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Effect of Obesity on the Pharmacokinetics of Drugs in Humans

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Abstract

The prevalence of obesity has dramatically increased in recent years and now includes a significant proportion of the world's children, adolescents and adults. Obesity is linked to a number of co-morbidities, the most prominent being type 2 diabetes mellitus. While many agents are available to treat these conditions, the current knowledge regarding their disposition in the obese remains limited.

Over the years, both direct and indirect methodologies have been utilized to assess body composition. Commonly used direct measures include underwater weighing, skinfold measurement, bioelectrical

impedance analysis and dual-energy x-ray absorptiometry. Unfortunately, these methods are not readily available to the majority of clinicians. As a result, a number of indirect measures to assess body composition have been developed. Indirect measures rely on patient attributes such as height, bodyweight and sex. These size metrics are often utilized clinically and include body mass index (BMI), body surface area (BSA), ideal bodyweight (IBW), percent IBW, adjusted bodyweight, lean bodyweight (LBW) and predicted normal weight (PNWT).

An understanding of how the volume of distribution (V_d) of a drug changes in the obese is critical, as this parameter determines loading-dose selection. The V_d of a drug is dependent upon its physiochemical properties, the degree of plasma protein binding and tissue blood flow. Obesity does not appear to have an impact on drug binding to albumin; however, data regarding α_1-acid glycoprotein binding have been contradictory. A reduction in tissue blood flow and alterations in cardiac structure and function have been noted in obese individuals. At the present time, a universal size descriptor to describe the V_d of all drugs in obese and lean individuals does not exist.

Drug clearance (CL) is the primary determinant to consider when designing a maintenance dose regimen. CL is largely controlled by hepatic and renal physiology. In the obese, increases in cytochrome P450 2E1 activity and phase II conjugation activity have been observed. The effects of obesity on renal tubular secretion, tubular reabsorption, and glomerular filtration have not been fully elucidated. As with the V_d, a single, well validated size metric to characterize drug CL in the obese does not currently exist. Therefore, clinicians should apply a weight-normalized maintenance dose, using a size descriptor that corrects for differences in absolute CL between obese and non-obese individuals.

The elimination half-life ($t_{½}$) of a drug depends on both the V_d and CL. Since the V_d and CL are biologically independent entities, changes in the $t_{½}$ of a drug in obese individuals can reflect changes in the V_d, the CL, or both.

This review also examines recent publications that investigated the disposition of several classes of drugs in the obese – antibacterials, anticoagulants, antidiabetics, anticancer agents and neuromuscular blockers.

In conclusion, pharmacokinetic data in obese patients do not exist for the majority of drugs. In situations where such information is available, clinicians should design treatment regimens that account for any significant differences in the CL and V_d in the obese.

Obesity is a well recognized global health problem. Although it was originally seen as an issue only in developed nations, current evidence demonstrates an increase in obesity prevalence in many lower- and middle-income countries.[1,2] In 2005, the WHO estimated the numbers of overweight and obese adults to be 1.6 billion and 400 million, respectively.[3] If current trends persist, up to 58% of the world's adult population will be either overweight or obese by 2030.[1] Even more alarming is the expansion of the obesity epidemic to the world's children and adolescents.[4] Regardless of the demographics, the driving forces behind the rise in obesity are believed to be multifactorial, involving an interplay of social, economic, behavioural and genetic factors.[5]

Epidemiological studies have linked obesity with hypertension, coronary artery disease, stroke, type 2 diabetes mellitus, osteoarthritis, major depression and several forms of cancer.[6] In fact, the relationship between obesity and type 2 diabetes may be analogous to the association between tobacco and lung cancer.[2] In particular, excess weight is thought to be the primary cause of 90% of type 2 diabetes cases.[7]

The rise in obesity, coupled with its associated comorbidities, suggests that clinicians will encounter obese patients with increasing frequency in their daily practice. Unfortunately, obese subjects are often excluded from clinical trials during the drug development process. As a result, information regarding the impact of obesity on the pharmacokinetics and pharmacodynamics of the majority of drugs remains limited. While oral drug absorption does not appear to be altered in obese individuals, differences in the distribution and clearance (CL) of certain drugs have been noted.[8-12] As these two parameters are integral determinants of the pharmacokinetic behaviour of a drug, a thorough understanding of their changes in the obese is a requisite to ensure safe and effective pharmacotherapy.

This article reviews the effect of obesity on the pharmacokinetics of drugs in humans. It is intended to serve as an update of previously published reviews[8-14] on this topic. A brief overview of the different measures to classify body composition is provided. This is followed by a discussion of the key pharmacokinetic parameters mediating drug disposition and their

potential alteration in the obese. Recent pharmacokinetic data for individual drugs are then presented.

1. Measures of Weight and Obesity

1.1 Direct Measures of Body Composition

While the direct quantification of body fat remains difficult, it can be indirectly defined as the difference between an individual's bodyweight and fat-free mass (FFM). Several quantitative methods have been employed over the years, with some of the more common being underwater weighing (hydrodensitometry), skinfold measurement, bioelectrical impedance analysis (BIA), and dual-energy x-ray absorptiometry (DEXA).

The oldest direct measurement technique is underwater weighing.[15] In this method, the subject is completely submerged in water and the resultant weight and/or volume of water displaced is recorded. This information is then combined with the individual's 'above water' weight to calculate the subject's whole-body density. Assuming a constant density for fat and fat-free tissues, the fraction of bodyweight that is composed of fat can then be determined. Recently, air-displacement plethysmography has often been utilized instead of underwater weighing. The principles of these two techniques are similar, except that in the former, the subject is placed in a closed air-filled chamber instead of a water-filled tank.[16]

Skinfold measurement is based on the assumption that total body fat is correlated with the amount of subcutaneous fat at certain anatomical sites. However, its reliability is only as good as the clinician's caliper measurement technique. Furthermore, skinfold measurement is not feasible for some obese patients because of the limited size of the calipers.[17]

Another procedure for determining FFM is BIA.[18] Four electrodes are attached to the subject and an electrical current is passed through two of them. The other pair of electrodes records the change in voltage as the current moves across the body. While body fat and bone impede the current's flow, the aqueous tissues readily conduct the current because of their electrolyte content. The measured impedance to current flow can then be used to estimate FFM. BIA is probably the most frequently used method for FFM determination because it is a noninvasive and low-risk procedure that provides rapid results.[15,19]

DEXA relies on the different x-ray attenuation properties of bone, lean tissue and fat to assess body composition.[20] The DEXA technique passes two x-ray beams of differing energies through the body. As the beams encounter the unique densities of fat and lean tissues, they are attenuated to differing degrees. The extent of attenuation is quantified for each energy beam, and the subsequent attenuation ratio is used to deduce the amount of bone and soft tissue present in the path of the beam. Whole-body scanning enables one to estimate an individual's FFM using specific attenuation formulae.[15,19]

Although these direct methodologies are useful for determining an individual's body composition, they are not readily available to the majority of clinicians. As a result, several indirect methods to describe body composition have been developed.

1.2 Indirect Measures of Body Composition

Indirect measures of body composition rely on patient attributes that are readily measurable – height, weight and sex. Weight and size descriptors utilized in pharmacokinetic studies and clinical practice include the following: body mass index (BMI), body surface area (BSA), ideal bodyweight (IBW), percent IBW, adjusted bodyweight, lean bodyweight (LBW) and the newly described predicted normal weight (PNWT). A brief overview of these metrics is provided in sections 1.2.1–1.2.5. For a more thorough analysis of these size descriptors, interested readers are directed to a recent review by Green and Duffull.[14]

1.2.1 Body Mass Index

BMI is calculated by dividing the total bodyweight (TBW) in kilograms by the square of the height in metres (i.e. kg/m^2). This is the WHO's preferred measure for classifying obesity, and it is used to stratify individuals into three primary groups: BMI $<18.5\ kg/m^2$, underweight; BMI 18.5–24.99 kg/m^2, normal weight; and BMI $\geq 25\ kg/m^2$, overweight. The overweight group is comprised of four additional designations: BMI 25–29.99 kg/m^2, pre-obesity; BMI 30–34.99 kg/m^2, obesity class I; BMI 35–39.99 kg/m^2, obesity class II; and BMI $\geq 40\ kg/m^2$, obesity class III.[21] Obesity class III is also commonly referred to as morbid obesity. Although this measure is widely utilized because of its simplicity, the primary limitation of using BMI to classify obesity is its failure to distinguish between adipose tissue and lean muscle mass. Since the same BMI may not correspond to the same degree of adiposity across populations, the widespread adoption of BMI as a dosing scalar has not occurred.

1.2.2 Body Surface Area

Like BMI, BSA is based on weight and height, and does not account for sex. The original equation was derived on the assumption that BSA depended on height, weight and some

constant. This ultimately resulted in the following formula: BSA (m^2) = $(TBW)^{0.425} \times (\text{height in cm})^{0.725} \times 0.007184$.[22] In 1987, a simplified formula was introduced: BSA (m^2) = $[(TBW) \times (\text{height in cm})/3600]^{1/2}$.[23] This size descriptor is extensively used in oncology to determine the dosages of many anticancer agents. However, the utility of BSA in dosing obese patients is still uncertain. In fact, many clinicians assign a BSA value of $2\ m^2$ when dosing an individual whose actual BSA exceeds this arbitrary cut-off.[24]

1.2.3 Ideal Bodyweight

The concept of IBW was initially derived from insurance data tables that related size to mortality. Subsequently, an empirical equation to estimate IBW was calculated by Devine:[25] IBW (kg) = 45.4 kg (49.9 kg if male) + 0.89 × (height in cm – 152.4). IBW differs from BSA and BMI in that sex enters into the calculation. As a dosing scalar, IBW is not an optimal metric, since all patients of the same sex and height would receive the same dose regardless of body composition. The concept of adjusted bodyweight tries to overcome this limitation by adding to IBW some proportion of the difference between TBW and IBW for dosing purposes. Clinically, adjusted bodyweight is frequently used for aminoglycoside dose calculation.[13]

1.2.4 Lean Bodyweight

LBW is a size descriptor of weight devoid of almost all adipose tissue. It is closely related to the concept of FFM – consisting of extracellular fluid, muscle, bone and the vital organs – and the two terms are often used interchangeably.[26] The most commonly used equations to estimate LBW are the following: males, LBW (kg) = 1.10 × TBW – 0.0128 × BMI × TBW; females, LBW (kg) = 1.07 × TBW – 0.0148 × BMI × TBW. However, as noted by Green and Duffull,[27] these formulae may be physiologically inaccurate at the extremes of height and weight. This limitation can be seen by the fact that LBW reaches a peak, then begins to decrease, as TBW increases (figure 1a). Consequently, a semi-mechanistically-derived method for estimating LBW was developed in 2005, based on bioelectrical impedance data.[26] The corresponding formula for this LBW calculation is LBW (kg) = (9270 × TBW)/(A + B × BMI), where A and B are 6680 and 216, respectively, for males, and 8780 and 244, respectively, for females. Since this LBW calculation does not begin to decrease with increasing TBW (figure 1b) and correlates well with the earlier formula for normal-weight individuals[26,28] (figure 1c), it appears to be a more appropriate means of calculating LBW in obese and non-obese individuals.

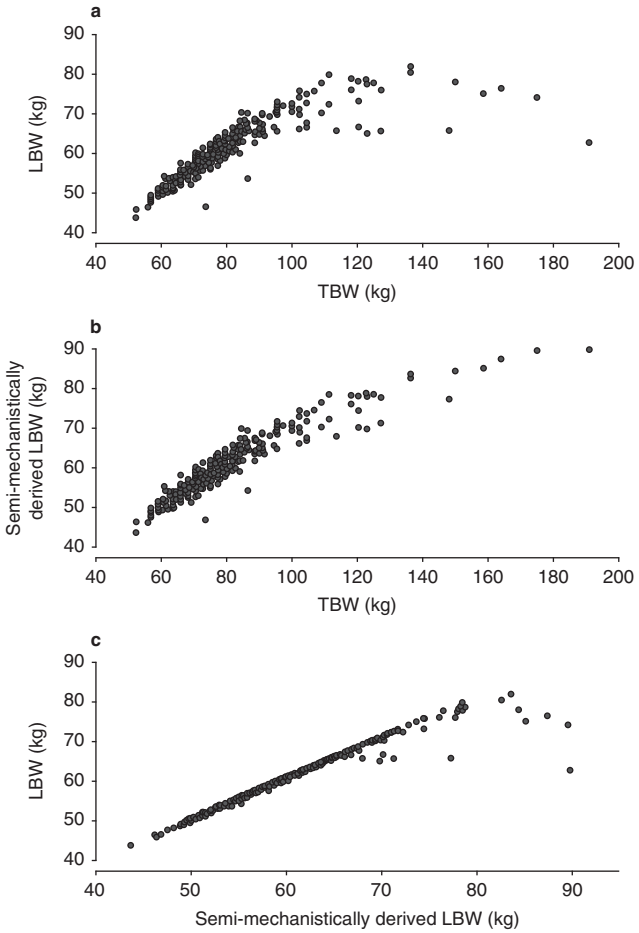

Fig. 1. Comparison of the two approaches for determining lean bodyweight (LBW) in males. Using demographic data from our laboratory, the relationship between total bodyweight (TBW) and LBW was examined. (**a**) LBW was calculated using the following formula: LBW = 1.10 × TBW – 0.0128 × BMI × TBW. (**b**) LBW was determined from the following semi-mechanistically derived equation:[26] LBW = (9270 × TBW)/(6680 + 216 × BMI). (**c**) Relationship between the calculated LBW for each individual using the two different approaches. Similar observations were noted for females when analogous plots were constructed (data not shown). **BMI** = body mass index.

1.2.5 Predicted Normal Weight

The weight descriptor PNWT was recently developed as a means to predict the expected normal weight of an overweight or obese individual.[29] PNWT is equal to the sum of an individual's LBW and a fraction of the individual's excess fat content that represents predicted normal fat mass. For males, PNWT (kg) = 1.57 × TBW – 0.0183 × BMI × TBW – 10.5. The corresponding formula for females is PNWT (kg) = 1.75 × TBW – 0.0242 × BMI × TBW – 12.6. PNWT is unique in that it was specifically developed to characterize the pharmacokinetics of drugs. Since PNWT was derived using earlier equations for LBW, its accuracy may diminish at the extremes of height and weight.[14]

The estimation of body composition in older individuals is complicated by the fact that the ratio of adipose to lean tissue tends to increase with age, even without significant changes in TBW.[30] Of the aforementioned size metrics, only the semi-mechanistic LBW descriptor[26] appears to account for these age-related changes, since it was derived using bioimpedance data.

Among the available size descriptors, BMI and percent IBW (TBW/IBW × 100) have been the two most frequently used to classify obesity. Using demographic data accumulated in our laboratory, we investigated the relationship between percent IBW and BMI. As depicted in figure 2, a high degree of correlation was observed for both males (figure 2a) and females (figure 2b) over a wide range of bodyweights. Similarly, BSA and the semi-mechanistically derived LBW descriptor[26] appear to be highly correlated for both males (figure 2c) and females (figure 2d). This latter finding corroborates a recent report by Han et al.[31] Therefore, the data in figure 2 illustrate that there is some redundancy among the indirect measures of obesity. This also suggests that there may not be an optimal anthropometrically based methodology to define adiposity at the present time. Nevertheless, the recent derivation of a size descriptor using mechanistic principles is intriguing and might represent a step forward in our understanding of how best to define body composition, should its utility be demonstrated in future pharmacokinetic investigations.

2. Key Measures of Drug Disposition

2.1 Volume of Distribution

The volume of distribution (V_d) is the term used to relate the total amount of a drug in the body to the concentration of the drug in a given compartment. The pharmacokinetic behaviour of most drugs is best described by a multi-compartment model as opposed to the simpler model containing only one compartment. Unfortunately, characterization of the V_d in a multi-compartment model is problematic as there is an infinite number of volumes of distribution after drug administration.[32] Of these, the volume of distribution at steady-state (V_{ss}) and the volume of distribution during the elimination phase (V_z) are the two most commonly reported. As proportionality constants, the V_{ss} is only valid at a single point in time, while the V_z is valid at all times following distribution equilibrium.[33]

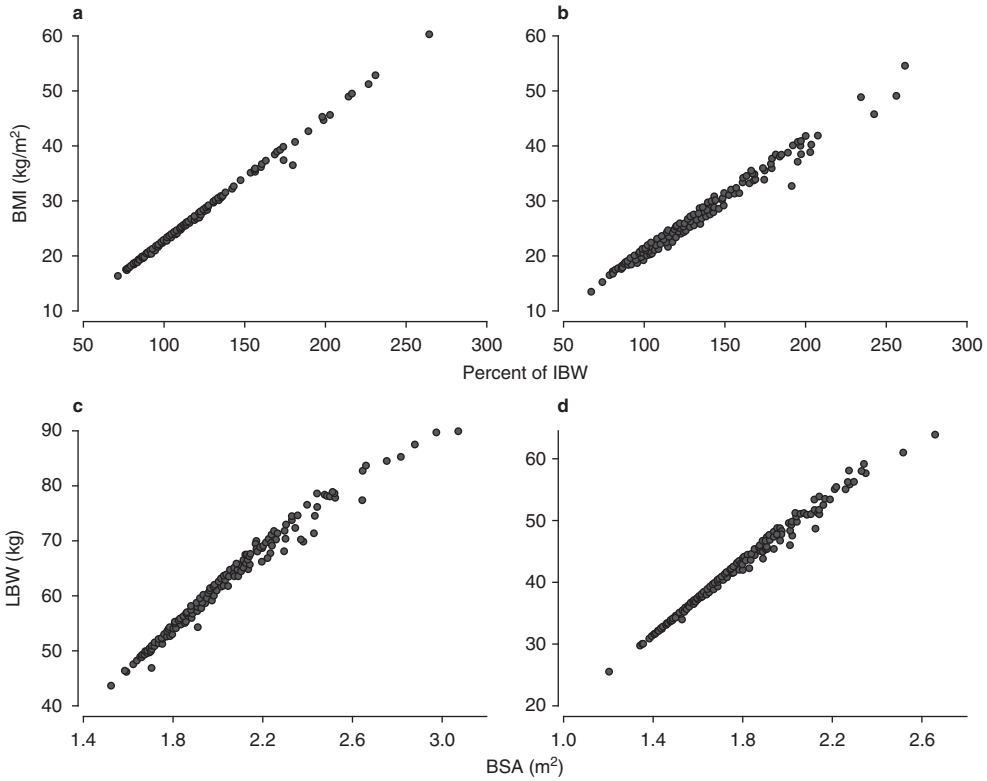

Fig. 2. Relationship between select size descriptors. Using demographic data from our laboratory, the relationship between percent of ideal bodyweight (IBW) and body mass index (BMI) was examined for (**a**) males and (**b**) females. The relationship between body surface area (BSA) and lean bodyweight (LBW) was also determined for (**c**) males and (**d**) females, using the semi-mechanistic equations described by Janmahasatian et al.[26] in 2005.

Unless the drug is being administered as a constant intravenous infusion and steady state has been achieved, the V_{ss} will underestimate the true extent of distribution. Furthermore, the V_{ss} and V_z differ in their pharmacokinetic stability in that V_{ss} estimates are highly sensitive to changes in the initial distribution phase.[33] As a result, the V_z is a more appropriate means of describing the extent of drug distribution.

The V_d of a drug provides an estimate of the extent to which a drug distributes into extravascular tissues. Therefore, drugs with extensive tissue uptake generally have larger volumes of distribution. However, V_d information alone is insufficient to determine the actual sites of distribution. Such information can only be provided by direct measurement of tissue concentrations, which is usually not possible in clinical pharmacokinetic studies. This lack of information regarding the tissue concentrations of a drug complicates the optimization of drug dosing in the obese. In fact, a recent study[34] has demonstrated that obese and non-obese individuals may have significantly different drug plasma concentrations but similar tissue concentrations.

Following drug administration, drug distribution into the various tissues of the body will depend on several factors that are mainly related to the physiochemical attributes of the drug: the molecular size, degree of ionization, lipid solubility, and ability to cross biological membranes. The V_d of relatively lipophilic drugs – as assessed by the partition (octanol/water) coefficient of the drug or high-performance liquid chromatography retention index – is usually altered to some extent in the obese.[9] This makes intuitive sense, with obese individuals having an increased absolute amount and proportion of adipose tissue as compared with non-obese individuals. Nevertheless, there is wide variation in the effect on the V_d, since the affinity of each drug for the excess adipose tissue is unique. Figure 3 schematically represents two extreme situations. Figure 3a represents a non-lipophilic drug whose distribution into the excess adipose tissue is limited, such that the pharmacokinetic volume of the peripheral compartment is similar in obese and lean individuals. In contrast, figure 3b depicts the case of a drug whose distribution markedly increases in obese subjects – a phenomenon seen with many lipophilic psychotropic drugs, including benzodiazepines and tricyclic antidepressants.[8,11]

Tissue blood flow and plasma protein binding also influence drug distribution. Tissue perfusion may be reduced in obese individuals,[35,36] and alterations in cardiac structure and function have been observed in the obese.[37] These haemodynamic changes could potentially alter drug distribution and CL in obesity. With regard to plasma protein binding,

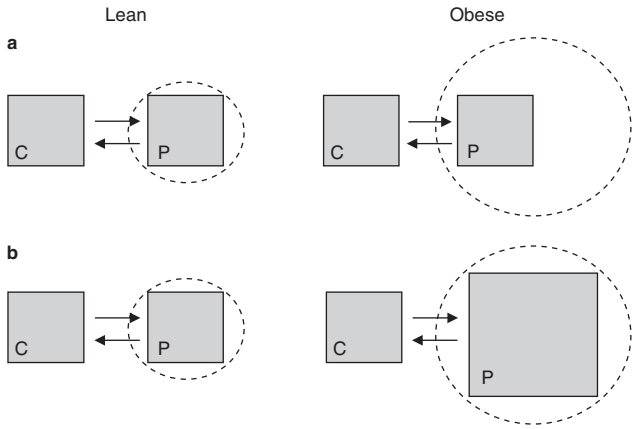

Fig. 3. Impact of obesity on the volume of distribution (V_d), assuming a two-compartment model. (**a**) Example of a drug that does not readily distribute into excess adipose tissue, such that the V_d is similar in lean and obese individuals. (**b**) Example of a drug with extensive distribution into excess adipose tissue, such that the V_d is markedly increased in obesity. The dashed circles represent the degree of adiposity. **C** = central compartment. **P** = peripheral compartment.

obesity does not appear to have an impact on drug binding to albumin.[38,39] Data from studies investigating drug binding to α_1-acid glycoprotein in obese individuals have been contradictory.[40-43]

An understanding of how the V_d of a drug changes in obesity is of particular interest, as this is the principal parameter determining loading-dose selection. In pharmacokinetic studies in the obese, the V_d is often expressed as the absolute V_d (uncorrected for weight) and a weight-normalized V_d, such as the V_d/TBW or V_d/IBW. Comparison of these weight-normalized estimates between obese and non-obese individuals provides insight into how a drug distributes into excess weight. If V_d/TBW estimates are similar in obese and non-obese individuals, the drug exhibits marked uptake into adipose tissue. Accordingly, a weight-based loading dose for such a drug should use TBW to ensure that obese patients attain maximum plasma concentrations (C_{max}) that are similar to those seen in non-obese individuals. Conversely, if the absolute V_d of a drug is increased in the obese, the finding that the V_d/TBW is significantly lower in obese individuals than in non-obese individuals indicates incomplete distribution of the drug into excess bodyweight over IBW. In such an instance, IBW or LBW may be a better metric than TBW for calculating an appropriate loading dose.

Ideally, a single universal size metric would characterize the V_d of all drugs, regardless of body composition. A recent analysis[14] attempted to determine the best size metric to describe the V_d in the obese. Using prior studies that assessed the quantitative relationship between the V_d and various weight

metrics, the authors found that the best size descriptor was largely dependent on the particular drug being studied. Nevertheless, TBW was the best single descriptor for characterizing the V_d in obese subjects – identified as the optimal metric in 40% of the studies in which it was considered. Size descriptors that included fat mass (TBW, percent IBW, BMI) were preferred for moderately to highly lipophilic drugs in the obese.

In summary, the current evidence indicates that V_d changes in the obese are drug-specific and, for the most part, can be attributed to the physiochemical properties of the individual drug.

2.2 Clearance

CL is the essential pharmacokinetic parameter to consider when devising a maintenance dose regimen, as it is inversely related to the steady-state plasma concentration. Unlike for V_d, the physiochemical attributes of a drug have little impact on CL, as this parameter is largely controlled by physiology. For any organ, CL can be defined as the volume of blood from which the drug is completely removed in a given allotment of time. Therefore, the CL of a drug will depend upon the blood flow to the organ and the ability of the organ to extract the drug from the blood.

For the majority of drugs, the liver is the principal organ mediating CL. Obesity has been linked to nonalcoholic fatty liver disease,[44] and the accumulation of fat in the liver of obese individuals may alter hepatic blood flow.[45] In turn, these pathological changes might have an impact on hepatic drug CL. There is also limited evidence of an increase in cytochrome P450 (CYP) 2E1 activity with obesity,[46,47] with a reduction in activity noted after weight loss.[47] As few drugs are substrates for CYP2E1, the clinical significance of this finding is probably minimal. In regard to phase II conjugation pathways, the results of studies with oxazepam, lorazepam, and acetaminophen (paracetamol) have suggested that TBW-proportional increases in glucuronidation and sulfation occur in obese individuals.[48,49]

The other primary organs involved in the CL of drugs are the kidneys. The processes involved in drug elimination through the kidneys include glomerular filtration, tubular secretion and tubular reabsorption. The effect of obesity on these functions is not clear.[9,10] Studies of creatinine CL, used to estimate the glomerular filtration rate (GFR), have found increased, decreased or similar GFR measurements in obese versus non-obese individuals. The variable results probably reflect the imprecision of creatinine CL as an index of the GFR. More recently, a study using [^{125}I]Na iothalamate CL to reflect the GFR revealed a nonsignificant trend towards higher mean values in morbidly obese females as compared with normal-weight controls (116 vs 93.5 mL/min).[50]

As was the case with the V_d, there is no single valid method to relate drug CL to the degree of obesity. Nevertheless, the aforementioned analysis[14] found that LBW was the best descriptor in 35% of the studies in which it was considered. From a physiological standpoint, this seems plausible, as the major drug-clearing organs (the liver and kidneys) are constituents of LBW.

In a recent commentary, Han et al.[28] proposed three observations regarding drug CL and obesity: (i) obese individuals exhibit higher absolute drug clearances than their non-obese counterparts do; (ii) CL does not increase linearly with TBW; and (iii) CL and LBW are linearly correlated. Findings from several studies – including some in section 3 of this review – are in agreement with observations 1 and 2. Presently, less evidence exists to support observation 3. Based on their observations, Han et al.[28] contended that the semi-mechanistically derived LBW[26] is an ideal size descriptor to ascertain the impact of body composition on drug CL. However, this assertion has recently been challenged.[51] At the very least, future studies designed to specifically address the merits of this LBW-based strategy for predicting drug exposure in the obese are warranted.

To summarize, the CL of a drug is largely determined by physiological processes, some of which may be altered in the obese. Presently, there is no single, well-validated weight descriptor to characterize drug CL in this population. The therapeutic objective would be to apply a weight-normalized maintenance dose (mg/kg) using the size descriptor that corrects for differences in the absolute CL among obese and non-obese individuals.

2.3 Elimination Half-Life

The elimination half-life ($t_{½}$) of a drug may also be altered in obese individuals. The $t_{½}$ of a drug can be calculated using the following formula: $t_{½} = (\ln 2 \times V_d)/CL$. This form of the mathematical relationship among the three pharmacokinetic parameters correctly places the two independent variables on the right and the dependent variable on the left. As described above, the V_d and CL are biologically independent entities, with the V_d being largely dependent on the physiochemical attributes of a drug and CL being predominantly the result of hepatic and renal physiology. Since the $t_{½}$ is dependent on both the V_d and the CL, changes in the $t_{½}$ could reflect changes in the V_d, the CL, or both. Clinicians must theoretically be cautious

when comparing $t_{½}$ values between obese and non-obese individuals. Specifically, the use of the $t_{½}$ can be misleading when it is used as the sole estimate to compare drug-metabolizing capacity between obese and non-obese subjects. An example of this phenomenon has been shown for diazepam and its metabolite, desmethyldiazepam.[52,53] While the $t_{½}$ of each agent was markedly prolonged in obese subjects, the metabolic CL of each compound was similar in obese and non-obese individuals. Instead, the alteration in the $t_{½}$ was the result of an increase in the V_d.

3. Impact of Obesity on the Pharmacokinetics of Specific Drugs

3.1 Antibacterials

Two studies have explored the impact of obesity on the pharmacokinetics of the lipopeptide antibacterial daptomycin (table I). In one study by Dvorchik and Damphousse,[54] a single dose of intravenous daptomycin at 4 mg/kg TBW was given to six moderately obese, six morbidly obese, and 12 non-obese subjects matched for sex, age and renal function. The absolute CL and V_z of daptomycin were increased in the moderately and morbidly obese groups as compared with the matched non-obese controls. However, when corrected for TBW, the CL and V_z were lower in obese individuals. The $t_{½}$ of daptomycin was similar in all subject cohorts and was not significantly correlated with BMI ($r^2 = 0.006$).

Another study, by Pai et al.,[50] investigated the single-dose pharmacokinetics of daptomycin 4 mg/kg TBW in seven morbidly obese females and seven non-obese females matched for age, race, and serum creatinine. The mean daptomycin doses were 461 mg and 236 mg in the two groups, respectively. The absolute CL and V_z were both greater in the obese cohort, although the differences were not statistically significant. Accordingly, the increases in the C_{max} and the area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC_∞) seen in the morbidly obese subjects were mostly likely due to the higher dose received, as opposed to differences in CL or distribution. This study also observed no differences in daptomycin protein binding (~90%) and $t_{½}$ values between the two groups.

In both studies, the absolute daptomycin CL and V_z were higher in obese individuals – although the difference was not statistically significant in the study by Pai et al.[50] Even though the increases were not completely proportional to weight, the authors of each study did not recommend altering the 4 mg/kg TBW dosing regimen. This conclusion is supported by the fact that the higher C_{max} and AUC_∞ values observed in obese individuals are within the range reported to be safely tolerated by healthy subjects[55] and might be advantageous, given the concentration-dependent activity of daptomycin.[56-58]

The pharmacokinetics of a single 1 g dose of ertapenem have been determined in three groups of healthy subjects stratified by BMI.[59] The mean BMIs for the normal-weight, class I–II obesity and class III obesity groups were 22.5, 33.4 and 43.4 kg/m^2, respectively. Each cohort was comprised of five men

Table I. Mean pharmacokinetic parameters of 4 mg/kg of daptomycin in obese and non-obese subjects

	Dvorchik and Damphousse[54]				Pai et al.[50]	
	moderately obese	matched controls[a]	morbidly obese	matched controls[a]	morbidly obese	matched controls[b]
BMI (kg/m^2)	33.2	24.3	46.2	24.3	46.2	21.8
C_{max} (mg/L)	57.8*	46.3	67.0*	53.2	67.3*	42.3
AUC_∞ (mg • h/L)	420.5*	322.4	547.8*	418.8	581*	346
CL (L/h)	0.86*	0.72	1.02*	0.70	0.82	0.73
CL/TBW (L/h/kg)	0.010*	0.012	0.008*	0.010	0.007*	0.012
CL/IBW (L/h/kg)	0.016*	0.015	0.016	0.011	0.016	0.013
V_z (L)	9.0*	7.1	11.3*	7.4	10.0	7.69
V_z/TBW (L/kg)	0.11*	0.12	0.09*	0.11	0.09*	0.13
V_z/IBW (L/kg)	0.17	0.15	0.18*	0.12	0.19*	0.14
$t_{½}$ (h)	7.3	6.8	8.1	8.0	8.7	7.7

a Non-obese subjects matched for sex, age and creatinine clearance.

b Non-obese subjects matched for sex, age, race and serum creatinine.

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; **BMI** = body mass index; **CL** = total body clearance; **C_{max}** = maximum plasma concentration; **IBW** = ideal bodyweight; **$t_{½}$** = elimination half-life; **TBW** = total bodyweight; **V_z** = volume of distribution during the elimination phase; * $p < 0.05$ vs corresponding matched control group.

and five women. TBW-corrected ertapenem CL was higher in the normal-weight group (0.024 L/h/kg) than in the class I–II obesity group (0.019 L/h/kg) and the class III obesity group (0.015 L/h/kg). The difference in TBW-corrected ertapenem CL was also significant between the class I–II obesity and class III obesity groups. Accordingly, ertapenem exposure was reduced in obese patients. These findings suggest that obese individuals may need a larger ertapenem dose than their non-obese counterparts.

Hollenstein et al.[34] conducted a study that compared plasma and interstitial fluid concentrations of ciprofloxacin after a 2.85 mg/kg TBW intravenous bolus dose was given to healthy subjects. The average BMI of the 12 subjects in the obese group was 41.0 kg/m^2. Twelve age- and sex-matched normal-weight subjects comprised the control group, with a mean BMI of 19.8 kg/m^2. The plasma C_{max} (9.97 mg/L) and AUC from 0 to 6 hours (AUC_6) [6.18 mg • h/L] were significantly higher in the obese group than in the non-obese controls (2.59 mg/L and 3.02 mg • h/L, respectively). Since no significant differences were observed in the $t_{½}$, V_{ss} or CL between the two groups, these increases appear to reflect the higher ciprofloxacin doses administered to obese subjects.

Microdialysis measurement of ciprofloxacin concentrations in interstitial space fluid of skeletal muscle tissue revealed similar C_{max} values in the obese group (2.16 μg/mL) and the control group (1.72 μg/mL). Obese subjects had a corresponding tissue AUC_6 of 2.57 μg • min/mL, which was not statistically different from the control group's value of 2.28 μg • min/mL. Skeletal muscle tissue penetration, measured as the $AUC_{tissue}/AUC_{plasma}$ ratio, was significantly reduced in obese subjects (0.45 versus 0.82). Similar findings were observed when ciprofloxacin concentrations in the interstitial space fluid of subcutaneous adipose tissue were compared. Therefore, the results of this study demonstrate that higher plasma concentrations in obese subjects do not necessarily translate into higher concentrations at the target site of the drug. Given the apparent impairment in tissue penetration in obese subjects, the authors recommended that ciprofloxacin should be administered according to TBW.[34] This recommendation differed from that of an earlier study,[60] which suggested that ciprofloxacin dosing in obese subjects should be based on an adjusted bodyweight equal to IBW plus 45% of the difference between TBW and IBW.

A recent case report[61] detailed piperacillin/tazobactam concentrations in a morbidly obese patient (BMI = 50 kg/m^2, TBW = 167 kg) being treated with 3.375 g every 4 hours for cellulitis. After the 20th dose of piperacillin/tazobactam, the patient's piperacillin C_{max} at steady state ($C_{max,ss}$) and AUC from 0 to 4 hours (AUC_4) were 67.39 mg/L and 126.48 mg • h/mL, respectively. These values were markedly lower than those derived from a representative population receiving the same dose: C_{max} 242 mg/L; AUC_4 249.15 mg • h/mL.

Seven obese patients receiving oral linezolid 600 mg every 12 hours for the treatment of cellulitis had linezolid serum concentrations measured prior to, then 1 and 6 hours after a dose.[62] The mean TBW was 146 kg (range 101–196 kg). Each patient had received a minimum of three doses (range 3–12) before post-dose linezolid pharmacokinetics were determined. The mean concentration 1 hour after linezolid administration (the estimated C_{max}) was 12.3 μg/mL. The mean AUC from 0 to 12 hours (AUC_{12}) and the $t_{½}$ were 92 μg • h/mL and 6.5 hours, respectively. It should be noted that these reported pharmacokinetic parameters can only be described as general estimates because of the limited number of blood samples measured.

One case report[63] described linezolid disposition in an obese male, weighing 286 kg (BMI 86 kg/m^2), receiving 600 mg orally every 12 hours for the treatment of cellulitis. After the 12th dose, the 2- and 7.5-hour serum linezolid concentrations were 5.07 and 2.01 mg/L, respectively. The V_d was 135.7 L – far greater than the V_{ss} of 30–50 L in non-obese individuals.[64]

The linezolid concentrations approximating the C_{max} in the aforementioned reports were lower than those noted for healthy subjects receiving similar linezolid dosing regimens, whose mean C_{max} values ranged from 16.3 to 24 μg/mL.[65,66] At the very least, these findings suggest that linezolid disposition may be altered in the obese, indicating the need for additional pharmacokinetic investigations in this patient demographic.

3.2 Anticoagulants

3.2.1 Argatroban

Rice et al.[67] conducted a retrospective analysis of patients who had received anticoagulation therapy with argatroban because of an assumed, or past, diagnosis of heparin-induced thrombocytopenia. Eighty-three patients were identified who had sufficient data available to calculate their BMIs. They were stratified into a non-obese group (BMI ≤30 kg/m^2, n = 51) and an obese group (BMI >30 kg/m^2, n = 32). The median initial dose of argatroban in both groups was 1.0 μg/kg/min, suggesting that no specific dose adjustment was made for obese patients by prescribers. The median, activated partial thromboplastin time (aPTT)-adjusted maintenance dosages were 1.2 and 1.1 μg/kg/min in the non-obese and obese groups, respectively. Thus, it seems that argatroban dosage requirements were independent of the patient's BMI in this population. Although this study had the inherent limitations of a retrospective

analysis, it appeared to indicate that TBW can be successfully used to initially dose argatroban in obese and non-obese patients; thereafter, aPTT-adjusted doses should be employed.

3.2.2 Low-Molecular-Weight Heparins

Because of their more predictable bioavailability and anticoagulant effects, low-molecular-weight heparins are being increasingly used in place of unfractionated heparin.[68] Several studies have investigated their disposition in the obese.

Enoxaparin sodium was administered to 24 obese and 24 age-, sex-, and height-matched non-obese subjects.[69] The mean BMIs in the two groups were 22.4 and 34.8 kg/m^2. Factor anti-Xa activity and factor anti-IIa activity were measured as surrogate markers of enoxaparin sodium pharmacokinetics after once-daily subcutaneous administration and after a 6-hour intravenous infusion of 1.5 mg/kg TBW (table II). After subcutaneous dosing, the mean area under the plasma activity (effect)-time curve from time zero to infinity ($AUEC_\infty$) for anti-Xa activity was statistically greater in obese subjects on days 1 and 4. Obese subjects also had a small, but statistically significant, increase in the observed $t_{½}$ for anti-IIa activity after one dose. On day 4 of subcutaneous administration, the median time to reach the C_{max} (t_{max}) for both anti-Xa and anti-IIa activity was significantly increased by 1 hour in obese subjects, suggesting a slower rate of absorption.

Intravenous administration of 1.5 mg/kg TBW of enoxaparin sodium as a 6-hour infusion resulted in higher observed maximum activity (A_{max}) and $AUEC_\infty$ values for both anti-Xa and anti-IIa activity in the obese cohort (table II). The absolute CL and V_{ss} for anti-Xa activity were significantly increased in obese subjects (0.99 vs 0.74 L/h and 5.77 vs 4.37 L, respectively). When normalized to TBW, these parameters were lower in obese individuals, indicating that the increase was not completely proportional to weight.[69] The results of this study suggest that TBW might not be the best metric for calculating weight-based doses of enoxaparin sodium.

Bazinet et al.[71] conducted a clinical study that compared anti-Xa activity in hospitalized patients who were prescribed subcutaneous heparin 1.5 mg/kg TBW once daily or 1 mg/kg TBW twice daily. The patients were stratified by BMI, and anti-Xa activity was measured 4 hours after a steady-state dose. For once-daily administration, the 62 patients with BMIs of 18–30 kg/m^2 had a mean anti-Xa activity of 1.13 IU/mL, compared with 1.15 IU/mL for the 30 patients with BMIs >30 kg/m^2. In patients receiving twice-daily injections, the mean anti-Xa activity in patients with BMIs in the 18–30 kg/m^2 range was 1.12 IU/mL, compared with 1.17 IU/mL in patients with BMIs >30 kg/m^2. The authors concluded that BMI does not have a marked impact on anti-Xa levels after TBW dosing of enoxaparin sodium.

A pharmacokinetic-pharmacodynamic modelling study[72] investigated enoxaparin sodium disposition in 96 patients with BMIs ranging from 15 to 45 kg/m^2. This study identified LBW as a key covariate for enoxaparin CL. Subsequent dosing simulations using the derived pharmacokinetic model suggested that therapeutic anti-Xa activities would be obtained for

Table II. Mean pharmacokinetic/pharmacodynamic parameters of low-molecular-weight heparins in obese and non-obese individuals

Drug/dosage	Anti-Xa factor activity						Anti-IIa factor activity						Reference
	A_{max} (IU/mL)		$AUEC_\infty$ (IU • h/mL)		$t_{½}$ (h)		A_{max} (IU/mL)		$AUEC_\infty$ (IU • h/mL)		$t_{½}$ (h)		
	obese	control	obese	control	obese	control	obese	control	obese	control	obese	control	
Enoxaparin sodium													
1.5 mg/kg/day SC													
day 1	1.38	1.34	17.01*	14.87	5.1	4.9	0.17	0.19	1.69	1.53	3.6*	2.8	69
day 4	1.56	1.49	20.78*	17.52	5.8	5.6	0.19	0.19	1.63	1.57	3.1	2.8	
1.5 mg/kg IV infusion	1.77*	1.54	15.64*	13.95	5.0*	4.6	0.38*	0.31	2.22*	1.82	1.4	1.5	69
Tinzaparin sodium[a]													
75 IU/kg SC[b]	0.34	0.30	3.29*	2.36	3.9	NR	0.12	0.10	1.21*	0.77	5.3	NR	70
175 IU/kg SC	0.81	0.87	9.99	9.55	4.2	NR	0.34	0.33	4.34*	3.53	5.4	NR	

a The obese group was defined as individuals weighing 100–160 kg. The control group was derived from historical data in subjects weighing <100 kg.

b The control group values were weight adjusted and scaled to 75 IU/kg (assuming linear pharmacodynamics), using previous data from patients who had received a fixed 4500 IU tinzaparin sodium dose.

A_{max} = maximum observed activity; **$AUEC_\infty$** = area under the plasma activity (effect)-time curve from time zero to infinity; **IU** = international units; **IV** = intravenous; **NR** = not reported; **SC** = subcutaneously; **$t_{½}$** = elimination half-life; * $p < 0.05$ vs control group.

most patients if a 1 mg/kg LBW dose was administered every 8 hours.

Thus, it appears that there is a lack of consensus regarding the optimal size descriptor for determining weight-based doses of enoxaparin sodium. Future studies to examine clinical outcomes in obese patients receiving doses based on different weight metrics are warranted.

The anti-Xa and anti-IIa activities after administration of tinzaparin sodium to subjects weighing between 100 and 160 kg have also been reported.[70] Subjects received single subcutaneous injections of 75 and 175 IU/kg TBW. The mean BMI of the 37 subjects was 43.0 kg/m^2. The resultant mean A_{max}, $AUEC_\infty$ and $t_{½}$ values are displayed in table II. Since a normal-weight control group was not included in the study, anti-Xa and anti-IIa activity parameters from prior studies in normal-weight subjects were included for comparison. For the tinzaparin sodium 75 IU/kg dose, the anti-Xa and anti-IIa activity $AUEC_\infty$ values were moderately increased in obese subjects. When 175 IU/kg was administered, only the anti-IIa activity $AUEC_\infty$ statistically differed between the two groups. The study also found that the anti-Xa and anti-IIa activity A_{max} and $AUEC_\infty$ values were independent of TBW and BMI. Therefore, this study indicated that TBW-adjusted doses of tinzaparin sodium appear to be appropriate in the obese.

One study[73] estimated the V_d and CL of dalteparin sodium after subcutaneous administration of 200 IU/kg/day, or 120 IU/kg twice daily, based on the indication for treatment. Ten obese and ten age-, sex-, IBW-, and creatinine CL-matched control patients were enrolled. The mean V_d in the obese group was greater than the control group estimate (12.4 vs 8.4 L), but this difference was not statistically significant. Likewise, obese patients had a small increase in CL as compared with controls (1.30 versus 1.11 L/h). The authors concluded that dalteparin sodium dosing in the obese should be given on the basis of TBW or an adjusted bodyweight equal to IBW plus 40% of the difference between TBW and IBW.

3.3 Antidiabetic Agents

Sulfonylureas are a class of antidiabetic drugs that are widely used in clinical practice. The impact of obesity on the disposition of an 8 mg glimepiride dose was studied in 14 morbidly obese patients (≥200% of IBW) and 14 control patients (90–110% of IBW) with type II diabetes (table III).[74] The mean BSA-normalized CL after oral administration (CL/F) was approximately 2.11 L/h/1.73 m^2 in both cohorts. Obese patients had a lower, but not statistically significant, BSA-normalized V_d after oral administration (V_d/F) [26.0 vs 32.8 L/h/1.73 m^2]. The median $t_{½}$ also did not differ between the two patient populations. Consequently, the authors concluded that no specific dosage adjustment is necessary in the obese.

Pharmacological modulation of the glucagon-like peptide-1 pathway has resulted in new therapeutic agents for the treatment of type II diabetes. The pharmacokinetics of sitagliptin, a dipeptidyl peptidase-IV inhibitor, in obese, nondiabetic men and women between the ages of 45 and 63 years have recently been explored.[75] Thirty-two subjects with a mean BMI of 33.7 kg/m^2 were included in the study. Twenty-four participants received a 200 mg oral dose of sitagliptin twice daily for 28 days. The other eight subjects received placebo. Table III displays the pharmacokinetic variables after the initial dose (day 1) and after one dose on day 28. This study did not include a normal-weight control group. However, the C_{max} and AUC_{12} measurements were quite similar to those previously reported in studies of healthy male subjects (within 15% of their IBW) given 200 mg once daily.[76,77] Thus, the current evidence implies that obesity fails to dramatically alter sitagliptin disposition.

3.4 Anticancer Agents

Proper dose selection of anticancer agents is especially challenging. Because of the inherent cytotoxic effects of these agents, clinicians must balance the risks of high doses with potentially worse treatment outcomes if doses are reduced. In this context, the lack of information regarding dosing in the obese is particularly problematic. Since definitive guidelines have not been developed, clinicians often calculate the requisite dose using an alternative to TBW in the obese.[24]

Sparreboom et al.[78] conducted an analysis of pharmacokinetic data obtained from subsets of adult patients being treated with at least one of the following agents: doxorubicin, topotecan, irinotecan, carboplatin, cisplatin, paclitaxel and docetaxel. The patients were stratified into two groups based on BMI: lean controls (BMI ≤ 25 kg/m^2) and obese patients (BMI ≥ 30 kg/m^2). For each agent, the CL, V_d and $t_{½}$ were determined from individual patient concentration-time curves. Table IV provides a summary of the pharmacokinetic parameters for each drug in the two studied groups.

A trend towards higher absolute CL values in obese patients was observed for each drug. However, the differences only reached statistical significance for cisplatin and paclitaxel. When the CL values were normalized for BSA using TBW in the calculation, no statistically significant differences were observed between lean controls and obese patients. In regard to the absolute V_{ss}, higher measurements were noted in obese patients for doxorubicin, irinotecan, carboplatin and paclitaxel, but these

Table III. Pharmacokinetics of oral antidiabetic agents in obese and non-obese individuals

Drug	Dosage	C_{max}		AUC		Reference
		obese	control	obese	control	
Glimepiride[a]	8 mg SD	410 ng/mL	547 ng/mL	2818 ng • h/mL	3205 ng • h/mL	74
Sitagliptin[b]	200 mg bid					
day 1		2280 nmol/L	NA	14.7 μmol • h/L	NA	75
day 28		2920 nmol/L	NA	20.4 μmol • h/L	NA	

a Values are expressed as arithmetic mean.

b Values are expressed as geometric mean.

AUC = area under the plasma concentration-time curve; **bid** = twice daily; **C_{max}** = maximum plasma concentration; **NA** = not applicable (not included in the study); **SD** = single dose.

differences were not statistically significant. Significant increases in the V_{ss} were observed for docetaxel and cisplatin in obese patients. The obese and non-obese groups had comparable $t_{½}$ values for all drugs except docetaxel, for which the $t_{½}$ increased in obese individuals.[78]

Busulfan is a bifunctional alkylating agent that is utilized in the treatment of cancer and in regimens designed to prepare the bone marrow for haematopoietic stem cell transplantation. In a retrospective analysis[79] of 279 patients aged between 12 and 60 years, the impact of obesity on the CL/F of busulfan was examined. While absolute CL/F did not statistically differ between normal-weight and underweight patients, obese and severely obese patients had absolute CL/F estimates that were significantly greater than those of their normal-weight counterparts, with increases of 17% and 32%, respectively. When corrected for TBW, busulfan CL/F was 32% higher in underweight patients, 12% lower in obese patients, and 21% lower in severely obese patients as compared with normal-weight patients. However, normalization of CL/F to BSA, or to an adjusted bodyweight equal to IBW plus 25% of the difference between TBW and IBW, resulted in comparable values among the four BMI groups studied. Consequently, the authors suggested that oral busulfan dosing should be based on BSA or adjusted bodyweight.

Additional evidence for adjusted bodyweight- or BSA-based busulfan dosing has been provided by the results of a recent, retrospective, population pharmacokinetic study using data from 127 patients who were administered the drug intravenously.[80] Specifically, no significant differences in BSA- or adjusted bodyweight-normalized intravenous CL were noted among BMI classes when patients were stratified using the same classification scheme as was used in the above oral busulfan investigation.[79] Taken together, these two studies suggest that dosage of busulfan in obese patients should be normalized based on BSA or adjusted bodyweight.

The pharmacokinetics of doxorubicin and etoposide in a morbidly obese 14-year-old boy with Hodgkin's disease (BMI 46.3 kg/m^2; BSA 2.56 m^2) have recently been detailed.[81] Using a growth curve for boys aged 6–18 years, the maximum expected bodyweight for the patient was determined to be 76 kg. Utilization of this weight resulted in an adjusted BSA value of 1.91 m^2, which was subsequently used to dose doxorubicin and etoposide. The patient's doxorubicin and etoposide CL estimates were similar to those previously reported for similarly treated, non-obese patients.[82-84]

Another report[85] detailed the case of a 53-year-old obese female (BMI 47 kg/m^2; BSA 2.34 m^2) being treated with high-dose cyclophosphamide, thiotepa and carboplatin for metastatic breast cancer. The patient's actual BSA and TBW were used for dosage calculation. After the initial infusions, the patient's AUC estimates for each drug were markedly higher than the median AUC values derived from a sample of 24 non-obese patients undergoing similar treatment. The authors concluded that initial thiotepa, cyclophosphamide and carboplatin doses in the morbidly obese should be calculated using an adjusted bodyweight – IBW plus 40% of the difference between TBW and IBW – in place of TBW.

Taking all of the above data into consideration, it appears that obesity alters the pharmacokinetics of some, but not all, anticancer agents. Accordingly, the decision of which weight metric to use in dosing obese patients must be individualized for each drug until larger prospective studies are conducted. At the present time, little evidence is available that supports arbitrary dose capping in the obese, especially since this practice may lead to suboptimal treatment outcomes.[86]

3.5 Neuromuscular Blockers

The pharmacodynamics of cisatracurium[87] and rocuronium[88] in morbidly obese and non-obese women have recently been compared in two similarly designed studies. Each

study enrolled two groups of morbidly obese females (BMI >40 kg/m^2) undergoing laparoscopic gastric banding surgery. One group received doses of cisatracurium or rocuronium based on TBW, while the other group received IBW-based doses. The normal-weight control group comprised females with BMIs between 20 and 24 kg/m^2 who received TBW-based doses for gynaecological laparoscopic surgery.

The median time to the onset of action of cisatracurium was significantly longer in the cohort of obese patients receiving IBW-based doses (table V).[87] When doses were based on TBW, virtually identical median times to the onset of action were observed in the obese and control groups. The duration of action of cisatracurium was longer in obese patients administered TBW-based dosing than in non-obese controls. However, the duration of action in obese subjects administered IBW-based doses was shorter than the corresponding time for the control group. Thus, it appears that neither IBW nor TBW is the optimal weight metric for calculating cisatracurium doses in morbidly obese patients.

As seen in table V, no statistically significant differences in the onset of action of rocuronium were noted among control subjects and obese subjects administered TBW- or IBW-based doses.[88] An approximately 2-fold increase in the duration of action was observed in obese patients administered TBW-based doses as compared with those administered IBW-based doses and control patients administered TBW-based doses. Consequently, the authors recommended that morbidly obese patients should receive rocuronium doses based on IBW.

Pühringer et al.[89] also conducted an investigation involving rocuronium disposition after TBW-based dosing in non-obese and obese females (mean BMIs 21.9 and 34.3 kg/m^2, respectively). Pharmacokinetic analysis of rocuronium plasma concentrations revealed no significant differences in the initial disposition half-life ($t_{½\alpha}$) of rocuronium, the terminal $t_{½}$ ($t_{½\beta}$), and the absolute V_{ss} and CL. Although the mean time to the onset of action was increased in the non-obese control group, this difference failed to reach statistical significance (table V). In contrast to the findings of the aforementioned rocuronium study, the duration of action was nearly identical in the two weight groups. This discrepancy is most likely due to differences in the obesity populations studied. Specifically, the mean BMI in the obese group was notably higher (43.8 kg/m^2) in the study by Leykin et al.[88]

3.6 Miscellaneous Agents

3.6.1 Drotrecogin Alfa (Activated)

Drotrecogin alfa (activated) is a recombinant form of human activated protein C that is used in the treatment of sepsis. The proper dose of drotrecogin alfa (activated) to administer to patients weighing >135 kg has received a great deal of attention in recent years because this patient demographic was excluded from the pivotal phase III clinical trial.[90-92]

Levy et al.[92] conducted a clinical study in 32 patients weighing ≤135 kg and 20 patients weighing >135 kg. The mean bodyweights of the two groups were 93 kg and 158 kg. Both groups received drotrecogin alfa (activated) infusions of 24 μg/kg/h based on TBW. At steady state, the median plasma concentrations of activated protein C – derived from both endogenous levels and exogenous drotrecogin alfa administration – were 51.9 and 56.5 ng/mL for the ≤135 kg and >135 kg groups, respectively. The median estimates of the $t_{½}$ were almost identical in the two groups (16.6 vs 16.0 minutes). The TBW-normalized plasma CL had a median value of 0.45 L/h/kg in the ≤135 kg group, while the analogous parameter estimate for

Table IV. Pharmacokinetic parameters of anticancer agents in obese and non-obese patients[78] [a]

Drug	No. of patients		V_{ss} (L)		CL (L/h)		CL/BSA (L/h/m^2)		$t_{½}$ (h)	
	obese	control	obese	control	obese	control	obese	control	obese	control
Doxorubicin	23	41	14.5	14.0	60.5	57.6	29.5	34.1	8.4	8.8
Topotecan	21	108	28.6	30.0	21.7	19.6	11.3	12.4	0.9	1.1
Irinotecan	25	102	130	122	32.5	28.7	15.1	16.6	17.8	19.6
Carboplatin	14	64	17.5	15.5	6.48	5.88	3.2	3.49	1.9	1.8
Cisplatin	23	165	58.9*	50.2	60.0*	53.3	28.3	30.2	0.7	0.7
Paclitaxel	14	38	6298	4295	383*	318	200	191	11.4	9.4
Docetaxel	21	92	978*	531	40.0	36.8	19.4	21.2	16.9*	10.0

a Values are expressed as geometric mean. The control and obese groups comprised patients with BMIs ≤25 kg/m^2 and ≥30 kg/m^2, respectively.

BMI = body mass index; **BSA** = body surface area using actual bodyweight; **CL** = total body clearance; $\mathbf{t_{½}}$ = elimination half-life; $\mathbf{V_{ss}}$ = volume of distribution at steady state; * $p < 0.05$ vs control group.

Table V. Onset and duration of action of neuromuscular blockers in obese and non-obese patients

Drug (dose)	Onset of action (sec)			Duration of action (min)			Reference
	obese: TBW dose	obese: IBW dose	control: TBW dose	obese: TBW dose	obese: IBW dose	control: TBW dose	
Cisatracurium 0.2 mg/kg[a]	132	182*	135	74.6*	45.0*	59.1	87
Rocuronium 0.6 mg/kg[a]	77.0	87.5	66.5	55.5*	22.3	25.4	88
Rocuronium 0.6 mg/kg[b]	65	NA	100	29.5	NA	28.4	89

a Values are expressed as median.

b Values are expressed as mean.

IBW = ideal bodyweight; **NA** = not applicable (not included in the study); **TBW** = total bodyweight; * $p < 0.05$ vs control group.

the >135 kg group was 0.42 L/h/kg. None of these observed differences were statistically significant. In addition, when TBW-normalized plasma CL was plotted as a function of TBW, the slope of the regression line did not differ from zero. Consequently, the authors concluded that TBW-based infusion rates of drotrecogin alfa (activated) are appropriate in patients with weights >135 kg.

3.6.2 β-Adrenoceptor Antagonists: Propranolol and Atenolol

The pharmacokinetics of oral propranolol and atenolol were studied in 43 subjects stratified into three weight groups.[93] The first group was comprised of 18 non-obese control subjects with a mean BMI of 24.0 kg/m^2. The other two groups enrolled obese subjects who differed in their serum cholesterol and triglyceride levels. The normolipaemic group (n = 9) and hyperlipaemic group (n = 16) both had mean BMIs of 35.6 kg/m^2. After oral administration of 80 mg of propranolol, a large degree of variability between subjects was observed for all of the measured pharmacokinetic parameters. In turn, no statistically significant differences were noted among the three groups in the propranolol AUC_∞, C_{max}, t_{max}, $t_{½}$ and total or TBW-normalized V_d/F and CL/F. These findings were in agreement with the results of a prior study[94] that administered propranolol intravenously and observed similar AUC_∞, V_{ss}, CL and $t_{½}$ measurements in obese and non-obese individuals.

When subjects were administered 100 mg of atenolol orally, small but statistically significant differences were noted in the AUC_∞, C_{max} and TBW-normalized CL/F among the three cohorts. Lower mean TBW-normalized CL/F estimates were observed in the obese normolipaemic group (0.07 L/h/kg) and the obese hyperlipaemic group (0.06 L/h/kg) than in non-obese controls (0.10 L/h/kg). No statistical differences were observed in the $t_{½}$, absolute V_d/F, TBW-normalized V_d/F and absolute CL/F.[93]

The results of this study demonstrate minimal changes in propranolol and atenolol pharmacokinetics in obese normolipaemic, obese hyperlipaemic and non-obese subjects. Since propranolol and atenolol differ in their lipophilicity, the data also illustrate that the disposition of a drug in the obese cannot be adequately predicted by its physiochemical attributes alone.

3.6.3 Quinine

The pharmacokinetics of quinine in nine obese Thai males and eight age-matched lean controls were compared after a single 600 mg oral dose of the sulfate salt.[95] The mean percentage of IBW in the obese group was 143%, while the analogous value for the control group was 95%. TBW-normalized CL/F was significantly lower in the obese group as compared with the lean control group (0.064 vs 0.096 L/h/kg). However, the IBW-normalized CL/F estimates did not differ statistically between the two groups (0.091 L/h/kg for both). These results indicate that maintenance doses of quinine should be based on IBW as opposed to TBW.

3.6.4 Norethisterone (Norethindrone) and Ethinylestradiol

The disposition of norethisterone (norethindrone) [1 mg] and ethinylestradiol (35 μg) in obese and non-obese women has been reported after daily administration of a combination oral contraceptive product for 20 days.[96] The non-obese group consisted of 12 women with BMIs ≤27 kg/m^2. Twelve women with BMIs between 30 and 35 kg/m^2 comprised the obese cohort. A nonsignificant increase in norethisterone CL/F was noted in the obese women (16.1 vs 14 L/h). Similarly, a trend towards higher ethinylestradiol CL/F was observed in the obese cohort (45.1 vs 33.5 L/h). These findings suggest that obese women might have reduced exposure to both norethisterone and ethinylestradiol as compared with non-obese women. Interestingly, several epidemiological studies[97-99] have indicated that increased weight may be associated with an increased risk of oral contraceptive failure.

4. Discussion and Conclusion

The database describing the disposition of drugs in obesity, though still incomplete, is increasing. The principles outlined in earlier reviews[8,11] continue to be valid. Drug lipophilicity is an imperfect measure to predict drug distribution in obese individuals; however, for most drugs that are studied, it contributes substantially to the variance in calculated peripheral compartment volumes of distribution. For example, the absolute V_d of the relatively hydrophilic drug, daptomycin, increases by approximately 2–4 L in the obese (table I). In contrast, the analogous increase for a highly lipophilic drug, docetaxel, is greater than 400 L (table IV).

Measures of the degree of obesity in pharmacokinetic studies have generally been indirect, and these measures are highly correlated, suggesting that conclusions from pharmacokinetic studies will be similar irrespective of the measure used. A number of different drugs and classes have been studied since the last reviews, particularly antibacterials and anticoagulants. These new data generally support past findings that drug dosing to a given drug exposure across a range of bodyweight must be individualized for the drug. One conclusion that could be drawn from such an observation would be that drugs, at least within chemically similar groupings, should be evaluated in clinical pharmacokinetic studies performed in obese individuals. Alternatively, a more reasonable conclusion would be to study only drugs with a narrow therapeutic index, as only in such cases will dose alterations based on bodyweight have clinical importance.

Other conclusions that have more importance for clinical pharmacokinetics are that the determinants of peripheral drug distribution are not well understood. Certainly, tissue binding, organ blood flow, drug plasma protein binding and the ionization state are important determinants. However, the available clinical pharmacokinetic data indicate that even when these variables are taken into consideration, considerable variance in drug distribution remains.

With regard to drug CL, the findings are somewhat more conclusive. Drugs that undergo renal or phase I metabolic CL have little change in CL as a function of bodyweight. This is reassuring, as CL is the determinant of drug exposure with long-term drug dosing. Going forward, the clinical pharmacokinetics of obesity will be appropriately linked with clinical pharmacodynamics, as has been the case in recent studies of anticoagulants. An understanding of sources of variability in exposure/effect relationships, with obesity being a potential source of variability, will lead to improved clinical therapeutics.

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