Mechanistic investigations into the physiological and biochemical differences between patients have only recently begun to help explain what was previously categorized as "inter-subject variability." Additional factors, including the particular drug formulation or delivery system, have been implicated in observed sex-based and race-based differences in pharmacokinetic response. Drug absorption following intramuscular injection can be highly variable if the injection is mistakenly placed in the overlying tissues, a situation that is more likely to occur in women than men. Slower gastric emptying in women can significantly delay the onset of effectiveness of enteric-coated dosage forms, and differences in gastric pH can affect the drug solubility and dissolution rate. Slower drug release rates designed into many extended release dosage forms interact with the differential locations and populations of intestinal and hepatic transporters and metabolizing enzymes to cause significant sex-based and race-based differences in plasma drug concentrations. Increased efforts to identify and understand the interplay of an individual’s physiological makeup, dietary intake, environment, and the drug products he or she uses are needed to be able to provide optimal drug therapy regimens to each patient.

INTRODUCTION

The effectiveness of a medication is determined by how much of the drug is present at its site of action and how long sufficient concentrations of the drug remain at the site. There are many factors that determine a drug’s disposition after administration, and for simplicity, the traditional parameters of absorption, distribution, metabolism, and excretion can be used to form a basis for categorization of the relevant factors. Sex-based variations may occur in any of the steps involved in a drug’s disposition. The challenge to developing safe and effective medications and medication regimens for all users is in determining when the differences between populations become clinically relevant. The first step for a drug to reach its site of action is its absorption following administration (if not administered intravenously). Mass-produced, commercially available drug products are manufactured to high quality standards that ensure the reproducible release of drug from the product for subsequent absorption. Because the various sites of absorption are also sites where gender and sex differences can be found, the fixed-release patterns of some drug products can lead to different absorption patterns, resulting in
sex-based differences in response to a specific drug product.

EVIDENCE FOR GENDER-BASED DIFFERENCES IN PHARMACOLOGICAL RESPONSE DUE TO DOSAGE FORM OR ROUTE OF DELIVERY

Parenteral administration

The intravenous administration of a parenteral drug product eliminates the need for drug absorption into the vasculature; thus, no sex-based absorption differences would be expected. Once in the bloodstream, drug concentrations may differ between the sexes because of variations in protein binding, distribution, and clearance (metabolism and elimination) of the drug, which are nicely summarized in the recent review by Schwartz\(^1\) and are also addressed by other authors in this issue. When a drug is administered intramuscularly or subcutaneously, however, the drug must move through the tissue spaces and partition into the microvasculature for systemic absorption. It is well accepted that, in general, women possess greater amounts of subcutaneous fat than men, and men have greater muscle mass than women. These differences can cause significantly different absorption profiles for drugs administered at these injection sites.

A classic example of such differences was reported in 1975 by Vukovich et al.\(^2\) for the antibiotic, cephradine. Each subject in the study received a 475-mg dose of cephradine (dose range 4.63–10.49 mg/kg) into the gluteus maximus, vastus lateralis, and deltoid muscles in a 3-way crossover study with a 1-week washout period between doses. Following administration to the vastus lateralis and deltoid muscles, no significant differences in the dose-normalized rate and extent of absorption were found between the male and female groups, but a striking difference was observed for administration via the gluteus maximus (Fig. 1). The C\(_{\text{max}}\) in females was only 40% of the level measured in males, and the total area under the curve (AUC) (extent of absorption) in females was 70% of that in males. The authors observed that the subcutaneous fat layer of the female subjects was thicker than that of males, and it was likely that the intended intramuscular dose was actually administered to the subcutaneous tissues of the female subjects. Similarly, Modderman et al.\(^4\) reported that the initial (1 week) serum concentrations of dapsone administered to the gluteus muscle in females were lower than those in males, yet serum concentrations were much higher in the females compared with males after 4 weeks. These authors also attributed the differences to the likely subcutaneous rather than intramuscular administration of the drug in the female subjects.

Sex-based differences in side effect profiles have also been reported for intramuscularly and subcutaneously delivered vaccines. No differences in titers (6–24 weeks) were detected after intramuscular or subcutaneous delivery of an
aluminum-containing anthrax vaccine, yet subcutaneous nodules, erythema, and induration shortly after vaccination were much more common in women than in men after subcutaneous administration. No differences in the side effect profile were noted when the subjects were stratified by race, however.

Although not extensively reported, sex-based differences in drug response can occur following parenteral administration. The source of these differences can be as simple as the needle length used for a supposed intramuscular injection or can involve complicated physiological responses to the drug moiety or even to the excipients contained in the drug formulation.

Oral administration

Several basic physiological characteristics that have significant effects on dosage form performance and on drug absorption in the gastrointestinal tract differ significantly between men and women. The basal gastric pH in women is approximately 0.5 units greater than in men, which can lead to variations in the rate of dissolution of drugs that have pH-dependent solubility in acidic environments. Gastric emptying is slower in women, sometimes leading to prolonged gastric retention of the dosage form and delayed drug absorption from the small intestine. These differences have been associated with unexpected variations in the performance between various formulations, particularly modified-release dosage forms.

Mojaverian et al. conducted a well-designed trial investigating the relationship between gastric emptying and enteric-coated aspirin performance in women and men to determine whether gastric emptying was responsible for some of the intersubject variability observed with this dosage form. In their study, each subject received two separate doses of a 648-mg enteric-coated aspirin tablet, one during the fasted state and one in the fed state 30 minutes after a 500-kcal breakfast. An 800-kcal lunch was eaten 4 hours after breakfast, and dinner was eaten at an appropriate time after gastric emptying of the enteric-coated tablet had been demonstrated. Gastric emptying of a coadministered Heidelberg capsule was used as a surrogate for the emptying of the intact enteric-coated tablet into the small intestine.

Examples of the salicylate plasma concentrations obtained from a male and a female subject are shown in Figure 2. In the male subject during the fasting state, the enteric-coated tablet emptied from the stomach in ~30 minutes, and measurable plasma concentrations of salicylate were detected shortly thereafter as the enteric coating dissolved from the tablet and aspirin was released and absorbed in the small intestine. In the fed state, the enteric-coated tablet emptied after approximately 5 hours, and again salicylate concentrations were measured shortly thereafter and remained detectable for the following 10 hours.

In one of the female subjects, gastric emptying and the resulting salicylate plasma concentration-time profile in the fasted state were similar to
those of the male subject. In the fed state, however, gastric emptying did not occur for nearly 10 hours, and salicylate levels were measured in the plasma at least 35 hours after administration. The extended period over which the tablet remained in the stomach of this female subject was due to the continuous fed state motility pattern brought about by the consumption of both breakfast and lunch within a short (4-hour) interval. Although not an uncommon time frame for these respective meals, the time span did not allow for the complete emptying of the first meal before the second meal was ingested. As a result, the enteric-coated tablet remained intact in the stomach at low pH until fasted state motility patterns forced it to empty into the small intestine. The low pH gastric environment in the stomach did not allow for dissolution of the enteric coat, and the aspirin contained in the tablet could not be released until the tablet reached the small intestine. Obviously, if this enteric-coated aspirin tablet had been used for pain relief by this female subject under similar conditions, she would not have experienced any pain relief for more than 10 hours after ingesting the dose. It is likely that she would have self-administered other pain relievers in the meantime, resulting in excess medication in her bloodstream after the enteric-coated dosage form began to deliver its dose.

Severe gastrointestinal complications related to dosage form performance are demonstrated by a series of studies investigating verapamil pharmacokinetics from various dosage forms. Verapamil, administered as an intravenous infusion (15 mg in 15 minutes) to a population of normal healthy adults ranging in age from 20 to 89 years, was cleared more rapidly in women than in men.5 This was believed to be due to the increased hepatic metabolism of verapamil, a P450 (CYP)3A substrate, in women. When 120 mg of immediate-release verapamil was administered to the same subjects, women showed slower clearance and higher bioavailability of the drug compared with men.6 The pharmacokinetic differences between the intravenous and oral routes of administration were attributed to the differing activities of intestinal P-glycoprotein, a drug efflux transport protein for which verapamil is a substrate, and intestinal P450 (CYP)3A between males and females. The same group of investigators later showed that clearance of a single dose of verapamil (120 mg) from an immediate-release (Calan, G.D. Searle & Co., Skokie, IL) and a sustained-release (Calan SR) dosage form was slower in women than in men when investigated in a group of healthy volunteers.10 The bioavailability of the immediate-release dosage form was reported to be greater than the bioavailability of sustained-release verapamil,10 further suggesting that intestinal metabolism plays a significant role in the absorption and disposition of verapamil after oral administration.

Given that the release of verapamil from sustained-release dosage forms is slower than from immediate-release systems, it might be expected that gender differences based on intestinal mechanisms might be amplified because of the limited ability of the slower release systems to build up sufficient concentrations in the gut lumen to saturate the intestinal enzymes and transporters. Previously, Gupta et al.11 reported that age and gender influenced the clearance of both enantiomers of verapamil after 5 days of administration of an extended-release, delayed-onset dosage form. The resulting R-verapamil and S-verapamil plasma concentrations were both nearly 2-fold greater in healthy elderly women compared with healthy elderly men (Fig. 3). On further analysis, however, gender differences were no longer statistically significant if the AUC values were corrected for the subject’s lean body mass.

Recently, Kang et al.12 reported a population pharmacokinetic analysis of verapamil clearance after administration of one of four different sustained-release verapamil delivery systems to patients already established on oral sustained-release verapamil. Each of the subjects remained on a once-daily dosing regimen for a period of 7 or 12 weeks, after which verapamil and norverapamil enantiomer plasma concentrations were measured. The clearance in females was found to be faster than the clearance in males, opposite to the results reported previously in healthy subjects. No differences among the four sustained-release delivery systems could be detected. These new results suggest that further studies need to be conducted to clearly determine the basis for the clearance differences observed between age and sex cohorts and between healthy and diseased patients.

A similar population pharmacokinetic analysis of nifedipine by Krecic-Shepard et al.13 showed that there were both sex and racial differences detectable in a group of hypertensive subjects receiving sustained-release nifedipine products. Women had faster clearance of nifedipine than...
men, and white subjects had faster clearance than black subjects. The use of alcohol and smoking status also affected clearance of nifedipine in all subjects, again suggesting that these clearance differences were related to differences in metabolism between the groups. Because of the limited number of patients randomized among the different sustained-release products, it was not possible to demonstrate definitive clearance differences between the formulations, but detection of sex-related differences only with the Adalat formulation (Miles Inc., Elkhart, IN) suggests the possibility of clearance differences resulting from product-specific drug release patterns.

From these limited examples, it is clear that sex-based differences in drug response can be due to the drug itself, resulting from the activity of transporters or metabolizing enzymes. It can also be due, in some part, to the interaction of the physiological differences between the sexes and the site of drug release and subsequent absorption controlled by the delivery system. The combination of sex-based physiological differences with the fixed-release rate of these oral delivery systems leaves open a myriad of possibilities for differences in pharmacokinetics and pharmacodynamics to occur.

Transdermal administration

There are known physiological differences between the skin of males and females and between the skin types of various racial and ethnic populations. Surprisingly, resulting sex-based differences in transdermal absorption from patches or topically applied dosage forms have not been clearly demonstrated. Transdermal clonidine patches were tested in a combined African American and Hispanic American community, and no differences in clinical antihypertensive response based on either gender or ethnicity were found. When investigating the pharmacokinetics of nicotine administered via a transdermal patch (Nicoderm, Marion Merrell Dow, Kansas City, MO), no differences were observed in the study population based on gender, but a significant difference in the Cmax and AUC values were found between obese and normal-weight men. An in vitro investigation of the transdermal permeability of fentanyl and sufentanil also showed no statistically significant differences between skin samples.
stratified by gender or by age. Other investigators have shown that transepidermal water loss, a measurement of skin barrier function (inverse of permeability), does differ based on skin type but was not related to gender and was only indirectly related to race. In these studies, the subjects were classified based on skin type, which was assigned categorically based on skin, eye, and hair color combined with an estimate of the ease of tanning or sunburning, African American, Filipino, and Hispanic subjects with dark hair, brown eyes, and the darkest skin pigment possessed greater skin barrier functionality and faster recovery from stratum corneum removal compared to a group of primarily Asian and white subjects with lighter skin pigment, hair, and eye color.

The lack of reported sex differences in the transdermal delivery of drugs, in light of the obvious physiological differences between various populations, clearly demonstrates that more research needs to be focused on the mechanistic understanding of transdermal drug absorption and the resulting clinical response. Identification of the particular skin factors associated with differences in skin permeability and determination of the interaction between these factors and transdermally administered drugs can increase the ability to identify and counteract sex-based and race/ethnicity-based differences in drug response to these delivery systems.

Respiratory administration

Age-based and sex-based differences in lung physiology should also be associated with differences in pharmacokinetic and pharmacodynamic responses to inhaled medications. Both the volume and the functional capacity of the pulmonary system are approximately 25% lower in women than in men. Given the reliance of many propellant-driven and dry powder inhaler delivery systems on inspiratory air flow, the reduced inspiratory air flow in women is likely to affect the amount of drug delivered from these devices. One report of a sex-based difference in absorption after pulmonary delivery describes the reduction of cyclosporin A blood levels in females after receiving a 20-mg dose (20 1-mg actuations) via a propellant-driven metered-dose inhaler. No differences were measured at a 10-mg dose level, however, leading to the conclusion that the differences at the higher dose were related to the inhalation technique. Obviously, further well-controlled and well-designed studies are needed to determine if differences in physiology translate to sex-based differences in response to inhaled medications.

GAPS IN EVIDENCE

From the previous examples, it is apparent that there are sex-based differences in pharmacokinetics associated with various delivery systems and routes of administration that add to the potential for differences in pharmacological and metabolic profiles of drugs. The effect of gender on drug response has begun to be studied only recently for most drug products, and even more recently, the effects of specific dosage forms (including bioequivalent dosage forms) and routes of administration have begun to be investigated. A cursory survey of the online 2004 Physicians Desk Reference revealed prescribing information for 13 delayed-release and 66 sus-

<table>
<thead>
<tr>
<th>Table 1: Prescribing Information for Modified Release Dosage Forms about Sex-Based or Racial Differences</th>
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<tbody>
<tr>
<td><strong>Description contained in prescribing information</strong></td>
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<tr>
<td><strong>Delayed release n = 13</strong></td>
</tr>
<tr>
<td>No sex differences observed</td>
</tr>
<tr>
<td>(after BSA or BW correction)</td>
</tr>
<tr>
<td>Sex differences observed</td>
</tr>
<tr>
<td>No data about sex differences available</td>
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<tr>
<td>No section about sex effects</td>
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<tr>
<td>No racial differences observed</td>
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<td>Racial differences observed</td>
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<td>No section about racial differences</td>
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From Physicians Desk Reference.21

SR, sustained release; ER, extended release; CR, controlled release; BSA, body surface area; BW, body weight.
tained/extended/controlled-release drug products; most were branded pharmaceutical products from innovator companies. The prescribing information regarding sex and racial differences for these products is summarized in Table 1. The vast majority of product descriptions had no information about sex (41 of 66) or race (53 of 66) effects on the pharmacokinetics or response of the drug. Of the remaining drug products, several reported data on the presence or absence of sex and racial differences in controlled studies, and a few mentioned that no information was available about sex or racial differences. Although newer drug products were far more likely to have specific information about sex and race effects, the paucity of data available both in the scientific literature and from reference resources regarding these differences, coupled with the lack of standards to incorporate a knowledge of the differences into prescribing and use practices, is a clear demonstration that many issues remain to be addressed.

Although it may be somewhat overwhelming to contemplate the number and types of investigations required to completely elucidate gender and race differences in medication response, there are some changes to the scientific literature that could have an immediate impact on this effort. (1) The complete demographics of the study population should be described, and appropriate subgroup analyses should be conducted for all new literature reports. (2) All published pharmacokinetic data should be analyzed based on subject body mass or, more appropriately body mass index (BMI) because some sex-based pharmacokinetic differences that have been observed are really not due to sex when the body size of the individual subjects is included in the analysis.20,22,23 (3) Authors, editors, and abstracting services should select keywords that would allow studies to be indexed based on the composition of the study population whether or not a sex or racial subanalysis was conducted. In addition, inclusion of details about the medication dosage form and route of administration in the indexing would assist in identification of relevant data for analysis of sex and racial differences due to delivery system design.

RELEVANCE AND FUTURE DIRECTIONS

Returning to verapamil as an example, sex-based differences in plasma concentrations between a brand name product and several generic products were deemed “clinically insignificant” in a group of elderly hypertensive patients based on observed antihypertensive effectiveness.24 Others, however, have reported that elderly people are more responsive to verapamil therapy than younger patients,25 and still others have reported that the side effect profile of verapamil is different between women and men.26 All these related, yet sometimes conflicting, conclusions derived from discrete patient groups suggest that far more work needs to be done to determine the actual interacting factors responsible for the differences.

More pragmatically, although many investigators have demonstrated differences in the pharmacokinetics, pharmacodynamics, and side effect profiles of various drugs because of gender, race, and age, most drug products continue to be produced with a limited selection of dose strengths, making dose individualization difficult. The limited number of dose strengths available significantly decreases the likelihood for human error in manufacturing, prescribing, and dispensing, yet it severely limits the ability to dose individual patients based on body mass, genetic makeup, concomitant drug use, or dietary intake. Thus, incorporation of the knowledge of population differences in drug response into the design of dosing regimens for individual patients remains an elusive goal. To begin moving toward this goal, increased efforts must be made to include men and women and subjects from a variety of racial and ethnic backgrounds in clinical trials. In addition, the data obtained must be accurately analyzed for detection of differences between these subgroups while exercising extreme caution in the consideration of confounding variables, including concomitant drug and nutraceutical intake, dietary intake, and environmental factors. Only then will there be sufficient evidence from which to draw valid conclusions about the clinical impact of sex-based or race-based differences and to provide the rationale for development of specific drug products to address these individual needs.

REFERENCES

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