RACIAL, ETHNIC AND GENDER DIFFERENCES IN RESPONSE TO MEDICINES

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SUMMARY

In recent years, researchers have found significant differences among racial, ethnic and gender groups in the ways they respond to and metabolize drugs, and experience side effects. Most studies have focused on cardiovascular, psychotropic and central nervous system drugs. Alcohol, antihistamines and analgesics are other agents with varying effects among different racial, ethnic and gender groups. The Food and Drug Administration (FDA) noted last year that Asian-Americans show increased sensitivity to beta blockers. It also observed that African-Americans are less responsive to ACE inhibitors. Gender differences in drug therapy seem to basically evolve around psychotropic drugs. Environmental, cultural and genetic factors are involved in determining response to medicines in different racial, ethnic and gender groups. Continued research in this area will undoubtedly reveal significant information regarding racial, ethnic and gender differences in response to drugs. These developments will impact on how clinical trials are conducted and challenge conventional thoughts regarding restricted formularies.

KEY WORDS

racial, ethnic, gender, cardiovascular, psychotropic, central nervous system, polymorphism, debrisoquin, acetylation, mephenytoin

INTRODUCTION

The premise that a drug will act identically in two different people or in two different races, ethnic or gender groups must be reevaluated. For a growing number of drugs, the percentage of patients who react differently or adversely is determined by their racial and ethnic background, as well as sexual differences. In a recent article written by Gibson /1/, he uses the term "one size does not fit all" to illustrate the fact that racial, ethnic and sex-related differences must be taken into account in prescribing drug therapy. Factors that affect drug response based on racial and ethnic differences basically fall into three categories: environmental, social (psychosocial) and genetic /2/; the last being the major cause of normal differences in drug responses. The major drug classes that show varying effects among racial, ethnic and gender groups are the antipsychotics, benzodiazepines, antidepressants, cardiovascular/antihypertensives, atropine, analgesics, antidiabetic agents and alcohol.

This review focuses primarily on the effects that racial, ethnic and gender differences have on drug response. Even though therapeutic response, metabolism and side effects may differ with various medicines due to racial, ethnic and gender differences, clinical significance is often not established. Therefore, formulary decisions must be balanced to take into account cost, group differences and clinical significance.

FACTORS AFFECTING DRUG RESPONSE

Environment

Environmental factors may have significant influences on drug response, metabolism, disposition and excretion. These factors are shown in Table 1. It is well known that diet can play a major role in the absorption, and therefore plasma blood level, of a drug. This is often noted with antibiotics. In the case of griseofulvin, a fatty diet enhances its absorption. It is also known that, with some of the fluoroquinolones, absorption is delayed when taken in the presence of food. Cigarette smoking, as well as heavy drinking, are known to activate liver enzymes, thus fostering drug metabolism /3/. Data seem to indicate that as the diet becomes more European, drug metabolism becomes more rapid /4/. Pregnancy, stress, diurnal rhythms and fever

TABLE 1

Factors affecting drug responses in different racial and ethnic groups

I.	Environmental	
	▸ Age	▸ Chronic alcohol ingestion
	▸ Gender	▸ Cigarette smoking
	▸ Multiple Disease States	▸ Pregnancy
	▸ Diet	▸ Stress
	▸ Fever	▸ Diurnal rhythms
II.	Cultural (Psychosocial)	
	▸ Attitudes	
	▸ Beliefs	
	▸ Family influence	
	▸ Therapy expectations	
III.	Genetic	
	▸ Pharmacogenetics	
	▸ Genetic polymorphism	

may operate independently or simultaneously in the same individual, thus affecting, in different ways and to different degrees, the processes of drug absorption, distribution, biotransformation and excretion.

Cultural (psychosocial) factors

Drug efficacy and compliance are affected by cultural or psychosocial factors such as communication skills, attitudes, beliefs, therapy expectations and family influences. A therapeutic effect of using placebos in controlled clinical trials is well known. It is not known why a placebo has a therapeutic effect; however, a positive attitude about the potential benefit of the medication taken, albeit a placebo, may be a factor in drug response. Cultural beliefs may also affect compliance and drug response. Contrasting cultural beliefs across ethnic groups can affect medication compliance. Kinsey *et al.* /5/ reported that 61% of their depressed, medicated refugee patients showed no tricyclic antidepressants (TCAs) in their blood. The majority of them admitted

to not taking the prescribed TCAs and pretended compliance for various reasons. Asian refugees typically expected medicines from the Western culture to work quickly, have a high potential for severe side effects, and to be effective only for the control of the superficial manifestations, not the underlying condition of the disease. Therefore, the belief in and expectation of psychiatric medication may have played an important role in patient compliance in this group.

Genetics

Genetic factors are the major determinants of normal differences in drug responses. Genetically determined normal variabilities in the way individuals metabolize (i.e., oxidize and acetylate) drugs are major determinants of racial and ethnic differences in response to medicines. The focus of this discussion is on pharmacogenetic metabolism related to debrisoquine, acetylation, and mephenytoin polymorphisms (Table 2). These are the most important clinical polymorphisms because many drugs are metabolized by their pathways.

Debrisoquine is an antihypertensive agent that was found to exhibit a genetic polymorphism in its oxidative metabolism /6/. Two distinct

TABLE 2

Some drugs that show genetic polymorphism in drug metabolism

Debrisoquine Polymorphism	Acetylation Polymorphism	Mephenytoin Polymorphism
Amitriptyline	Clonazepam	Diazepam
Imipramine	Nitrazepam	Imipramine
Chlomipramine	Hydralazine	Mephobarbital
Nortriptyline	Procainamide	Hexobarbital
Chlorpromaxine	Isoniazid	
Perphenazine	Caffeine	
Haloperidol	Clonazepam	
Labetalol		
Metoprolol		
Timolol		
Propranolol		

Adapted from Levy /2/

phenotypes were observed in the population with a urinary ratio of debrisoquine to its main 4-hydroxy metabolite. Those individuals who were deficient in their ability to oxidize the substrate are called poor metabolizers (PM), whereas extensive metabolizers (EM) biotransform a substantial amount of the drug to its metabolite. The prevalence of the PM phenotype in different group studies ranges between 2% and 10%. with Asians being identified with no or very few poor metabolizers (Table 3) /7/.

Polymorphic *N*-acetylation was first studied when serum concentrations of isoniazid showed substantial interindividual variability /8/. Patients were classified as slow acetylators (SA) or rapid acetylators (RA) according to their ability to metabolize isoniazid. American and European Caucasians and American Blacks have approximately equal numbers of SAs and RAs, whereas in Japanese and Canadian Eskimo subjects, the percentage of RAs is high and SAs is low (Table 4) /9/.

The polymorphism of mephenytoin hydroxylation also varies according to racial and ethnic differences. Drugs showing differences in metabolic rate include imipramine and diazepam (Table 2). The

TABLE 3

Incidence of poor/slow metabolizers in different racial groups

Metabolic Polymorphism	Drug Examples	Poor/Slow Metabolizers (%) Caucasian	Asian
Debrisoquine	desipramine amitriptyline haloperidol metaprolol phenacetin	6-10	<1
Acetylation	caffeine hydralazine procainamide isoniazid	50	7-22
Mephenytoin	diazepam imipramine	3	25-50

Adapted from Levy /2/

TABLE 4

Incidence of slow acetylators in racial and ethnic groups

Group	Slow Acetylators (%)
Caucasians	50
American Blacks	50
Japanese	10
Canadian Eskimo	5
Egyptians	80-90
Moroccans	80-90
Chinese	15

From Nakamura *et al.* /10/

incidence of poor metabolizers (PM) is 2-5% among Caucasians, between 15-20% in Japanese, and no PMs were found among Panamanian Cuna Amerindians (Table 3) /10/.

DRUG RESPONSE TO RACIAL AND ETHNIC DIFFERENCES

The drug categories that have been studied the most and shown to be most clinically significant in their actions with regard to racial and ethnic differences are cardiovascular and central nervous system agents. The specific agents to be discussed are the antihypertensives and psychotropic drugs.

Antihypertensive agents

Any of the major classes of antihypertensive agents may be effective in black patients; however, there are some more predictable than others and some require lower doses for an equivalent effect (Table 5) /2/. For example, monotherapy with beta blockers and ACE inhibitors has

TABLE 5

Racial and ethnic differences in response to antihypertensive agents

Drug Class/Examples	Clinical Response
Diuretics	Blacks respond better to monotherapy than whites
Beta-blockers	Blacks respond less than whites
Labotalol	Blacks seem to respond as well as whites
ACE Inhibitors	Monotherapy is less effective in blacks than whites; no difference if diuretic is added
Propanolol	Chinese are twice as sensitive to effects on blood pressure and heart rate
Calcium Channel Blockers	Blacks respond to monotherapy as well as whites

Adapted from Levy /2/

been shown to be less effective in blacks than in white hypertensive patients /11/. On the other hand, diuretics and calcium channel blockers have proven to be effective.

The reasons for these differences may be due to differences in renal physiology, which may be genetically determined. For example, the renin-angiotensin system is more frequently suppressed relative to sodium intake and excretion in blacks than in whites /12/. It has been shown that 36-62% of black hypertensives have relatively suppressed plasma renin activities as compared to 19-55% of white hypertensives /13/. Even in normotensive patients, plasma renin activity is lower in blacks than in whites /14-15/. Therefore, ACE inhibitors and beta blockers, which are both believed to work by lowering plasma renin, would be less effective in blacks who already have lowered renin levels. Even though blacks tend to fall into the low-renin category, with a volume-dependent, salt-sensitive type of hypertension, there are sub-groups within the black population that do respond to ACE inhibitors and beta blockers. Therefore, beta blockers must be specifically directed toward the individual patient.

Evidence exists that blacks may even respond differently to different beta blockers. For example, unlike propranolol, the beta blocker labetolol is equally effective in both black and white hypertensive patients /16/. Also, blacks respond to beta blockers in combination with diuretics as well as Caucasians /17/.

Antipsychotic agents

Racial and/or ethnic differences need to be considered in decisions regarding psychotropic drugs (Table 6). Growing evidence seems to indicate that the pharmacodynamic and pharmacokinetic influences of these agents may undoubtedly differ between races, and these differences can affect clinical outcome.

Comparisons of antipsychotic activity among different racial groups reveal both similarities and potentially important differences (Table 6) /18/. Blacks, whites and Hispanics do not differ in their pharmacokinetics or dosage requirements of antipsychotic drugs; Asians seem to have a lower threshold than whites for both the therapeutic and adverse effects of these agents. Increased absorption, reduced hepatic hydroxylation and pharmacodynamic factors all play a role in dosage differences. Midha /19-21/, Adams /22/, and Jann *et al.* /23/ showed

TABLE 6

Racial and ethnic differences in response to central nervous system agents

Drug Class/Examples	Clinical Response
Benzodiazepines	Chinese require lower doses; more sensitive to sedative effects than whites
Haloperidol	Blacks and whites seem to have same degree of adverse effects. Asians require lower doses
Lithium	Asians may require lower doses than whites
Alcohol	Asians are more sensitive to adverse effects than whites

Adapted from Levy /2/

that Chinese patients showed higher haloperidol plasma concentrations than Caucasians, Hispanics and blacks. Additionally, the haloperidol dosage required for the Caucasian and black groups was significantly greater than for the Chinese group to achieve comparable plasma levels.

It should be noted that the use of antipsychotics in blacks is more frequent than in other racial groups /24/. This may be explained, in part, by the fact that black patients generally receive more severe diagnoses, such as schizophrenia, as opposed to an anxiety or mood disorder /25/. Perhaps for similar reasons, blacks tend to receive substantially higher doses of antipsychotics. This may also be due to the stereotype that blacks are more difficult to manage and less compliant /24/.

Antidepressant agents

There is not much published information regarding differences in antidepressant pharmacology among black, Caucasian, Hispanic and Asian patients. Additional controlled pharmacokinetic and pharmacodynamic studies with these classes of drugs need to be carried out before any changes in clinical applications of tricyclic antidepressants in different racial groups can be made.

General findings seem to indicate that African-American patients show higher plasma tricyclic antidepressant levels and faster therapeutic response. Also, black patients tend to manifest a greater degree of toxic effects compared to Caucasians /24/. While many studies indicated that Hispanic and Asian patients required lower doses of tricyclic antidepressants, the results were inconsistent. Hispanic patients also appeared to experience more overall side effects with antidepressants than Caucasians; however, a single-dose study comparing plasma nortriptyline levels and clearance rates in healthy Hispanic and Caucasian volunteers failed to demonstrate any major differences between the two groups /26,27/. Therefore, the role of racial and ethnic differences in response to antidepressants remains unclear because of limited, and sometimes conflicting, data.

Antianxiety agents

A single-dose pharmacokinetic study utilizing alprazolam showed that Asians manifested significantly higher plasma concentrations, decreased clearance, and longer half-lives than did Caucasians /28/. Lin

et al. /28/ showed that the clearance rate of diazepam was higher in Caucasians, suggesting that diazepam is metabolized at a significantly higher rate in Caucasians than Asians.

Pharmacokinetic differences in the metabolism of these benzodiazepines may be due to the fact that Asians (e.g., Japanese) have a higher incidence of poor metabolizers (PM) than Caucasians /2/.

Based on the data observed, it is suggested that Asian psychiatric patients will require smaller initial and continuing doses of benzodiazepines, i.e., alprazolam and diazepam, for similar clinical effects compared to Caucasian patients /29/.

DRUG RESPONSES TO GENDER DIFFERENCES

The gender of an individual is a factor that can often lead to interindividual differences in the metabolism of drugs /30/. Studies carried out to assess sex differences in drug metabolism are inconclusive, because confounding factors, such as menstrual cycle and the use of oral contraceptives, frequently were not taken into consideration /31/. However, in those studies where gender differences in metabolism/ pharmacokinetics exist (Table 7), women tend to have higher plasma concentrations than men. When the pharmacokinetics of lidocaine and chlordiazepoxide were examined with respect to gender

TABLE 7

Some drugs with gender-related differences in pharmacokinetic properties

Drugs	Classification
Acetaminophen	Analgesics, Antipyretic
Chlordiazepoxide	Antianxiety
Diazepam	Antianxiety
Lidocaine	Antiarrhythmic
Oxazepam	Antianxiety
Prednisolone	Steroid
Propranolol	Beta Blocker
Salicylates	Analgesics, Antiinflammatory
Temazepam	Antianxiety

Adapted from Bonate /31/

differences, it was found that elimination half-life in females was larger compared to males due to either increased volume of distribution or decreased clearance /32/.

In general, drugs that are metabolized by hepatic oxidation have impaired metabolic clearance and prolonged elimination half-life in females who are on oral contraceptives compared to those who are not /31/. The clinical significance of gender-related differences in the pharmacokinetic properties of some drugs has not been clearly established. Giudicelli and Tillement concluded that it is unnecessary to change dose or frequency of administration of a drug based on gender-related differences in metabolism /30/.

Physiological differences (Tables 8 and 9) between the sexes in hormone and enzyme levels and basal metabolism influence the metabolism of various drugs /33/. For example, gender differences in muscle mass, disposition of muscle tissue and vascular resistance could cause variation in response to intramuscular injections. Gender differences in gastric motility and secretion and metabolic rate may influence plasma levels of orally administered drugs. However, it must be pointed out that the clinical significance of these influencing factors remains to be established.

TABLE 8

Possible physiological differences between the sexes that influence drug metabolism

o	Metabolic rate
o	Hormonal status
o	Enzyme activity
o	Muscle mass
o	Disposition of adipose tissue
o	Gastric motility and secretion
o	Pregnancy

TABLE 9

Some reported gender differences in drug therapy

Drug	Gender	Proposed Mechanism
Antipyrine	Males	Decreased metabolism
Phenytoin	Females	Decreased serum level
Acetylcholine	Males	Greater metabolism
Erythromycin oral	Females	Decreased absorption following administration
Haloperidol	Females	Increased control of psychotic patients
Tricyclic Anti-depressants	Females	Increased sensitivity
Chloropromazine	Females	Increased side effects

Adapted from Proksch and Lamy /33/

Gender differences in drug therapy probably have been studied the most with the psychotropic agents. This could be due in part to the observation that females have higher admissions rates than males for mental disorders and a greater degree of severity of symptoms /34,35/. In one study, male schizophrenic patients required less medication, lower doses and had a more favorable outcome to therapy than female patients /37/. However, findings from a more recent study by Yonkers *et al.* /38/ indicate that women have greater efficacy of antipsychotic agents and a greater likelihood of adverse reactions. It is clear that the gender differences require more extensive controlled studies.

CONCLUSIONS

The premise that a drug will act identically in two different people or in two different races, ethnic groups or cultures, has been challenged and found to be flawed. For a growing number of drugs, the percentage of patients who react differently or adversely is determined

by their racial and ethnic background. The study of racial, ethnic and gender differences in response to medicines has been primarily limited to a few classes of drugs. However, future studies will likely reveal significant data regarding these differences in the action of many additional drugs.

Cost is often the driving force in a managed care environment with a restricted formulary. The formulary must not be so restrictive that it ignores the fact that patients in specific groups metabolize drugs differently, have different clinical responses and experience different side effects. Therefore, racial, ethnic and gender differences require us to balance control of drug cost with the need for individualized therapy.

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