D6 enzyme is absent (poor metabolizer status) in about 8% of Caucasians and about 2% of most other populations. Gene duplication is also not uncommon for *CYP2D6*, with 12 or more copies previously reported.[139] Individuals with increased *CYP2D6* copy number are considered ultrarapid metabolizers.

Variant alleles in poor and intermediate metabolizers of CYP2D6 have been associated with increased plasma metoprolol levels even after extended year-long dosing. Poor metabolizers also have corresponding changes in their ratio of metoprolol to alpha-hydroxy-metoprolol metabolite.[140] Some small studies have failed to reveal significant adverse events or BP effects associated with metabolizer status, despite changes in pharmacokinetic parameters.[26] However, a prospective, double-blind, longitudinal study of metoprolol use found significant differences in diastolic blood pressure (DBP), QT interval, heart rate, and incidence of bradycardia.[27,28] As such, the Dutch Pharmacogenomics Working Group (DPWG) has endorsed *CYP2D6* screening with the use of metoprolol.[29] The group recommends selection of an alternate drug or a 75% dose reduction in poor metabolizers, 50% dose reduction in intermediate metabolizers, and titration up to a maximum of 250% of the normal dose in ultrarapid metabolizers.

The role of *CYP2D6* has been explored with other beta blockers, including carvedilol. Genotype appears to affect carvedilol clearance and concentration.[35,141] Analogously, genotype is a predictor of drug dose in retrospective analyses.[2] However, alterations in clinical phenotype or therapy response have not been observed.[2,141] Variant alleles in *UGT1A1* have also been shown to alter clearance and glucuronidation of carvedilol, without affecting clinical phenotype.[142]

CLINICAL SUMMARY

- Genetic variation contributes to interindividual differences in antihypertensive agent response.
- Although multiple single-nucleotide polymorphisms are associated with antihypertensive drug metabolism, pharmacodynamic effects, and efficacy, most identified polymorphisms do not have a level of evidence necessary to support routine clinical use.
- Genome-wide association studies have uncovered promising variants that require further prospective investigation to warrant broad implementation into clinical practice.

Other cytochrome P450 enzymes similarly alter antihypertensive medication metabolism. Losartan is a prodrug metabolized into its active carboxylic acid metabolite by CYP2C9 and CYP3A4. The metabolite is predominantly responsible for the angiotensin II receptor antagonism of losartan. Losartan's FDA label cautions that in approximately 1% of individuals, minimal conversion of losartan to the active metabolite occurs. *In vitro* studies have suggested that CYP2C9 contributes to losartan metabolism to a greater extent than CYP3A4.[40] Candidate pharmacogenomic analyses have illustrated that the *CYP2C9**3 reduced function allele is associated with decreased formation of losartan's active metabolite.[41,143] Limited clinical data are available to confirm pharmacodynamic effects. However, associations have been uncovered between the *3 allele and less favorable BP and proteinuria reduction in Caucasians with CKD.[144] In the Losartan Intervention for Endpoint reduction in Hypertension study, homozygotes with the *2 allele had decreased losartan response; however, this association did not remain significant after adjusting for multiple testing.[42]

Data regarding amlodipine and verapamil are less convincing. These calcium channel blockers are known to be metabolized by CYP3A4 and CYP3A5 through drug interaction data. In a small Korean population, amlodipine concentrations (area under the curve and C_{max}) were reduced in individuals with a CYP3A5*1/*1 genotype.[145] These data are the opposite of those expected, and conflict with *in vitro* data suggesting amlodipine is primarily metabolized by CYP3A4.[146] Although a single study revealed associations between genotype and the pharmacokinetics of amlodipine, *CYP3A5* genotypes have not been found to be associated with amlodipine efficacy.[145,147] Similarly, the *CYP3A5**3 and *6 alleles were not significantly associated with verapamil response.[148] In contrast, the single nucleotide polymorphisms (SNPs) rs2740574 and rs2246709 affecting CYP3A4 metabolism were associated with verapamil use and target BP goals in the African American Study of Kidney Disease and Hypertension Trial.[147] More studies are required to understand the clinical relevance of cytochrome P450 pharmacogenetics in calcium channel blocker metabolism.

Hydralazine undergoes phase II biotransformation by N-acetyltransferase 2. A slow acetylation phenotype is found in 90% of North Africans, 50% of Caucasians, and up to 30% of Asians.[149] The slow phenotype is associated with the *NAT2**5, *6, and *7 alleles. The FDA label of hydralazine warns that plasma levels of hydralazine vary widely among individuals. Patients with *5, *6, and *7