MINIREVIEW

Pharmacokinetic Considerations in Obesity

ROBERT A. BLOUIN* AND GRAHAM W. WARREN

Contribution from *Division of Pharmaceutical Sciences, College of Pharmacy and Graduate Center for Toxicology, University of Kentucky, Lexington, Kentucky 40536-0082.*

Introduction

Obesity is a disease characterized as a condition resulting from the excess accumulation of body fat. In conjunction with increased stores of body fat, obesity has also been associated with increased mortality influenced by increased incidence of hypertension, atherosclerosis and coronary artery disease, diabetes, cancers of the breast, colon, prostate, endometrium, ovary, and cervix, and decreased overall survivability when compared with nonobese counterparts.[1-5] As a consequence, obese individuals generally require more therapeutic intervention earlier in life than nonobese individuals. A very important consideration for pharmacological treatment of obese individuals is the possible discrepancies between obese and nonobese individuals in pharmacokinetic and/or pharmacodynamic activities of a drug. Changes in pharmacokinetic parameters such as volume of distribution or clearance can significantly alter the pharmacologic impact of a drug; therefore, it is important to characterize the properties of drugs in obese individuals.

The direct causes of obesity are difficult to discern due to the plethora of physiological changes associated with obesity. Furthermore, characterizing metabolic and genetic differences between obese and nonobese individuals has proven complex resulting in broad scale attempts to study genetic and nutritional models of obesity in animals. These animal models can be used to help determine the possible causes and effects of obesity in humans resulting in possible agents to attenuate the causes and effects of obesity.

There have been several references reviewing the causes and pharmacological implications of obesity.[6-12] These show the effects of obesity on the pharmacokinetics of drugs in obese subjects; however, there have been considerable advances in the understanding of obesity, particularly in the genetic causes and changes in genetic expression asssociated with obesity. This article will attempt to comprehensively review current knowledge regarding obesity ranging from genetic and nutritional animal studies to pharmacokinetic studies of specific drugs in humans.

Obesity and Drug Absorption

The effects of obesity on absorption and overall bioavailability is poorly understood. In contrast to expected decreases in bioavailability associated with increased splanchnic blood flow in obesity,[23] the bioavailability of midazolam[13] and propanolol,[14] two compounds with moderate to high hepatic extraction, was shown not to be significantly different between obese and lean individuals. Body weight was shown to have no effect on the bioavailability of cyclosporine in renal transplant recipients.[15] No statistically significant difference in the bioavailability of dexfenfluramine could be established between obese and normal-weight individuals.[16] Overall, studies indicate no significant difference in absorption between obese and lean subjects.

Obesity and Drug Distribution

The volume of distribution of a drug is dependent on a number of factors including tissue size, tissue permeability, plasma protein binding, and the affinity of drugs for a tissue compartment.[17] These factors can be affected by the

* Corresponding author: Tel: 606-257-5736. Fax: 606-257-7564. e-mail: rblou1@pop.uky.edu.

physical and chemical properties of a drug in addition to the presence of many disease states. Obesity is a disease state associated with changes in plasma protein binding constituents[18,19] and increases in adipose tissue mass and lean body mass,[20] organ mass,[21,22] cardiac output,[23,24,25] cardiac size and blood volume,[23,24] and splanchnic blood flow[23] relative to normal-weight individuals.

A general trend has been observed for predicting changes in volume of distribution in obese subjects. Increasingly lipophilic substances, based upon the octanol/water lipid partitioning coefficients (LPC), are generally increasingly affected by obesity. Less lipophilic compounds, with lower LPCs, generally have little to no change in volume of distribution with obesity. There are exceptions to this generalization: cyclosporine, a highly lipophilic compound with a relatively large volume of distribution, has been shown in separate experiments to have comparable absolute volumes of distribution (V_{dss}) in both obese and normal-weight individuals.[15,26]

The effect of high lipid partition coefficients in barbiturates was demonstrated by Cheymol[8] when increasing LPC were correlated with increases in distribution into adipose tissue. Thiopental[27] and diazepam,[11,28] with corresponding LPC values of 676[29] and 309,[30] show significant increases in volume of distribution (V_{dss}) for obese individuals relative to normal-weight individuals. In both cases, the volume of distribution increased for both absolute volume of distribution and when normalized for total body weight. However, the absolute distribution (V_{dss}) of digoxin[31] and procainamide[32] has been shown to remain relatively consistent between obese and normal-weight individuals despite relatively high LPC values,[29,33] and the distribution of digoxin decreased in obese individuals when normalized to actual body weight.[31] Others have shown that digoxin does not have extensive distribution into adipose tissue.[34] These results are supportive of the explanation by Christoff et al.[32] that the high LPC values are too low to enhance distribution into adipose tissue. Ritschell and Kahl[33] have developed equations based upon several parameters (i.e., LPC, plasma protein binding, ionization, normal-weight volume of distribution, and body weight parameters) to help determine volume of distribution in obese individuals, but there has been little further experimental support of these equations.

Polar compounds have been shown to have several different relationships between body weight and volume of distribution. Theophylline, shown not to correlate well with ideal body weight (IBW) or total body weight (TBW),[35,36] was shown to adhere well to the following power equation suggested by Rizzo et al.:[37]

$$V_{d} \text{ (in liters)} = 1.29 \text{TBW}^{0.74}$$

Several authors[38,39] agree that a better relationship between aminoglycoside volume of distribution and body weight is given in the following equation proposed by Bauer et al.:[40]

$$V_{d} \text{ (in liters)} = (0.26 \text{ L/kg})[\text{IBW} + (\text{CF} \times \text{AW})]$$

where CF is a correction factor between 0.2 and 0.5 and AW = TBW − IBW (adipose weight).

Neuromuscular agents are another group of generally polar compounds. The best method of calculating dosing strategies might be to base calculations on IBW. In one study, it was shown that the absolute volume of distribution (V_{dss}) of atracurium is unchanged in obese individuals.[41] At the same time, the volume of distribution corrected for TBW decreased. Some lipophilic substances, such as the β-adrenergic receptor blockers bisoprolol and nebivolol, also

have volumes of distribution that decrease when corrected for TBW.[42,43] These decreased volumes of distribution when corrected for TBW indicate that these drugs distribute less into excess adipose tissue. Bisoprolol was shown to have an increased apparent volume of distribution but decreased volume when corrected for TBW. The authors concluded that these parameters indicated that bisoprolol distributed primarily into excess lean body mass relative to excess adipose tissue.

Plasma protein binding is an important determinant of a drugs pharmacokinetics. Changes in the concentrations of plasma binding proteins or alterations in the affinity of plasma proteins for substrate could affect the movement of drug into tissue compartments. The major plasma proteins are albumin, primarily responsible for binding acidic drugs, α_1-acid glycoprotein (AAG), primarily responsible for binding basic drugs, and lipoproteins. Studies have shown that drugs primarily bound by albumin (e.g., thiopental[27] and phenytoin[18,19,44]) show no significant changes in protein binding in obese individuals; however, the binding of drugs to AAG have been shown to increase and decrease in obesity. Benedek et al.[19] showed a significant increase in AAG concentrations in obese individuals with concomitant decreases in the free fractions of propanolol, principally bound by AAG. Cheymol et al.[45] showed no significant differences in AAG between obese and lean individuals; however, a decrease in volume of distribution of propanolol was observed which was more consistent with increased plasma protein binding. Derry et al.[46] also observed an increase in AAG with no change in the plasma free fraction of triazolam, a drug principally bound by AAG. These results indicate the possibility that plasma protein binding affinity may change in obesity without changes in protein concentrations. The plasma protein binding of verapamil, also associated with AAG binding, was unchanged between obese and nonobese individuals.[47] Due to higher triglyceride and cholesterol levels common in obesity, lipoprotein levels may be elevated in obese individuals; however the ramifications of elevated lipoprotein levels has been poorly studied and is not well understood to date.

The clearance of drugs can also be affected by obesity, though increases in clearance do not necessarily reflect changes in the half-life of a drug. The half-life of a drug can be related to both volume of distribution and clearance through the following relationship:

$$t_{1/2} = (V_{d})(0.693)/\text{CL}$$

The half-life of a drug may increase without changes in clearance. Abernathy et al.[48] showed a significant increase in the plasma half-life of desmethyldiazepam without changes in clearance. Rather, the change in half-life was attributed to the increase in volume of distribution in obese individuals. LeJeunne et al.[42] demonstrated increased absolute volume of distribution (V_{dss}) and increased clearance of bisoprolol with no change in plasma half-life in obese versus nonobese individuals. These studies demonstrate the interrelationships between half-life, volume of distribution, and clearance as well as indicates the usefulness of volume of distribution and clearance over plasma half-life for a given drug.

Obesity and Drug Clearance

Changes in Metabolic Enzymes in Obese Humans—Measuring changes in hepatic metabolizing enzymes in humans is difficult due to the general lack of enzyme specific markers of metabolic activity. As a result, relationships are usually drawn between pharmacokinetic behavior

of a drug in humans and measured metabolic enzyme levels in animals. Important considerations are presented by the fact that fatty infiltration characterizes the livers of most individuals.[49] This fatty infiltration generally resembles mild alcoholic hepatitis in moderately obese individuals,[49] but morbidly obese individuals have markedly increased liver damage.[50] These factors could have a significant impact on the metabolic activity of the liver thereby dictating the importance of characterizing metabolism in obese individuals. There are some determinants of metabolic activity in humans that are generally considered as definitive markers for enzyme levels that have been used to show differences between obese and normal-weight individuals. These markers and the effects of obesity are discussed in the following paragraphs. Unless stated otherwise, clearance parameters are not normalized for body weight.

It was previously thought that hepatic oxidative metabolism was essentially unchanged in the obese individual when compared to a normal-weight individual. Caraco et al.[51] used obese and lean volunteers to evaluate the pharmacokinetics of antipyrine, a marker for hepatic oxidative metabolism. In the obese group, plasma half-life increased, apparent volume of distribution increased (but decreased when corrected for TBW), and the clearance remained unchanged. When volunteers were enrolled in a weight reduction program, obese individuals showed decreased half-life, decreased volume of distribution (increased when corrected for TBW), and a nonsignificant increase in clearance after losing weight. The nonsignificant changes in clearance indicate that the oxidative pathways employed by the liver for antipyrine metabolism remain unchanged between obese and normal-weight individuals; however, antipyrine undergoes extensive hepatic oxidative metabolism through multiple oxidative pathways, and a change in singular pathways would be difficult to assess.

Metabolism of chlorzoxazone to 6-hydroxychlorzoxazone has been used as a marker for hepatic cytochrome P450 (CYP) 2E1 activity in humans. O'Shea et al.[94] showed increased chlorzoxazone clearance in obese individuals as well as increased formation clearance of 6-hydroxychlorzoxazone from chlorzoxazone. The increase in chlorzoxazone clearance was attributed to increased CYP2E1 activity associated with obesity. The authors further stated that the increase in CYP2E1 activity may predispose obese individuals to CYP2E1-mediated toxicities associated with the production of toxic metabolites from environmental agents.

The formation of 6β-hydroxycortisol and N-methylerythromycin from cortisol and erythromycin has been shown to provide a general marker for cytochrome P450 3A activity in humans.[52,53] Hunt et al.[52] performed a study in volunteers to monitor the metabolism of cortisol and erythromycin to 6β-hydroxycortisol and N-methylerythromycin. Using these parameters as measures of CYP3A activity in humans, it was found that a negative correlation existed between percent IBW and N-methylerythromycin production. In contrast, cortisol metabolism showed no negative correlation between percent IBW and urinary 6β-hydroxycortisol/cortisol ratios. The authors thought that similar correlations should be drawn between percent IBW and N-methylerythromycin and percent IBW and 6β-hydroxycortisol/cortisol ratios. Another study by Hunt et al.[53] supported changes in CYP activity in humans by showing a negative correlation between erythromycin N-demethylation and percent IBW in elderly subjects. These contrasting studies demonstrate the difficulties associated with correlations between specific markers of drug metabolism and specific CYP isoform modulation.

Using drugs that are primarily transformed via Phase II conjugation pathways, glucuronidation and sulfation have been shown to increase in obese individuals. The clearance of oxazepam and lorazepam, benzodiazepines excreted primarily in the form of glucuronide conjugates, was shown to increase in obese individuals.[54] In another study, acetaminophen clearance was shown to increase with obesity,[55] though not as significantly as the increases shown with oxazepam and lorazepam.[54] It has been shown that acetaminophen is eliminated as both a glucuronide and sulfate conjugate in humans[56] whereas oxazepam and lorazepam are excreted primarily as glucuronide conjugates. It is likely that obesity affects different pathways through different mechanisms and levels: where glucuronidation might be significantly enhanced, sulfation may only be slightly to moderately enhanced due to obesity.

Other evidence supporting differential regulation of Phase II pathways are studies showing that the clearance of salicylate[57] and procainamide[32] is not significantly different between obese and lean individuals. Salicylate is conjugated to the glycine, phenolic, and acyl glucuronide, and procainamide is primarily acetylated. Together these results indicate that these pathways may not be significantly affected by obesity in humans.

Another interesting consideration in determining the metabolic activity of obese individuals is considering changes in metabolism in tissues other than the liver; specifically, due to the significant increase in adipose tissue in obese individuals, changes in metabolism within adipose tissue could be significant. Rafecas et al.,[58] using white adipose tissue from obese and lean patients, observed an increase in insulin cleavage in obese subjects relative to normal-weight subjects. In the absence of reduced glutathione, no insulin was cleaved, indicating that glutathione transhydrogenase, present in white adipose tissue, was likely the only enzyme responsible for insulin cleavage within white adipose tissue. The authors stated that hyperinsulinemia common in obesity may be offset by the substantial increase in adipose tissue possessing high intrinsic insulin cleaving activity. The results of this study point to the possibility that adipose tissue might play a significant role in energy regulation in obese individuals. Further evidence suggests that adipose tissue may play a role in the increased clearance of prednisolone in obese men.[59] The interconversion of prednisolone and prednisone is dependent on 11-hydroxysteroid dehydrogenase, an enzyme present in adipose tissue; therefore, the increase in adipose tissue may provide an alternative site of clearance for prednisolone.

In a series of studies, the pharmacokinetics of carbamazepine was evaluated in obese subjects before and after significant weight reduction[60] and in obese versus lean subjects.[61] In the first study, obese subjects were monitored to establish the pharmacokinetic parameters of carbamazepine, and then each subject was entered into a weight reduction program, regulating diet and exercise, after which the same pharmacokinetic parameters were assessed and compared for each individual. After significant weight reduction, the formerly obese individuals had a decreased plasma half-life, increased clearance, decreased absolute volume of distribution (Varea) with respect to bioavailability, and no significant change in Varea when normalized for total body weight. In the second study, relative to normal-weight individuals, obese individuals had increased absolute volume of distribution (Varea), increased plasma half-life, and unchanged clearance values. The disparity between changes in clearance remains unexplained, but it is important to note that obesity may be associated with changes in blood flow or metabolic activity. Further comparison between the two studies indicates that, for car-

bamazepine, the increased volume of distribution and half-life associated with obesity may involve reversible processes that may disappear following weight reduction.

Changes in Renal Function in Obese Humans

Elimination of a drug through the kidney can be accounted for by glomerular filtration, tubular secretion, and tubular reabsorption; however, there are several discrepancies regarding the influence of obesity on these functions. Davis et al.[62] and Stockholm et al.[63] have independently shown increases in glomerular filtration, measured using creatinine clearance, in obese women as compared to normal-weight women. Dionne et al.[64] has also shown increased creatinine clearance in obese subjects when compared to historical values of creatinine clearance; however, Ducharme et al.[65] showed decreased glomerular filtration via creatinine clearance in obese individuals from a patient population study of vancomycin pharmacokinetics. Reiss et al.[66] and Allard et al.[67] showed no significant difference between creatinine clearance in obese versus nonobese individuals. There are also discrepancies between studies of drug primarily excreted by glomerular filtration. Historical evidence has shown that the aminoglycoside antibiotics[68] including gentamicin[69,70] and vancomycin[71] are associated with increased clearance in obese individuals; however, recent evidence has shown that vancomycin clearance is unchanged in obese individuals greater than 1.3 times their IBW.[64] One possible explanation for these discrepancies might be due to the difference in extent of obesity and/or associated renal pathology.

Tubular function (i.e., tubular secretion and tubular reabsorption) in the kidney is often difficult to ascertain; thus, conclusions regarding tubular function are often indirect. Changes in tubular function have been indicated in several studies. The renal clearance of ciprofloxacin,[67] cimetidine,[72,73] procainamide,[32,45] and lithium[66] has been shown to increase in obese individuals. Since the renal excretion of ciprofloxacin,[92] cimetidine,[95] and procainamide[32] involves primarily glomerular filtration and tubular secretion, the increases in renal clearance of ciprofloxacin, cimetidine, and procainamide accompanied by a disproportionate increase in glomerular filtration supports increased tubular secretion in obese individuals. Renal clearance of lithium primarily involves glomerular filtration and tubular reabsorption;[93] consequently, the increase in the renal clearance of lithium with no increase in glomerular filtration[66] supports decreased tubular reabsorption in obese individuals.

Obesity and Drug Pharmacodynamics

A final but equally important consideration when developing a dosing strategy for an individual involves the consideration of drug efficacy. Obese subjects were shown to have increased sensitivity to triazolam as measured by a sedation score upon administration of a second dose.[46] The same dose of triazolam was used for both obese and nonobese individuals. Varin et al.[41] showed that even though obese individuals were exposed to significantly higher plasma concentrations of atracurium, no change was seen in the duration of neuromuscular blockade. The authors attributed this change in sensitivity to a combination of protein binding effects and desensitization of acetycholine receptors. Desensitization of acetylcholine receptors has been associated with chronic inactivity.[74,75] It is important to note that, with the plethora of probable genetic and nutritional changes associated with obesity, changes in receptor expression or affinity for ligand could be altered resulting in differential pharmacotherapeutic effects in obese individuals as compared to lean individuals.

Changes in Metabolic Enzymes in Obese Animals

The influence of pathophysiologic and morphologic changes associated with obesity on hepatic metabolism is not well understood. Before the late 1980s, studies correlating obesity-associated changes with either hepatic drug metabolizing enzymes (e.g., hepatic cytochrome P450) or drug markers (e.g., antipyrine) were nonexistent. In 1989, Corcoran et al.[12] showed no significant difference in CYP concentrations between obese and lean rats; however, total CYP increased per liver in the obese overfed rat. Beginning in the early 1990s, studies began showing changes in hepatic CYP resulting from obesity using both animal models and human markers. Studies dating as far back as the 1970s have indicated changes in Phase II metabolism pathways associated with obesity. The following paragraphs describe differences in Phase I and Phase II metabolism in obese animal models.

Research has been conducted to determine the effects of either genetically or nutritionally induced obesity in mice and rats. Irizar et al.[76] observed decreased total CYP expression in genetically obese (fa/fa) Zucker rats. When expressed as CYP activities per nmol of total CYP, CYP1A, CYP2B, CYP2E, CYP3A, and CYP4A were shown to increase in obese rats using specific substrates. Absolute CYP activities increased for CYP1A and CYP3A in obese rats whereas the increase in expression of other CYP isoforms resulted primarily due to the decrease in overall CYP levels. Anti-mouse CYP2D antibodies showed a decrease in apoprotein in obese rats when compared with normal rats. The investigators indicated the possibility that reduced growth hormone (reduced in obese male animals and shown to be partially responsible for the regulation of CYP3A expression) caused the increase in CYP3A activity. These results illustrate the possible ramifications of genetically induced obesity; however, parallels to humans are difficult to establish due to difficulty in characterizing the genetic causes of obesity in humans.

An alternative model of obesity uses nutritional modulation to induce obesity. Salazar et al.[79] previously reported an increase in CYP2E1 in obese overfed rats. Raucy et al.[77] used overfed Sprague Dawley rats to observe the effects of obesity on the expression of CYP2E1. Following 52 weeks of nutritional overfeeding, obese rats showed increased total CYP relative to control rats, unchanged CYP reductase and cytochrome b5, increased CYP2E1, and unchanged CYP2C11 and CYP3A. A strong correlation was also shown between CYP2E1 activity and CYP2E1 protein immunoblot staining thereby reducing the significance of posttranslational modifications common to CYP2E1. The authors further indicated that ketosis, often implicated as the mechanism by which CYP2E1 is increased, is likely not the primary mechanism of upregulation due to the fact that no significant increases were observed in CYP2B1 or CYP reductase activities also commonly associated with ketosis. Contrasting the genetic versus nutritional models, there appears to be a different mechanism of metabolic regulation influenced by either genetic expression or metabolic changes resulting in possible functional (i.e., enzymatic expression) and morphological (i.e., fatty infiltration in the liver associated with obesity) changes in obese rats. The importance of these factors could easily manifest itself by causing possible increases in toxicity following drug administration such as with the increased acetaminophen toxicity associated with obesity.[78]

Chaudhary et al.[80] provided evidence that glucuronidation increased and sulfation pathways were unaffected in

the genetically obese Zucker rat. Using acetaminophen as a substrate for glucuronidation and sulfation, the investigators observed no difference between urinary excretion of acetaminophen sulfate and increased urinary excretion of acetaminophen glucuronide in the genetically obese Zucker rat when compared to normal-weight rats. No change was observed for γ-glutamyl cysteine synthetase; however, total glutathione and UDPGT increased in obese rats relative to normal-weight rats. This is an important observation indicating that obese rats might have higher conjugation and detoxification pathways, but there is some discrepancy to this conclusion in that Barnett et al.[81] observed lower glutathione-S-transferase and total glutathione in genetically obese (ob/ob) mice indicating possibly higher susceptibility to toxicity in obese mice. The ob/ob mouse model associates noninsulin dependent diabetes with obesity which likely manifests differential enzymatic expression mechanisms than nondiabetes-associated obesity. Consequently, direct correlations between the two models is impossible, but the observation should be made that there are several presently unidentified mechanisms involved in obesity that could possibly result in the regulation and differential expression of many enzymes. An argument against the possibility that obese rats might have higher glutathione conjugation capacity is the fact that others have shown increased acetaminophen toxicity in obese rats indicative of depeted glutathione.[78]

Sastre et al.[82] used an overfed Wistar rat and Swiss mice model to demonstrate that overfed mice had lower levels of both reduced glutathione and oxidized glutathione than chow fed mice. This study seemed to parallel the study by Barnett et al.[81] using a genetically obese mouse model in that both models show a decreased propensity of obese mice for glutathione dependent conjugation and protection against cellular insult. The contrast mentioned before between obese Zucker rats and obese mice is also likely influenced by species specific differences in obesity, another complication in the elucidation and parallel application of obesity associated mechanisms involved in pharmacokinetic changes.

Contrasting the nutritional versus genetic models of obesity, differences can be seen between genetic obesity and nutritional obesity for both Phase I and Phase II enzymatic pathways. It should be noted that genetically induced obesity is targeted for a specific gene, but nutritional obesity can have effects on multiple genes that in turn can effect the expression of many other genes. Consequently, the pathways associated with nutritional obesity may be more variable and harder to elucidate. On the other hand, several current reviews[83–86] cover the genetic causes and effects of obesity should the reader be interested in broadening his/her knowledge of the genetic influences of obesity. Using genetic models, obesity has been linked to deficiencies in leptin, a hormone shown to be secreted by adipocytes[87] that reduces body weight and food intake in both obese and nonobese animals.[88] Research into the interactions of leptin with the body and the effects of obesity on leptin levels is generating volumes of new information into the molecular mechanisms of obesity and the possibilities that obesity might be under hormonal control. Several reviews[89,90] evaluate the current understanding of leptin and its relationship with the body.

Pharmacotherapeutic Toxicity in Obesity

The toxicity of substances can change with obesity. With possible increases in metabolism such as with the CYP system, drugs can be converted to toxic metabolites at higher rates; however, toxic drugs may also be converted to inactive metabolites at higher rates. Changes in the

clearance, volume of distribution, bioavailability, or pharmacodynamics may affect the toxic potential of a drug. Additionally, changes in excretion mechanisms can alter the toxicity of a compound by either increasing exposure through decreased clearance or vice-versa. One study by Georgiadis et al.[91] observed the possible increases or decreases on the toxicity associated with the administration of a plethora of highly toxic chemotherapeutic agents to obese versus lean subjects with small-cell lung cancer. According to the study, no correlation could be established between obesity and increased toxicity for patients receiving cyclophosphamide, methotrexate, lomustine, etoposide, and cisplatin. Perhaps the most important conclusion to be drawn from the information presented in this article is that each drug behaves differently. Predicting toxicity associated with obesity is very difficult if not impossible. The best approach for pharmacotherapeutics in obese individuals is to use previous knowledge and be conservative. Careful monitoring of the obese patient is necessary when administering drugs with a small therapeutic index.

Summary

Using the parameters of volume of distribution and clearance, a therapeutic dosing strategy can be developed for a drug. Consequently, the effects of physiological disorders on these parameters is important for accurate pharmacotherapeutics. Regarding obesity, the volume of distribution has been shown to change in many situations. Generally, more lipophilic compounds are affected by obesity to a greater extent than hydrophilic compounds. More lipophilic compounds are associated with increases in volume of distribution in obesity; however, there are exceptions to this relationship. High LPC values did not correspond with markedly increased volumes of distribution for digoxin,[31] procainamide,[32] and cyclosporine.[15,26] Consequently, prior knowledge of the effects of obesity on specific drugs is essential for accurate dosing strategies based upon volume of distribution; generalizations among similar groups of drugs does not always result in proper physiologic responses between obese and lean individuals.

The clearance of a compound depends on the metabolic activity of characteristic enzymes that may be affected by obesity or diseases associated with obesity. Changes have been noted in both humans and animals for various CYP isozymes using either direct measurements (in animals) or through the use of metabolic markers (in humans) such as antipyrine or erythromycin. In addition, obesity has been associated with increased glucuronidation with questionable effects on sulfation. Changes between obese and lean subjects have also been observed for antioxidant systems including glutathione and catalase. It is important to note the variability in characterizing metabolic changes in obesity. Given the numerous possible genetic and environmental influences, predicting changes in metabolic activity can be difficult. Furthermore, there are possibilities that similar concentrations of a drug at its site of action may not elicit a similar response between obese and lean subjects, thereby making accurate therapeutic modifications more difficult for obese individuals.

Renal function, particularly glomerular filtration, has been shown to change with obesity. Increased glomerular filtration in some studies has been contradicted by decreases in glomerular filtration in other studies. These discrepancies illustrate the possible ramifications of different degrees of obesity, with morbidly obese individuals exhibiting different responses than moderately obese individuals. The effects of obesity on the toxicology of specific compounds is questionable depending upon not only the presence of enzymes that create toxic metabolites, but also

depending upon the presence of enzymes that remove toxic metabolites from the body. In conclusion, a safe therapeutic protocol for obese individuals should be based upon existing therapeutic information as well as careful monitoring of the patient during pharmacologic intervention.

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Acknowledgments