identified as a priority. Groups such as neonates and premature neonates, whose disease burden may make them therapeutic orphans, need their unique situation addressed, and every effort should be made to include therapies for the different age groups.

The subcommittee went on to decide that selection of medicines would, as a priority, reflect the needs of children under age 12 years of age. Although it acknowledged the need to consider specific medicines needs for adolescents aged 12 to 18, it was agreed that this subgroup can generally be treated with products designed for and studied in adults. The subcommittee also discussed criteria for selection of fixed-dose combination products, pediatric age categories, preferred dosage forms for pediatric use, and a position paper on off-label use.

The subcommittee proposed the first WHO Model List of Essential Medicines for Children and planned a comprehensive roadmap for the future, with a clear set of actions to be completed. Finally, specific areas were identified for further research and medicines development addressing pediatric populations. The full report of the subcommittee will be posted on the WHO medicines website (http://www.who.int/medicines/en).

In conclusion, the WHO has taken steps to map the global situation concerning access and use of pediatric medicines and has designed specific activities to fill existing gaps. Needless to say, there is a huge unfinished agenda, and resources must be harnessed within a short time frame. Success will be dependent on the quality of the response and on our ability to focus individual and collective responsibility. With the well-coordinated joint efforts of all stakeholders, including academia, industry, governments, nongovernmental organizations, and funding agencies, progress can be achieved and help provided to children, especially those in less favored settings.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Dosing in Obesity: A Simple Solution to a Big Problem

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The global epidemic of obesity has led to an increased prevalence of chronic diseases and need for pharmacological intervention. However, little is known about the influence of obesity on the drug-exposure profile, resulting in few clear dosing guidelines for the obese. Here we present a semi-mechanistic model for lean body weight (LBW) that we believe is sufficiently robust to quantify the influence of body composition on drug clearance, and is therefore an ideal metric for adjusting chronic dosing in the obese.

Obesity has reached epidemic proportions worldwide, and the obese can no longer be considered a minority demographic.[1] Despite increased pharmacotherapy among obese patients, there is a paucity of dosing guidelines for this population. This could be partly attributed to insufficient knowledge about pharmacokinetic parameters as a function of body composition due to the exclusion of obese subjects from clinical trials (in which body composition is defined as the differentiation of lean tissue from body fat in an individual). In addition, there has been no suitable size descriptor for dose adjustments across a wide range of body compositions.[2] It should be noted that dose adjustments referred to in this commentary pertain to maintenance doses, not loading doses.

This commentary aims to (i) present a recent derivation of a size metric, lean body weight (LBW), which takes into account changes in body composition that occur with obesity, and (ii) propose a hypothesis that LBW is sufficient to explain the influence of body composition on clearance and can therefore adequately predict drug exposure in the obese. We do this not only to highlight the complexity of designing appropriate studies to investigate the impact of obesity on drug clearance, but also to formally recommend that our hypothesis be the subject of future testing. It is our belief that dose individualization

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doi:10.1038/sj.clpt.2007.6100381

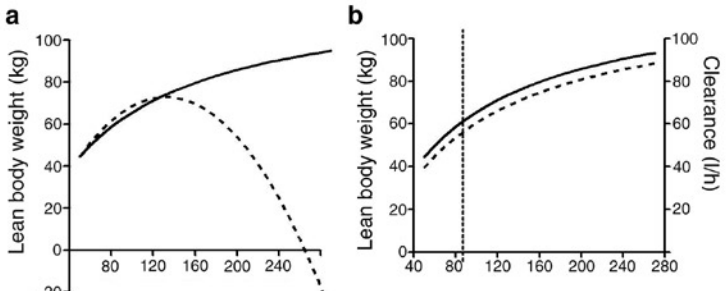

Figure 1 Relationship between LBW and WT for males of a standardized height of 1.7 m. (**a**) Comparison of LBW calculated using the semi-mechanistic LBW_{2005} equation (solid curve) and James' empirical LBW equation (dashed curve). James' equation generates predicted LBW values that increase to a peak before declining to negative values with increasing WT. (**b**) Graphical depiction of the three observations. All individuals with a WT above 87.5 kg (vertical dashed line) were considered obese (BMI > 30 kg/m^2). Comparison of clearance on the left and right of the "obesity line" shows that absolute clearance is greater in the obese than in the normal-weight subjects, illustrating Observation 1. Clearance (dashed curve) also increases nonlinearly with WT, illustrating Observation 2. The linear relationship between clearance and LBW is shown by the LBW (solid curve) and clearance graphs running parallel to each other, illustrating Observation 3.

can be significantly improved by understanding the quantitative relationship between body composition and drug clearance. We also believe that this relationship should be described by a mechanistically derived dosing scalar, thereby enabling it to provide quantitative predictions about the impact of body composition on the drug-exposure profile. This goal is in line with the Food and Drug Administration's (FDA) Critical Path Initiative,[3] which seeks to improve understanding of the exposure–response relationship.

In clinical practice, conventional methods of dose adjustment via weight-based regimens, *i.e.*, milligram per kilogram, assume that biological functions are directly proportional to total body weight (WT). However, 99% of the body's metabolic processes (including clearance) take place within lean tissues.[4] We contend that using WT to calculate maintenance doses for obese patients is scientifically unsound. The obese have a lower LBW/WT ratio overall,[5] although their total LBW is greater than that of normal-weight individuals. Because WT represents the integral of body components, it is too simplified for describing changes in body composition that occur with obesity. We believe that a two-compartment model, with LBW as Compartment 1, is the simplest model needed to adequately describe body composition.

LBW represents the sum of cellular mass and nonfatty intercellular connective tissue, such as bone (excluding fatty marrow), tendons, ligaments, and basement membranes.[4] It should be noted that individuals used in the derivation of James' LBW equations in 1976 (maximum body mass index (BMI) = 43 kg/m^2; maximum WT = 122 kg)[6] weighed considerably less than obese patients commonly found in the clinic today (maximum BMI = 100 kg/m^2; maximum WT = 273 kg).[7] This underrepresentation of obese subjects in James' population (only 9.2% of study subjects had a BMI > 30 kg/m^2) resulted in LBW equations that provided biologically implausible estimates of LBW in the form of negative values (**Figure 1a**).[8]

To overcome the limitations of James' empirical LBW equations, a semi-mechanistic model for LBW, based on bioimpedance, was developed in 2005 in a population with wide-ranging WTs that are representative of the current population. These equations are shown below; further details on their derivation are available in Janmahasatian *et al.*[9]:

For males:

$$LBW_{2005}\ (kg) = \frac{9270 \times WT\ (kg)}{6680 + 216 \times BMI\ (kg\ m^{-2})}$$

For females:

$$LBW_{2005}\ (kg) = \frac{9270 \times WT\ (kg)}{8780 + 244 \times BMI\ (kg\ m^{-2})}$$

One key advantage of the LBW_{2005} model, apart from agreeing well with James' LBW equations over normal ranges of height and WT, is that the estimate of LBW_{2005} never declines as WT increases (**Figure 1a**). These equations also have good predictive properties when compared with LBW derived from dual-energy X-ray absorptiometry (DXA),[9] a reference method for LBW estimation.

With LBW_{2005}, we now have a robust size descriptor capable of quantifying changes in hepatic and renal clearance for individuals of a wide range of body compositions, which sets the stage for a conceptual shift in the way we perceive the relationship between body composition and clearance. This relationship translates into the following hypothesized observations, which are graphically depicted in **Figure 1b**:

Observation 1: Absolute clearance is greater in obese individuals.

Observation 2: Clearance increases nonlinearly with WT.

Observation 3: Clearance correlates linearly with LBW.

Our proposal that LBW and clearance are linearly related is based on mechanistic principles derived from prior biological knowledge and differs from earlier investigations that drew empirical relationships between body composition and clearance. It is probable that technical challenges in measuring and relating pharmacokinetic parameters to LBW prevented the use of a mechanistic

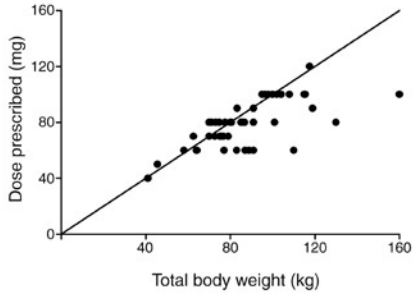

Figure 2 Dose of enoxaparin prescribed for patients of varying WTs. The solid line represents the calculated dose of enoxaparin based on the drug-label recommendation of 1 mg/kg. Patients with higher WTs have a tendency to be underdosed according to the label, because physicians often reduce doses to adjust for differences in body composition.

Table 1 Renal clearance of normal-weight and obese subjects

	Mean ± SD (range)		
	Normal-weight	**Obese**	***P*-value from repeated measures ANOVA**
Absolute clearance (ml/min)	90.90 ± 16.25 (69.0 – 124.0)	131.07 ± 34.62 (85.0 – 216.0)	<0.01
WT-normalized clearance (ml/min/kg)	1.40 ± 0.22 (1.04 – 1.82)	1.03 ± 0.19 (0.78 – 1.31)	<0.01
LBW-normalized clearance (ml/min/kg)	2.03 ± 0.35 (1.46 – 2.97)	1.88 ± 0.30 (1.53 – 2.55)	0.27

The obese population had significantly higher absolute clearance, in accordance with Observation 1, and significantly lower WT-normalized clearance, in accordance with Observation 2. When clearance was normalized to LBW_{2005}, no significant difference was observed between normal-weight and obese individuals, in accordance with Observation 3. WT, total body weight; LBW, lean body weight; ANOVA, analysis of variance.

approach when performing such studies. Although prior investigators alluded to the possibility that excess adipose tissue influenced pharmacokinetic parameters in the obese, we surmise that their progress was hindered by the use of inappropriate size descriptors such as ideal body weight (IBW).[10] IBW is a function of height and sex only, and does not take into account differences in body composition. Use of IBW as a surrogate for lean mass is inherently flawed, because it assumes that individuals of the same sex and height have exactly the same ideal (and presumably lean) mass. Understandably, this approach confounds the ability to identify the true impact of obesity and body composition on drug clearance.

Given the availability of methods to precisely determine LBW (*e.g.*, DXA, bioimpedance) and an improved understanding of how LBW changes across individuals of varying body composition (with the increased prevalence of obesity), we recommend that investigators design and analyze dose-exposure trials with clearance expressed as a function of LBW. Results from such studies can also be used to predict drug exposure in the obese, even if they were excluded from the studies. This provides a distinct advantage over empirical dosing strategies based on WT, which are likely to result in overdose when extended to the obese. In fact, physicians often attempt to adjust for altered body composition in the obese by arbitrarily reducing weight-based drug doses. A good example is the drug enoxaparin, which has a labeled dose of 1 mg/kg. An observational study ($n = 50$) has shown that physicians do not prescribe 1 mg/kg in the obese (probably because of the risk of adverse bleeding events) and arbitrarily reduce the dose to account for body composition (**Figure 2**).[11]

Having recognized the shortcomings of using empirical methodologies during the drug-development process, the FDA launched the Critical Path Initiative in 2004 to promote the concept that scientific tools for predicting and evaluating drug safety and efficacy should be developed mechanistically.[3] Although empirical methodologies can ensure that the drug is right for its intended therapeutic purposes by confirming its average effectiveness on a population level, ensuring the right dose on an individualized basis can be achieved only by using mechanistic approaches that build on improved insights into the influence of patient variables on the dose exposure–response relationship.[12]

Given that the concept of relating drug clearance to LBW rather than WT is relatively new, it is understandable that prior studies were not designed specifically to test this hypothesis. We have reanalyzed renal clearance data from a previous study using LBW_{2005} in which absolute clearance, as well as clearance values normalized by WT and LBW_{2005} for normal-weight and obese subjects, were compared using repeated-measures analysis of variance (**Table 1**) (unpublished data from S. Janmahasatian, S.B. Duffull, A. Chagnac, C.M.J. Kirkpatrick, and B. Green). The results of this study concur with our hypothesis that drug clearance for individuals of varying heights and WTs is the same after adjusting for body composition. They also imply that LBW is a useful dosing scalar that is transportable across all body compositions.

Although our hypothesis is novel, other investigators have similarly recognized the limitations of using conventional dosing scalars in obese patients. Shibutani *et al.*[13] observed that the absolute clearance for a hepatically cleared drug (fentanyl) was significantly higher in obese patients and that clearance increased nonlinearly with WT. They solved for their observations by deriving a size metric termed "pharmacokinetic mass" that increased linearly with clearance. We have compared their empirically derived "pharmacokinetic mass" with our semimechanistic LBW model for subjects with WTs and heights from 35 to 165 kg and 1.3 to 1.95 m, respectively, and found a close correlation between the two size descriptors ($R^2 = 0.92$ for males and $R^2 = 0.94$ for females). Their results agree with Observations 1 and 2 and indirectly accord with Observation 3, thus providing additional evidence in support of our hypothesis.

We have also reviewed other studies examining the influence of obesity on drug clearance published between 1978 and 2004 (**Supplementary Table S1** online). A complete reanalysis of the data is not possible because of unavailable published individual data and lack of studies specifically designed to test our hypothesis. Of the 72 studies, only 5 used LBW or a similar size metric ("pharmacokinetic mass"). The remainder defined obesity as a function of IBW or BMI. The inherent flaws of IBW as a surrogate for lean mass, as discussed above, only serve to confound the results. BMI is also an unsuitable body composition metric, because it does not distinguish between excess fat and a larger muscle/bone mass.

Author-reported conclusions from studies using IBW or BMI should therefore be interpreted with caution.

Nevertheless, these studies provide empirical support that body composition is sufficient to explain interindividual variability in drug clearance. The absolute clearance and clearance normalized by WT or LBW reported in the studies, where available, were tabulated. Studies that showed any of the three observations described above were deemed to support the hypothesis, and studies that showed nonsignificant results or were underpowered to show a difference were considered to fail to disagree with the hypothesis. Studies that showed any one of the three observations but showed the opposite for any of the other two conditions were regarded as disagreeing with the hypothesis. Of the 80 investigations carried out (some studies investigated more than one drug), 21.2% agreed with the hypothesis and 65% failed to disagree. An additional 10% disagreed but could be explained by confounders, leaving a 3.8% error rate, which is less than the commonly accepted alpha error of 5%. Despite the fact that these studies were not designed to directly address the hypothesis, the majority failed to disagree with the hypothesis, thus supplying empirical evidence for our proposed relationship between clearance and body composition.

We hope that future studies will place greater emphasis on reporting pharmacokinetic results that mechanistically quantify the relationship between clearance and body composition as a function of LBW, even if obese subjects are excluded from these studies. This approach will enable quantitative predictions about the dose exposure–response relationship in the obese, thereby optimizing pharmacotherapy. To ensure that future studies can evaluate our hypothesis, we suggest that investigators consider incorporating the following proposals into their trial designs:

1. Body composition should be measured as a function of LBW rather than IBW or BMI. This avoids the limitations of using IBW and BMI (whose flaws have been described earlier) to describe body composition. LBW should be estimated using derived equations (*e.g.*, Janmahasatian *et al.*[9]), DXA, or other established methods.

2. If the objective is to determine whether differences in drug clearance exist between obese and normal-weight subjects using null-hypothesis testing, the two groups must not be matched for any variable (*e.g.*, LBW) that correlates with clearance.

3. Studies should be designed from a "learning" perspective,[14] with a continuum of subject size ranging from normal-weight to obese and including a wide range of (and preferably stratified for) LBWs. Analysis should be based on regression techniques, allowing quantification of clearance as a function of LBW. This differs from the null-hypothesis testing approach, which provides only a yes–no answer to the question of interest.

The "one size fits all" concept of dosing is gradually being replaced by strategies aimed at delivering "personalized medicine" to patients. These have the potential to improve drug efficacy and minimize adverse events, hence optimizing patient care and reducing health-care costs from suboptimal dosing. In addition, the use of appropriate dosing scalars is likely to accelerate the approval of new drugs by ensuring drug safety across different patient subpopulations. We believe that using LBW as a dosing scalar is vital to achieving these goals, although we acknowledge that our proposed relationship between body composition and clearance accounts for only a portion of the predictable aspects of interindividual variability in drug clearance. Regrettably, despite an improved understanding of the physiologic changes associated with obesity and its rising prevalence worldwide, the FDA has yet to recognize obese patients as a separate entity with characteristics that differ from the rest of the population. A simple solution to overcome this lack of special dosing instructions for the obese is to design and analyze dose exposure–response studies using LBW as the size metric on clearance, and to report dosing recommendations as a function of LBW in drug labels. Furthermore, because LBW performs equally well in normal-weight and obese individuals, we postulate that results of dose-ranging studies using a milligram-per-kilogram-of-LBW approach in normal-weight subjects can be extrapolated to the obese population despite their exclusion from clinical trials. This strategy is timely, given the increased incidence of obesity-related comorbidities requiring pharmacotherapy, and provides physicians with opportunities to make meaningful clinical decisions about dosing in obesity.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt.

ACKNOWLEDGMENTS

P.Y.H. was supported by a grant from Pfizer Global R&D.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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