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A number of reports have identified differences in drug pharmacokinetics and pharmacodynamics between males and females, and between patients of different ethnicity. These differences are observed in both solid organ transplant recipients and in nontransplant patients. This review summarizes the pharmacokinetic differences thought to be dependent on sex and ethnicity noted with immunosuppressive agents commonly used in transplantation. This manuscript also touches on how these differences may translate into observed drug interactions. Furthermore, potential factors underlying the sex and ethnicity differences are evaluated. Current evidence points to differences in drug-metabolizing enzymes, transporters, cytokines, and environmental influences to account for the observed heterogeneity in drug response. Many of these factors seem to be under genetic control, and thus areas for further research are suggested.

Introduction

It has long been recognized that the prevalence of certain diseases may be largely related to ethnic group (i.e., sickle cell anemia in Africans) or patient sex (i.e., systemic lupus erythematosus in females). More recently, several high-profile research articles have reported the importance of sex and ethnicity in the evaluation of drug therapy in nontransplant patients. These observations are particularly interesting when one considers the role of this variability in solid organ transplantation and related drug therapies. It is well established that immunosuppressive agents, particularly cyclosporine, tacrolimus, and sirolimus, result in a great deal of interindividual pharmacokinetic variability, which may lead to observed pharmacodynamic variability. In fact, a number of reports claim sex- and ethnicity-based differences for immunosuppressive drugs commonly taken by solid organ transplant recipients.[1-15] This review will analyze the data surrounding the influence of sex and ethnicity on drug pharmacokinetics in solid organ transplantation, evaluate factors influencing these differences, and suggest areas for further study.

Influence of Ethnicity on Immunosuppressive Pharmacokinetics

Research in the area of pharmacogenetics has led to an increased amount of attention on elucidating the influence of "race" and "ethnic background" in clinical medicine, which has been referred to as "racial profiling."[16] Although we are all certainly part of the "human race," differences in our ethnic heritage have historically provided important information to the practicing clinician for how drug therapy should be chosen or evaluated in the individual patient.[16,17] For the purpose of clarification, ethnicity is defined as a shared origin, culture, language, religion, and sense of identity of a group over generations (both genetic and environmental factors), and is the preferred term.[18]

Table 1 summarizes important pharmacokinetic differences of ethnic group based on studies involving transplant patients and/or immunosuppressive medications.[1,3-7,9-13,15] In a study reported by Neylan,[5] African American renal transplant patients appeared to require higher doses of tacrolimus than Caucasian patients to achieve similar blood trough concentrations. In a separate tacrolimus pharmaco-

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Key Points

- Interindividual pharmacokinetic differences are common with many immunosuppressive agents.
- Evidence supports differences in drug pharmacokinetics based on sex and ethnicity.
- The underlying causes of pharmacokinetic differences likely relate to drug metabolizing enzymes, drug transporters, and environmental factors.
- Future research in this area will help to elucidate the reasons for these differences.

PHARMACOGENOMICS

The study of pharmacogenetic variability between subpopulations.

kinetic study,[10] the maximum concentration (C_{max}) was lower in African Americans than in both Latin and Caucasian Americans. Likewise, the absolute bioavailability and area-under-the-curve (AUC) values were found to be lowest in patients of African American descent and greatest in Caucasian Americans. Despite these differences, the metabolite formation was reduced in the African American participants when compared with the other 2 ethnic groups, suggesting that increased metabolism was not primarily responsible for the observed pharmacokinetic differences. Conversely, the cyclosporine doses necessary to achieve similar blood trough concentrations were similar for both groups in the Neylan study.[5]

In other studies, important differences in cyclosporine doses were observed between African American and Caucasian American transplant recipients, and these were largely attributed to reduced bioavailability in African and Caucasian Americans.[1,6,7,9] In contrast, cyclosporine pharmacokinetics did not differ between healthy male African Americans and Caucasian Americans in another study,[11] possibly suggesting environmental effects particular to transplant recipients.[6] Pharmacokinetic variables were similar in African and Caucasian American renal transplant recipients taking mycophenolate mofetil.[13] However, in that study,[13] mycophenolic acid C_{max} was statistically lower in African Americans compared with Caucasian Americans at one time point, and mycophenolic acid glucuronide was higher in African Americans for at least the first 7 days after transplant.

In one study, African Americans and Caucasians matched for age, weight, and time since renal transplantation received intravenous methylprednisolone.[3] African Americans demonstrated a lower total (bound and unbound) methylprednisolone clearance and volume of distribution, and corresponding increased toxicity.[3] In contrast, the free (unbound) methylprednisolone oral clearance and apparent volume of distribution in healthy Caucasian and African Americans did not differ in another study, although Caucasian Americans did appear to be less susceptible to the suppressive pharmacodynamic effects of prednisolone.[4]

The pharmacokinetics of sirolimus appear to be similar between African Americans and other ethnic groups when adjusted for dose, although it is generally accepted that higher doses are required in African Americans to prevent acute cellular rejection.[12] Similarly, African Americans require a higher dose of everolimus based on a 20% higher clearance compared with other ethnic populations.[15]

Interestingly, African American renal transplant recipients were recently found to be at a lower risk of death due to infection and higher risk of acute rejection relative to Caucasians in a large database analysis, suggesting an inadequate level of immunosuppression given to blacks.[19] Based on these differences, African Americans are thought to require higher doses of cyclosporine,[1,6,9] tacrolimus,[5,7,10] and sirolimus.[12] It has also been reported that African Americans are less likely to have a satisfactory response to corticosteroid treatment of rejection in renal transplantation compared with Caucasians.[20]

Influence of Sex on Immunosuppressive Pharmacokinetics

Gender is often used to describe differences between males and females; however, *sex* is the more appropriate term. Whereas gender reflects a difference in societal perspective, culture, or history, sex reflects a biological difference between males and females.[21]

Table 2 summarizes important pharmacokinetic parameters studied based on the influence of sex from research involving transplant patients and/or immunosuppressive medications.[1,2,4,7-9,14] Intra-

Table 1 | **Pharmacokinetic Differences Associated with Ethnicity**

Drug and Dosage Form	Population	Parameter	Findings
Methylprednisolone IV[3]	Renal Transplant	Total Cl	AA < C
		Total Vd	AA < C
Prednisolone oral[4]	Healthy	Free oral Cl	AA ≅ C
		Free apparent Vd	AA ≅ C
Tacrolimus oral[5]	Renal Transplant	Trough	AA ≅ C
		Dose	AA > C
Tacrolimus oral & IV[7]	Pre- and post-renal	Dose	AA > C
	transplant, & healthy	Trough	AA ≅ NB
		BA	AA < NB
		Cl	AA ≅ NB
		Vd	AA ≅ NB
	Liver transplant	Trough	AA < NB (NS)
Tacrolimus IV[10]	Healthy	C_{max}, AUC, BA	AA ≅ C ≅ LA
Tacrolimus oral[10]	Healthy	C_{max}	AA < LA < C
		AUC	AA < LA < C (NS)
		BA	AA < LA < C
		Metabolite C_{max}	AA < LA < C
Cyclosporine oral[5]	Renal transplant	Trough	AA ≅ C
		Dose	AA ≅ C
Cyclosporine oral & IV[1]	Uremic	BA	AA < C < LA
		Dose	AA > C
		C_{max}	C < LA
		Oral T ½, IV T ½, Vd, CL	AA ≅ C ≅ LA
Cyclosporine oral & IV[6]	Pre-renal transplant	BA	AA < C
		Cl	AA ≅ C
Cyclosporine IV[6]	Post-renal transplant	Dose, C_{ss}, Cl	AA ≅ C
Cyclosporine oral[6]	Post-renal transplant	Dose	AA > C
		BA	AA < C
		Cl	AA > C
Cyclosporine oral & IV[9]	Healthy	BA	AA < C
		AUC	AA < C
		Cl	AA > C
Cyclosporine oral standard[11]	Healthy	C_{max}, AUC, Cl	AA ≅ C
Cyclosporine oral microemulsion[11]	Healthy	C_{max}, AUC, Cl	AA ≅ C
Sirolimus oral[12]	Renal Transplant	Dose	AA = C
		C_{max}, AUC, Trough, oral Cl	AA ≅ C
Mycophenolate oral[13]	Renal Transplant	MPA AUC, ff	AA ≅ C
		MPA C_{max}	AA < C on day 7
		MPAG trough	AA > C until day 7
Everolimus oral[15]	Renal Transplant	Cl	AA > C

AA = African American, AUC = Area-under-the-curve, BA = bioavailability, C = Caucasian, Cl = clearance, C_{max} = maximal concentration, C_{ss} = concentration at steady state, ff = free fraction, IV = intravenous, LA = Latin American, MPA = mycophenolic acid, MPAG = mycophenolic acid glucuronide, NB = non-black, NS = not significant, T ½ = elimination half-life, Vd = volume of distribution.

venous methylprednisolone total clearance was more rapid in healthy females, compared with healthy males, in one study; however, the biologic effect of methylprednisolone was more pronounced in the women.[2] In another study,[4] orally administered prednisolone free oral clearance and apparent volume of distribution were higher in healthy men compared with women, but the pharmacodynamic effects were similar. Taken together, these studies suggest differences between agents, an environmen-

Table 2 | **Pharmacokinetic Differences Associated with Sex**

Drug and Dosage Form	Population	Parameter	Findings
Methylprednisolone IV[2]	Healthy	Total Cl	F > M
		Total T ½	F < M
Prednisolone oral[4]	Healthy	Free oral Cl	F < M
		Free oral Vd	F < M
Sirolimus Solution[8]	Microsomes	Metabolite formation	F > M
Tacrolimus IV[7]	Pre-renal transplant	AUC, Vd, T ½, Cl	F ≅ M
	Post-renal transplant	AUC, Vd, T ½, Cl	F ≅ M
	Healthy	AUC, Vd, T ½, Cl	F ≅ M
Tacrolimus oral[7]	Pre-renal transplant	C_{max}, AUC	F ≅ M
	Post-renal transplant	C_{max}, AUC	F ≅ M
		Trough	F ≅ M
	Healthy	C_{max}, AUC	F ≅ M
	Liver transplant	C_{max}, AUC	F ≅ M
		Trough	F ≅ M
Cyclosporine oral & IV[1]	Uremic	BA, C_{max}, Vd, Cl	F ≅ M
		IV T ½	F > M
Cyclosporine oral & IV[9]	Healthy	BA	F ≠ M[a]
		C_{max}	F ≠ M[a]
		Cl	F ≠ M[a]
		AUC	F ≅ M
Mycophenolate oral[14]	Renal Transplant	MPAG formation	M > F

AUC = area-under-the-curve, BA = bioavailability, C_{max} = maximum concentration, Cl = clearance, F = female, IV = intravenous, M = male, MPAG = mycophenolic acid glucuronide, T ½ = elimination half-life, Vd = volume of distribution.
a. There was a gender-dependent interaction between race and sex in these parameters.

tal difference in transplant recipients, or an increased oral bioavailability of the steroid in women (which would affect the determination of oral clearance and apparent volume of distribution).[4]

Cyclosporine exhibited a gender-dependent racial difference in another study, which compared pharmacokinetics in African Americans and Caucasian Americans.[9] In that study, the bioavailability was lower, and the clearance was higher in African Americans compared with Caucasian Americans, and both comparisons were affected by patient sex. African American females had the lowest C_{max}, the lowest bioavailability, and the highest clearance compared with African American males, and Caucasian American males and females. In contrast, uremic women given intravenous cyclosporine had a prolonged half-life compared with men, also suggesting differences between men and women regarding bioavailability. Interestingly, the metabolism of sirolimus was much more rapid in female than male hepatic microsomal preparations.[8] In contrast, the formation of mycophenolic acid glucuronide may be higher in males than females.[14]

ETHNICITY

A shared origin, culture, language, religion, and sense of identity of a group over generations.

A Logical Extension: The Influence of Sex and Ethnic Group on Drug Interactions

Drug interactions are a frequent adversary in clinical transplantation (for a detailed review, see Ref. 22), and it is not surprising that changes in immunosuppressive pharmacokinetics brought about by proposed ethnic- or sex-related differences would translate into differences in drug interactions. In a recent abstract, Tuteja et al.[23] reported that females had higher tacrolimus clearance than males at baseline, but the addition of ketoconazole resulted in a more substantial decrease in clearance and a more substantial increase in bioavailability in women compared with men. Evaluating trough concentrations, our own group[24] retrospectively observed that the presence of a drug interaction between fluconazole and cyclosporine or tacrolimus was dependent on sex and ethnicity, rather than fluconazole dose or route of administration. In short, African Americans and women were less likely to have increased calcineurin inhibitor trough concentrations than Caucasians and men. Of additional interest, the interaction appeared to be

greater with tacrolimus than cyclosporine, both during coadministration with fluconazole and after the discontinuation.

It appears that an effect of ethnicity may also translate into drug-food interactions, as grapefruit juice was recently reported to increase cyclosporine C_{max} and AUC to a greater extent in African Americans than Caucasian Americans, causing the initially lower absolute bioavailability in African Americans to become similar to Caucasian Americans (P = NS) during coadministration.[25]

Factors Potentially Contributing to Sex and Ethnic Differences

Sex and ethnicity appear to be factors that influence pharmacokinetics, and by extension, the pharmacodynamics of many immunosuppressant drugs; however, thought must be given to underlying factors known to influence drug pharmacokinetics. In general, pharmacokinetics is characterized by absorption, distribution, metabolism, and elimination, and there are a number of factors known to influence these parameters. Sex differences in drug pharmacokinetics and pharmacodynamics (for a detailed review, see Ref. 26) are well established. Likewise, differences in pharmacokinetics based on ethnicity are well established (for a detailed review, see refs. 27-28).

PHARMACOKINETICS

The study of the movement of a drug in the body.

The field of pharmacogenetics relates these differences to an individual's genetic makeup and specifically studies the effects of gene alterations on drug metabolizing enzymes, drug transporters, drug receptors, and/or targets to promote rational therapeutics.[29] The investigation of pharmacogenetic variability between subpopulations is known as pharmacogenomics. Together, the rapid progress being made in the elucidation of reasons for differences in patient response to drug therapy has led to an increased amount of information available to clinicians. The remainder of this section will focus on factors underlying pharmacokinetic variability as they probably relate to importance in the pharmacotherapy of transplant recipients.

Drug Metabolizing Enzymes

It is well established that many therapeutic agents, including several commonly utilized transplant medications, are metabolized by the cytochrome (CYP) P450-3A system. Specifically, cyclosporine, tacrolimus, sirolimus, steroids, and everolimus are all metabolized by the CYP3A system in both the liver and gastrointestinal tract.[15,22,30-32] Some early studies[33] proposed that the activity of human liver microsomal mono-oxygenases do not depend on age or sex, although it has been suggested that women clear CYP3A substrates more rapidly than do men.[8,31] More recently, CYP3A4 promoter and allelic variants have been noted to exist, and the functional significance of the promoter variants was reported to be relatively little to nonexistent, whereas the allelic variants may have altered activity.[34,35] One of those studies[34] evaluated differences in CYP3A4 expression based on the presence of a variant CYP3A4*1B (5′ promoter region polymorphism) found in African Americans, as compared to Caucasian Americans of European descent, and demonstrated that no significant difference in CYP3A4 activity existed between groups. Another study established that CYP3A5 was more frequently expressed in the livers of African Americans (60%), based on a higher presence of the CYP3A5*1 allele compared with Caucasian Americans (33%), who frequently had alternative splicing and less CYP3A5 expression.[35] These investigators suggested that the observed differences in CYP3A-dependent interracial variability in drug clearance may be due to the presence or absence of CYP3A5 and its genetic polymorphic/alternate splice variants.

It is well documented that variability does exist in the pharmacokinetics of transplant medications, and a recent abstract documented a higher frequency of the promoter variant, CYP3A4*1B, in liver transplant patients requiring low doses of tacrolimus (25%) when compared with patients requiring high doses (0%).[36] Conversely, the same mutant did not predict the dosing strata in renal transplant patients receiving the cyclosporine microemulsion formulation in another study.[37] Variability in cyclosporine clearance by the liver has been linked to heterogeneity in CYP3A4 activity in liver transplant recipients, although it only accounts for 40% of the variability in cyclosporine oral clearance.[38]

Membrane Transporters

The multidrug resistance protein (MDR) gene product, P-glycoprotein, is known to limit the

PHARMACODYNAMICS

The study of the actions/effects of a drug in the body.

BIOAVAILABILITY

The fraction of a dose absorbed into the systemic circulation after administration.

bioavailability of cyclosporine, tacrolimus, and sirolimus.[39,40] A study by Lown et al.[39] evaluated the influence of P-glycoprotein on the interpatient variation of oral cyclosporine clearance in renal transplant patients. No significant correlation was found between enterocyte concentration of P-glycoprotein and the expression of intestinal or liver CYP3A4, or between enterocyte P-glycoprotein and age or sex, although P-glycoprotein concentrations appeared to be higher in females. Erythromycin breath test, a probe for CYP3A activity, correlated highly with apparent oral cyclosporine clearance, accounting for 56% of the interpatient variation. With P-glycoprotein, no direct correlation was evident with any specific cyclosporine pharmacokinetic parameters, but in stepwise multiple regression analysis, a highly significant correlation between enterocyte P-glycoprotein content and oral cyclosporine pharmacokinetic variations was evident. In the final model, inclusion of erythromycin breath test values and P-glycoprotein content accounted for 73% of the interindividual variation in oral clearance. Other studies have also documented that many substrates are shared between CYP3A and P-glycoprotein, but the expression of the two do not appear to be directly interrelated.[41]

A separate study[42] has also documented that jejunal MDR1 mRNA expression, but not CYP3A4 expression, were inversely related to the tacrolimus concentration/dose ratio in liver transplant recipients. Additionally, high levels of MDR1 were associated with reductions in survival in this living donor liver population.[42] As previously outlined, reduced bioavailability of cyclosporine was observed in African Americans in several studies.[1,6,7,9] Consideration of these findings, along with the fact that the ethnicity-related differences in tacrolimus pharmacokinetics in one study[10] did not appear to be related to metabolism, suggests differences may be present in the expression of drug transporters in these patients. Since the MDR1 gene product, P-glycoprotein, appears to be highly important in the pharmacokinetics of many immunosuppressives, it is necessary to account for the factors underlying this observed ethnicity-linked pharmacokinetic variability.

These pharmacokinetic, and possibly pharmacodynamic, observations found with immunosuppressive behavior may be more readily understood when one considers the role of differences in drug transporter expression. Recently, Artursson's laboratory has elucidated the mRNA expression of several multidrug-resistance conferring proteins (MDRCPs) in the human jejunum and in Caco-2 cells.[43] In addition, our laboratory has recently established that differences in the expression of several MDRCPs occur in the small and large intestines of a Chinese patient when contrasted with expression in a Caucasian American.[44] The significance of the presence of multiple MDRCPs in the human intestinal tract will only be understood as the functional significance of these transporters is carefully elucidated. In addition, further elucidation of these pharmacogenomic differences in the expression and function of these MDRCPs is required to properly understand and interpret the observed pharmacokinetic differences in other ethnic populations.

Insight into differences in transporter expression in subpopulations has been reported recently. A number of variant alleles in the MDR1 gene have been identified.[45,46] At least one of these, the C3435T polymorphism, has been related to expressional and functional significance.[47] A recent study by Schaeffeler et al.[46] documented that the genotype distribution of this polymorphism known to affect MDR/P-glycoprotein expression differed between Africans, African Americans, and non-African populations. The highest frequency of the high-expression allelic pattern (homozygous for C allele) was seen in Africans (83%), followed by African Americans (61%), Japanese (34%), and Caucasians (25%). However, a recent study[48] was unable to demonstrate a difference in cyclosporine pharmacokinetics in a small group of healthy volunteers (n = 14) genotyped for the C3435T polymorphism.

As mentioned, a number of other transporters (MRP1, MRP2/cMOAT) in the same family as MDR1, the ATP-binding cassette (ABC) transporter family, are known to exist.[43-45] Furthermore, they are less well characterized with respect to transplant medication transport compared with P-glycoprotein, but they may contribute importantly to immunosuppressive pharmacokinetics.[45]

Environmental and Geographical Influences

Studies have demonstrated that the absorption profile of agents changes after transplantation.[1,6]

The gut metabolism and/or transport is known to be high for tacrolimus and cyclosporine, and subsequently limits their bioavailability.[32,39,40] Likewise, the bioavailability of mycophenolate mofetil and its active metabolite, mycophenolic acid, may be limited by P-glycoprotein.[49] It appears that receiving a transplant can induce P-glycoprotein expression and affect drug pharmacokinetics, and this appears to partially relate to the medications the patient receives after the transplant.[6,11,50]

It is also known that the cytochrome system is highly inducible based on exposure to compounds such as drugs, pollutants, and food, that results in an effect observed on the therapeutic agent's bioavailability.[51] Compounds in food, such as grapefruit juice, may also affect immunosuppressive drug pharmacokinetics, as well as CYP3A4 content in enterocytes.[52,53] It appears that the primary mechanism for grapefruit juice–induced increased cyclosporine exposure is inhibition of P-glycoprotein.[53] Likewise, differences in drug interactions with antifungal agents may be related to their differing effects on CYP3A or P-glycoprotein.[23-25] It should also be noted that other food products, including pineapple and onion, have been found to influence the pharmacokinetics of cyclosporine in animals.[54]

In addition, the study by Schaeffeler et al.[46] suggested that difference in P-glycoprotein expression in groups of different ethnicity could be related back to geographical origin and environmental exposures to infectious organisms, thus evolution may also play a role in determining pharmacokinetic variability.

Cytokines

In recent years, cytokine gene polymorphisms have been attributed to outcomes in transplant recipients.[55] Additionally, these differences have been attributed to ethnicity.[56] Interestingly, these cytokines, particularly interleukin-6, also affect the function of CYP3A.[51,57] Therefore, it is interesting to speculate that a complex interrelationship exists between drug pharmacokinetics, cytokine expression, and transplant outcomes.

Menstrual Cycle

Menstrual cycle–related changes in various diseases are known to exist.[58] Similarly, certain changes in drug response have been linked to the menstrual cycle. Menstrual cycle phase did not affect CYP3A phenotype with intravenous midazolam in one study,[59] but pharmacokinetic variability may exist.[26] In fact, the elimination of methylprednisolone was more variable during the luteal phase (all patients studied were in the luteal phase) in premenopausal women than it was in men in one study.[2]

Future Directions

Pharmacokinetic differences in transplant recipients do appear to be related to sex and ethnicity, but a number of underlying influences appear to cause this variability. Therefore, efforts should be aimed at accounting for interindividual variability in pharmacokinetic analyses rather than looking at sex and ethnicity as the source of differences. Characterization of both CYP isoforms and transporter expression/function differences appears to account for much of the variability with cyclosporine,[39] but other factors may be operative.[6] These factors likely include exposure to other medications or cytokine variants that may cause induction of metabolic enzymes, transporters, and drug targets. The investigation of the relative importance of each of these factors composes a significant area that requires considerable further study.

It appears that most of the baseline interindividual phenotypic variability can be linked to genetic variants of enzymes and proteins. With the completion of the Human Genome Project, these differences can be mapped to discover isoform-specific gene polymorphisms during drug development and clinical trials and can be rapidly incorporated into clinical practice with microarray (gene-chip) technology.[60] As these significant advances in polymorphism detection and in microarray technology find their way into clinical practice, one can envision a day when a "transplant chip" may be generated for assisting the clinician in selecting the optimal drug regimen and doses of individual agents based on characterization of important genes for metabolic enzymes, transporters, drug targets, and cytokines.

PHARMACOGENETICS

The study of genetically determined variations that affect the efficacy or safety of a drug.

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