The Role of Ethnicity in Variability in Response to Drugs: Focus on Clinical Pharmacology Studies

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Ethnicity is one factor that may account for the observed differences in both pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, resulting in variability in response to drug therapy. Given that the applicability of clinical study results to the treatment of an individual patient is a critical consideration in a physician's choice of drug therapy, drug development should seek 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. The clinical relevance of variability in drug response due to pharmacogenomics of drug-metabolizing enzymes was considered at a September 2004 workshop cosponsored by the US Food and Drug Administration (FDA), Johns Hopkins University, and the Pharmaceutical Research and Manufacturers of America (http://www.fda.gov/cder/Offices/OCPB/workshops.htm).[1]

The FDA recognizes that standard methods of defining racial and ethnic subgroups are necessary to ensure consistency in demographic subset analyses, to compare results across studies, and to assess potential subgroup differences in safety and effectiveness. The FDA published the Demographic Rule (CFR 314.50 d (5)) in 1998 and a guidance document in 2005 on collection of race and ethnicity data in clinical trials (http://www.fda.gov/cder/guidance/5656fnl.htm). Standard ethnicity categories, as recommended by the Office of Management and Budget and followed by the FDA, are "Hispanic/Latino" and "Not Hispanic/Latino." For race, the minimum categories recommended are American Indian/Alaska Native, Asian, black or African American, native Hawaiian or other Pacific Islander, and white. More detailed characterizations of race may be collected.

In 1999, the FDA, under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, published the guidance "Ethnic Factors in the Acceptability of Foreign Clinical Data" (E5 Guidance, http://www.fda.gov/cber/gdlns/ichethnic.txt). The guidance defines ethnic factors as those relating to races or large populations grouped according to common traits and customs and considers three major racial groups: Asian, black, and Caucasian. The guidance identifies situations for which drugs could be "ethnically sensitive" and suggests the types of bridging studies that may be required for extrapolating clinical trial results from one region to another. Factors that may contribute to such ethnic sensitivity of a drug include genetic polymorphisms in metabolic pathways, steep dose–response curves, and high intersubject variation in bioavailability. The E5 guidance provides a general framework for evaluating medicines with respect to their sensitivity to ethnic factors.

With accessible tools to address the mechanisms underlying variability in response to drugs, and in light of global approaches to drug development, it is useful to consider how this has been applied to drug development in the United States and identify opportunities for optimal consideration of ethnic differences in drug response, whether drug development programs are carried out in the United States or in other countries. This article highlights several aspects of ethnicity and pharmacogenomics as related to clinical pharmacology (for example, variability in drug-metabolizing enzymes, transporters, and drug targets that have a bearing on drug dose or on adverse drug reactions) and considers the implications of ethnic differences as they apply to early drug development.

MECHANISTIC BASIS FOR ETHNIC DIFFERENCES IN RESPONSE TO MEDICATIONS
Potential causes of variability in drug response include extrinsic factors such as food and concomitant medications as well as intrinsic factors such as gender, race and ethnicity, age, weight, renal or hepatic function, and genetic differences in

the expression of enzymes that metabolize or transport drugs or in the expression of targets of drug therapy. The FDA has provided recommendations relating to many of these factors in the context of drug development, the most recent being evaluation of study design with respect to concomitant medications.[2] A recent review of the drug metabolism area[3] suggests that one of the most important sources of variability in drug exposure is genetic variability in drug-metabolizing enzymes. Drug companies increasingly bank DNA samples to investigate this variability.[4] The potential contribution of critical drug-metabolizing enzymes, drug transporters, and drug targets to ethnic variability in drug exposure or in drug response can be gleaned from a review of differences in variant alleles with respect to function and prevalence in different populations as shown in **Table 1.** Although the clinical relevance of some variants (e.g., CYP2D6 and CYP2C19) is well characterized, the relevance of many of those listed in **Table 1** is as yet unknown. Differences among ethnic groups in drug-metabolizing enzymes and transporters could potentially result in variability in PK in early clinical pharmacology studies on which dose selection for phase II and III clinical studies may depend. Although this is plausible, there are no recent examples of this application in currently approved drugs. There is, however, a possible past example. It is striking that the dose range of many tricyclic antidepressants (e.g., desipramine and trimipramine) is wide (e.g., 25–300 mg). This may have been the result of observations of toxicity that result from the nearly 10-fold increase in desipramine area under the curve (AUC) in CYP2D6 poor metabolizers, who comprise ~8% of a typical white population. A low recommended starting dose allows for dosing in this subpopulation or other vulnerable population groups, such as the elderly and adolescents. Had the drug been initially used in a population with a very low prevalence of poor metabolizers, this need for a low starting dose might have been unrecognized. Whether studies are conducted within the United States or elsewhere, the potential contribution of genotype with respect to drug metabolism or transport pathway must be taken into consideration.

SURVEY OF ETHNICITY IN LABELING OF NMEs APPROVED FROM 2004 TO 2007

We conducted a survey of the approved labels of all small-molecule new molecular entities (NMEs) approved from 2004 through 2007 to determine the extent of race- or ethnicity-based information in the approved label with respect to PK, safety, and efficacy. The survey does not characterize the actual data collected in clinical trials; instead, it reflects the information expressed in the labeling. The results are shown in **Table 2.** In some cases, the labels reflect the fact that the PK of the drug was evaluated with respect to race, particularly over the period from 2005 to 2007, in which >50% of the labels had pharmacokinetic data based on race. The majority of the labels for NMEs approved during this period did not include evaluation of the effect of race/ethnicity on efficacy or safety, although over the period from 2005 to 2007 >50% of them overall included racial or ethnic demographic information in the descriptions

of clinical trials. This racial or ethnic demographic information was not necessarily reflected in efficacy or safety information. There were no instances of dosing based on ethnicity. Given that ethnicity/race information is almost always collected during clinical trials, its omission from labeling presumably means that nothing critical was observed or, alternatively, that the specific ethnic population was not large enough to allow identification of differences, if any.

The impetus for evaluating the effect of race or ethnicity on PK or PD of an NME could be based on knowledge of the drug metabolism pathway or transporters contributing to exposure. The contribution of specific metabolic pathways or transporters was identified in labels of the NMEs approved from 2004 through 2007, as shown in **Figure 1**. When such a pathway was described, the most commonly identified was CYP3A, consistent with the recognition that CYP3A is involved in the P450 metabolism of the largest number of metabolized drugs. Of note, the contribution of CYP3A5 to the CYP3A pathway was not mentioned. CYP3A5 has been shown to be differentially expressed in white and African-American populations as exemplified by tacrolimus (**Table 1**).[5] Pathways for metabolism and elimination information were not identified in the labels of 25 NMEs, many of which were not intended for oral administration. The absence of this information for a new drug could affect our understanding of the basis for outliers in either the safety or efficacy populations and could interfere with the ability to determine a rational dose for a drug in a specific population.

EXAMPLES OF ETHNIC DIFFERENCES IN EXPOSURE AND RESPONSE TO MARKETED DRUGS

Labeling for the most recently approved drugs did not identify ethnicity-related differences in PK or PD leading to differences in dosing. However, several important examples of ethnicity-related safety and efficacy information are included in the labels of older marketed drugs, in some cases based on data obtained following approval of the drug. As is the case with several of the following examples, the importance of ethnicity may not be known until the postmarketing stage.

Tacrolimus

Tacrolimus, indicated for prophylaxis of organ rejection in transplant patients, is extensively metabolized, primarily by CYP3A,[6] and is a substrate of P-glycoprotein (ABCB1). The label notes that a retrospective comparison in kidney transplant patients suggested that black (African-American) patients required higher tacrolimus doses to reach trough concentrations similar to those observed in white patients. This finding is supported by a published study[7] reporting small but significant differences ($P < 0.01$) in C_{max} (peak plasma concentration) and oral bioavailability (F), which were 1.2–1.8 times greater in white and Latin-American subjects than in African-American subjects. Whether these ethnic differences are related to genetic differences or to other factors contributing to expression of CYP3A5 or ABCB1 is unknown. Even within an ethnic group, there can be substantial variability in PK. For example, an approximately three- to fivefold range of 12-h postdose

Table 1 Ethnic differences in allele frequencies for selected enzymes, transporters, and pharmacologic targets

	Substrates	Variant alleles	Alteration in function	Allele frequencies (%)				
				White	Black	Asian	Chinese	Japanese
CYP2A6 (refs. 16,17)	Nicotine	*2	Reduced or virtually absent	0.7	1.1	—	0.4	0
		*4	Reduced or virtually absent	0; 1.2	0.6; 1.9	10.8[a]	6.7	19; 24.2
		*7	Reduced	0; 0.3	0	9.8[a]	3.1	9.8; 6.3
		*9	Reduced	8.0; 7.1	8.5; 7.1	19.3[a]	15.6	19.0; 20.3
		*10	Reduced or virtually absent	0	0	—	0.4	1.6
		*12	Reduced	2	0.4	—	0	0.8
		*17	Reduced	0	10.5	0	—	0
CYP2B6 (refs. 18–20)	Cyclophosphamide Efavirenz Nevirapine Bupropion Methadone	*4	Increased	6	2	4	—	—
		*5	No change	3; 12	5; 3	3	—	—
		*6	Reduced	28; 25.6	34; 32.8	23	16.2	18
		*7	Reduced	3	1	0	—	—
		*9	Reduced	1	1	0	—	—
		*11	Reduced	1	0	0	—	—
		*15	Unknown	0.4	0	0	—	—
		*16	Reduced	—	7	—	—	—
		*17	Unknown	0	6; 7.1	0	—	—
		*18	Reduced	0	9; 2.9	0	—	—
		*22	Unknown	3.3	1.1	0	—	—
CYP2C8 (refs. 21,22)	Repaglinide Paclitaxel	*2	Reduced	0.4	18	—	—	0
		*3	Reduced	13; 15	2	—	—	0
		*4	Reduced	7.5	—	—	—	0
CYP2C9 (refs. 22–24)	Warfarin Phenytoin Tolbutamide	*2	Reduced	10; 13.3; 8–14.9	3; 1–3.6	Absent or rare	0	0
		*3	More reduced	5.6; 8; 3.3–15.3	1; 0.5–2	—	2.5; 1.7–4.9	3.5[b]; 1.1–6.8
		*5	Reduced	0	3	0[a]	—	—
CYP2C19 (refs. 23,24)	Omeprazole Diazepam	*2	Nonfunctional	13.6; 15	17	—	29.7	34.5[b]
		*3	Nonfunctional	0; <1	<1	—	3.5	9[b]
		*17	Increased	20.1	—	—	0.5	0.5[b]
CYP2D6[c] (ref. 25)	Atomoxetine Codeine	PM	Nonfunctional	7.7	1.9–7.3	0–4.8	<1.0	0
		IM	Decreased	1–2	—	51	—	—
		UM	Increased	4.3	4.9	—	0.9	—
CYP3A5 (refs. 5,24)	Tacrolimus	*1B	None (controversial)	1.7 0 WC 0.5–3.0 WE	0 AA 0 Z	—	0	0[b]
		*1C	Unknown	1.7 4.6 WC 3.0 WE	7.0 AA 0 Z	0	0	0[b]
		*2	Unknown	0.7 WC 2.0 WE	0 AA 0 Z	—	—	—
		*3	No function	95.5 92.9 WC 70 WE	27.0–50.0 AA 77.6 Z	75.0	72.3	78[b]
		*5	Unknown	0 WC	0 Z	0.9	—	—
		*6	Decreased function	0 WC 0 WE	13.0 AA 22.0 Z	0	0	0[b]
		*7	No function	0	10.0 AA 10.0 Z	0	—	—

Table 1 Continued on next page

Table 1 Continued

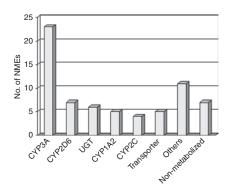|	Substrates	Variant alleles		Alteration in function	Allele frequencies (%)				
					White	Black	Asian	Chinese	Japanese
ABCB1 (P-gp)[d] (ref. 26)	Digoxin Cyclosporin Loperamide Verapamil Quinidine	*1		Unknown	15	15	15	—	—
		*13		Unknown	32	5	27	—	—
		*26		Unknown	10	9	5	—	—
		*21		Unknown	3	8			
		*11		Unknown	1	2	23	—	—
		*14		Unknown	7	2	2	—	—
ABCG2 (BCRP) (ref. 27)	Topotecan Irinotecan Mitoxantrone Doxorubicin Rosuvastatin Methotrexate	34G>A		Reduced	2	4	45[e]	20	15
		421C>A		Reduced	14	0	15[e]	35	35
SCLCO1B1 (OATP1B1) (refs. 28–32)	Pravastatin Rosuvastatin	*1b (388A>G)		Increased (possibly protein expression)	30; 30–51; 38	74; 75; 77	57–88	59.9	46.9; 53.7; 63–67
		*2		Unknown	2	0	—	—	0
		*4		Unknown	16	2	—	—	0
		*5 (521T>C)		Decreased	14; 2.4[f]	2	—	—	0.7
		*6		Unknown	2	0	—	—	—
		*7		Unknown	1	0	—	—	—
		*8		Unknown	1	0	—	—	—
		*9		Unknown	0	9	—	—	—
		*10		Unknown	2	0	—	—	—
		*11		Unknown	2	34	—	—	—
		*15 (both 388A>G and 521T>C)		Decreased	2.7[f]	—	—	14	3.7; 10.3
		*16		Unknown	7.9[f]	—	—	—	3.7
		*17 (388A>G and 521T>C, and −11187G>C)		Decreased	6.9[f]	—	—	—	13.3
UGT1A1 (refs. 33–35)	Irinotecan (SN38)	*6 (211G>A)	Homozygous	Reduced	0	0	—	—	4
			Heterozygous	Reduced	1.3	0	—	—	23
		*27 (229C>A)		Reduced	0	0	<1–3	—	—
		*28	(TA$_{7/7}$)	Reduced	12; 13	23	5	8	2
			(TA$_{6/7}$)	Reduced	39	—	20	14	—
UGT2B7 (ref. 36)	Morphine Zidovudine	*1 *1		None	25	—	—	—	43
		*1 *2		None	43	—	—	—	37
		*2 *2		Reduced transcription	23	—	—	—	4
VKORC1[h] (refs. 13,37)	Warfarin	−1639G>A	AA	Lower warfarin dose requirement	14.2	—	—	82.1	—
			AG		46.7	—	—	17.9	—
			GG		39.1	—	—	0	—
		1173C>T	CC		37.5[g]; 34	80.4	—	<1	—
			CT		50[g]; 49	18.7	—	14	—
			TT	Lower warfarin dose requirement	12.5[g]; 17	0.9	—	85	—

AA, African Americans; WC, white Canadian; WE, white European; Z, Zimbabwean.

[a]Asian refers to Korean. [b]Native Japanese. [c]For CYP2D6, PM denotes individuals with two of the following nonfunctional alleles: *3, *4, *5, *6, *7, *8, *14, *18, *21, and *44; IM denotes individuals with one nonfunctional alleles and one functional allele; UM denotes individuals with two or more copies of the functional alleles. [d]Mexican Americans had allele frequencies of 34% for *26 and 20% for *11 ; Asian refers to Asian Americans; allele frequencies are approximate based on the figure in ref. 26. [e]South East Asia (non-Chinese, non-Japanese). [f]Finnish. [g]European Americans. [h]1639 G>A is in linkage disequilibrium with 1173C>T.

Table 2 Survey of ethnicity data in labeling of new molecular entities approved 2004–2007

Year approved	No. of NMEs approved	No. (%) with PK data based on race/ethnicity	No. (%) with demographic information in the clinical sections
2004	31	5 (16)	10 (32)
2005	17	8 (47)	7 (41)
2006	17	11(65)	9 (53)
2007	16	7 (44)	11 (69)
Total	81	31(38)	37 (46)

NMEs, new molecular entities; PK, pharmacodynamic.

Figure 1 Distribution of enzymatic and transporter pathways of new molecular entities (NMEs) with known pathways approved from 2004 to 2007. Enzymes or pathways in the category labeled as "Others" included carbonyl reductase, esterase, hydrolysis, peptidase, FMO3, and dehydropeptidase.

tacrolimus concentrations has been reported in a cohort of black renal transplant patients of different origins (African-Caribbean, West African, East African) treated at one center in the United Kingdom.[8] This example illustrates the observation that although ethnicity may sometimes be the differentiating factor in pharmacokinetic behavior, a simple classification based on ethnicity often does not describe all of the variability. Accounting for the variability requires a further understanding of potential contributions from extrinsic and intrinsic factors.

Rosuvastatin

The pharmacologic activity of rosuvastatin (an HMG-CoA reductase inhibitor) in treating dyslipidemias is due primarily to the parent compound.[9] Approximately 10% of a radiolabeled dose is recovered as metabolite, which is formed primarily by CYP2C9. Because of the small contribution of CYP2C9 to rosuvastatin exposure, and because the most common variant alleles of CYP2C9 are not found in the Asian population at a higher frequency than in whites,[1] a higher systemic exposure in Asians than whites on the basis of P450-mediated metabolism would not be predicted. However, according to rosuvastatin labeling, "pharmacokinetic studies, including one conducted in the United States, have demonstrated an approximate 2-fold elevation in exposure in Asian subjects when compared with a Caucasian control group."[9] Similar differences have been observed between Asian and white subjects living in Singapore,[10] suggesting that these ethnic differences are independent of

geographic residence. A recently published abstract affirmed a higher exposure to rosuvastatin in Asian subjects (Chinese, Filipinos, Asian Indians, Koreans, Vietnamese, and Japanese) residing in the United States than in whites.[11] The factors associated with the observed ethnic difference have not yet been characterized, although genes for transporters including OATP1B1 (SLCO1B1) and breast cancer–resistant protein (BCRP, ABCG1) are candidates. Labeling in the United States recommends a low initial starting dose in Asians and attention to the potential for greater exposure relative to whites when considering dose escalation.

Warfarin

Race has been reported to contribute to variability in dosing requirements for warfarin in anticoagulation, with African Americans requiring higher doses and Asians requiring lower doses than whites. CYP2C9 is the enzyme primarily involved in warfarin PK. Variant CYP2C9 genotypes are associated with an increased risk of major hemorrhage, and the frequency of variant genotypes is significantly higher in European Americans than in African Americans.[12] Variations in the *VKORC1* gene that encodes for the pharmacologic target of warfarin, vitamin K epoxide reductase, contribute to differences in sensitivity to warfarin. One of the variants in VKORC1 associated with lower dose requirements is 1639 G>A, and the AA genotype is found in warfarin-sensitive patients. The frequency of the warfarin-sensitive AA genotype is higher in Chinese than in whites, with frequencies of 82% in Chinese and 14% in whites.[13] A genomic basis found in recent mechanistic studies supports the previously observed ethnic differences in warfarin dose requirements. This serves as an example of the need to understand potential reasons for pharmacokinetic or pharmacodynamic variability in clinical pharmacology or phase II studies so that dosing can be adjusted for relevant populations in later clinical studies.

Carbamazepine

There are many examples of variants in drug-metabolizing enzymes that could contribute to variability in exposure and drug response. The following example describes genetic variability in a drug target associated with toxicity. An important role has been observed for ethnicity in carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis. The incidence of Stevens–Johnson syndrome in Han Chinese is reportedly higher than in whites, and a strong association has been reported between HLA-B*1502 and the development of carbamazepine-induced Stevens–Johnson syndrome –toxic epidermal necrolysis in Han Chinese.[14] Allele frequencies of HLA-B*1502 differ among different ethnic populations (http://www.allelefrequencies.net). It is most prevalent in some Asian populations, including those of the Philippines, Malaysia, Thailand, and Singapore; in the Han Chinese population in Taiwan;[15] and in India, where the allele frequencies are from 2 to 22%, although in Japan the allele frequency is reportedly <0.3%. Among whites in the United States, the allele frequency is reportedly 0–1%. Although Stevens–Johnson syndrome is

not completely explained by the presence of HLA-B*1502, the ethnic distribution of this allele could explain why adverse events may be more rare in certain specific populations. This example also highlights difficulties that may occur in combining ethnic subgroups in clinical studies for drugs, because a response may have a strong genetic association that differs among subgroups.

DISCUSSION

These examples highlight ethnic differences in drug-metabolizing enzymes, transporters, and pharmacodynamic targets that contribute to differences in drug response. Ethnic or regional differences that could potentially contribute to differences in drug response include not only genetic differences (most of those described) but also diet, practice of medicine, and pattern of concomitant medication use. However, there is little evidence in the literature that these factors have been evaluated with respect to drug response. Although scientific data demonstrate genetic differences in the expression of drug-metabolizing enzymes, transporters, and targets, labeling of NMEs approved from 2004 through 2007 does not reflect the impact of these findings on race- or ethnicity-associated differences in PK or PD. This could be because of failure to study large enough numbers of diverse populations or because of relatively insensitive measures of differences, especially pharmacodynamic differences. Even within a population or ethnic group, the presence of a mixture of genotypes of a single determinant of drug exposure or response can be expected (the prevalence of the classic CYP2D6 poor metabolizer is higher in whites than in other races but is still only 8%, and there are poor metabolizers in all ethnic groups). There are other within-individual factors that affect the overall drug response, and these are not yet well characterized. Unless any one factor, such as a drug-metabolizing enzyme, plays the most prominent role in determining drug exposure and response, the impact of that factor may not be significant.

The examples given in this article illustrate instances of ethnic differences in PK (tacrolimus, rosuvastatin, and warfarin) and PD (warfarin and carbamazepine) that might, in some cases, be defined on the basis of genetic differences. Historically it is easiest to identify pharmacokinetic differences, and the increased use of population PK (http://www.fda.gov/cder/guidance/1852fnl.pdf) would help identify those differences. In some cases, however, as illustrated by warfarin, a precisely measured pharmacodynamic outcome could also be analyzed individually. Population PD could be useful in analyzing warfarin effects after correcting for CYP2C9 and VKORC1. Ethnic differences that must be considered during drug development are not simply those of a population outside the United States (e.g., an Asian or African region) as compared to a US population but different ethnicities even within the United States. The application of this information will be one factor that can contribute to the consideration of the risk-benefit ratio of a drug therapy in a specific patient.

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