Drug Disposition in Obesity: Toward Evidence-Based Dosing

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Abstract

Obesity and morbid obesity are associated with many physiological changes affecting pharmacokinetics, such as increased blood volume, cardiac output, splanchnic blood flow, and hepatic blood flow. In obesity, drug absorption appears unaltered, although recent evidence suggests that this conclusion may be premature. Volume of distribution may vary largely, but the magnitude and direction of changes seem difficult to predict, with extrapolation on the basis of total body weight being the best approach to date. Changes in clearance may be smaller than in distribution, whereas there is growing evidence that the influence of obesity on clearance can be predicted on the basis of reported changes in the metabolic or elimination pathways involved. For obese children, we propose two methods to distinguish between developmental and obesity-related changes. Future research should focus on the characterization of physiological concepts to predict the optimal dose for each drug in the obese population.

INTRODUCTION

Obesity represents a serious and increasing health problem worldwide. In the United States in 2009–2010, the prevalence of obesity [body mass index (BMI) > 30 kg/m^2] was 35.9%, and the prevalence of morbid obesity (BMI > 40 kg/m^2) was 6.3% (8.2% for women and 4.4% for men) (1). Alarmingly, the prevalence of overweight and obesity in children is also increasing. According to the most recent National Health and Nutrition Survey (2009–2010) 31.8% of US children and adolescents (age 2–19 years) are overweight (≥85th percentile of BMI for age), 16.9% are obese (≥95th percentile), and 12.3% are morbidly obese (≥97th percentile) (3). Worldwide prevalence rates for obesity in adults and overweight and obesity rates in children are also high, exceeding 24% in, for instance, Canada, Spain, the United Kingdom, Greece, Mexico, Saudi Arabia, Egypt, Australia, New Zealand, and some parts of South America (2).

Obesity increases the risk of many diseases and health conditions, such as hypertension, cardiovascular disease, dyslipidemia, type 2 diabetes, cancer, and osteoarthritis, thereby diminishing average life expectancy (4). In addition, obese individuals are also more likely to suffer from chronic pain (5, 6) and nosocomial infections (7, 8). Because these comorbidities often require pharmacotherapeutic or surgical and anesthetic treatment, an important question is how to optimize the dose of drugs, particularly in light of the fact that the morbidly obese patient group is increasing. In this respect, specific attention should be paid to obese children, who are likely to become obese adults. Comorbidities associated with childhood obesity are hypertension, obstructive sleep apnea, diabetes mellitus, and coronary artery disease, necessitating pharmacotherapeutic or even surgical or bariatric treatment (9, 10). Furthermore, obese children are also more likely to develop asthma or severe asthma (11), but their response to inhaled steroids is decreased (12). Moreover, overweight and obesity have been reported as independent predictors of the relapse risk of acute lymphoblastic leukemia (13). It cannot be excluded that these differences result from changes in the pharmacokinetics of chemotherapeutic agents in overweight or obese children. Therefore, it is of utmost importance to gain insight into how to adjust the dose of drugs in obese and morbidly obese children and adolescents. This issue should be viewed through the perspective of the fact that even in nonobese children, 37–80% of drugs are prescribed in an off-label or unlicensed manner (14–16).

In this review, we provide an overview of the current knowledge on changes in drug disposition in obese patients in relation to physiological changes associated with obesity. Our ultimate goal is to direct future research aiming for individualized dosing in this growing and heterogeneous patient population. We pay specific attention to changes in drug disposition in obese children.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH OBESITY

Obesity is associated with many physiological and pathophysiological changes that may affect drug disposition. Obesity and morbid obesity are not only associated with an increase in fat but also in lean body weight (LBW), which is the weight devoid of all adipose tissue. The percentage of fat mass per kilogram of total body weight increases more than LBW in obese patients, with, for instance, an increase in LBW representing 20–40% of total excess of weight in morbidly obese patients (17, 18).

To supply the excess body mass with oxygen and nutrients, blood volume, cardiac output, and capillary flow increase substantially in obese and, in particular, morbidly obese individuals (19–22). Serum albumin and total protein concentrations are reported to be comparable in lean and obese subjects, even though concentrations of alpha-1-acid glycoprotein are increased (23). In the cardiovascular system, the increased blood volume and cardiac output eventually leads to systemic

hypertension, left and right ventricular hypertrophy, and an increased risk for sudden cardiac death due to conduction disorders (24, 25). Pulmonary function is uniformly altered in obesity, with reduced lung volumes (26) and a higher incidence of obstructive sleep apnea syndrome (27).

Nonalcoholic steatohepatitis and histological abnormalities such as fatty infiltration in the liver are very common in morbidly obese patients (28, 29). Because of the accumulation of fat in the liver of obese individuals, functional morphology may be altered owing to sinusoidal narrowing (30, 31). However, because of increased blood volume and cardiac output, liver blood flow is not necessarily reduced in obese subjects (32). Although liver volume is reported to be increased in obese individuals (33), the results of studies on the influence of obesity on expression and function of CYP enzymes are inconclusive, with the exception of CYP3A and CYP2E1; the expression and function of these enzymes have been reported to be decreased and increased, respectively (34).

There are conflicting data on alterations in renal function. Irrespective of the presence of hypertension, investigators have reported increases in glomerular filtration rate and effective renal plasma flow (35–37). However, there is also evidence of unaltered renal function (38). In studies in Zucker rats with genetic obesity, researchers found that, after an initial increase in glomerular filtration rate, this rate normalized and subsequently decreased in the later stages of obesity, ultimately leading to end-stage renal disease (39–41). In morbidly obese patients who presented with proteinuria, one study reported focal glomerular sclerosis, diabetic nephropathy, or both (42). In addition, estimates of the creatinine clearance from standard formulas tend to be inaccurate in obese patients (43–45). Even though obesity-associated renal damage may be unpredictable, the available evidence indicates that it is best to use LBW in the Cockcroft-Gault formula for estimation of creatinine clearance in obese patients (44, 46).

With respect to the functioning of the gastrointestinal tract, studies in obese subjects have found accelerated gastric emptying of solids (47–50), high splanchnic blood flow (19), and increased gut wall permeability (51, 52). Because studies on the influence of obesity on intestinal transit time and motility have shown contradictory results, the exact impact of obesity on drug or nutrient absorption remains unclear (50, 53, 54). Wisén & Johansson (54) found that obese subjects had significantly higher absorption in the proximal small intestine. Studies on the influence of obesity on enterohepatic recirculation are lacking.

MEASURES TO QUANTIFY BODY SIZE AND OVERWEIGHT

BMI is the international metric recommended by the World Health Organization to classify obesity (55). A BMI value between 18.5 and 25 kg/m^2 is considered healthy. BMI values greater than 30 and 40 kg/m^2 indicate obesity and morbid obesity, respectively (55). As BMI does not differentiate adipose tissue from muscle mass, BMI should be considered a descriptor of body shape instead of a measure of body composition (56, 57). For a child's weight status (2–18 years), an age- and sex-specific percentile for BMI (BMI-for-age) is used because children's body compositions vary as they age and between boys and girls (58, 59). For children younger than 2 years, weight-for-length charts are used. Overweight is defined as a BMI between the 85th and 95th percentile and obesity above the 95th percentile for children of the same age and sex (60).

The value of the ideal body weight (IBW) parameter is most commonly calculated using the equation by Devine (61). Similar to BMI, this measure is rarely used as the basis for the individualization of drug dosage in obese patients, except for some specific drugs such as muscle relaxants (62–64) and remifentanil (65). This measure may lack predictive value for the dose adjustment of other drugs because it is based on height and sex only and does not consider body

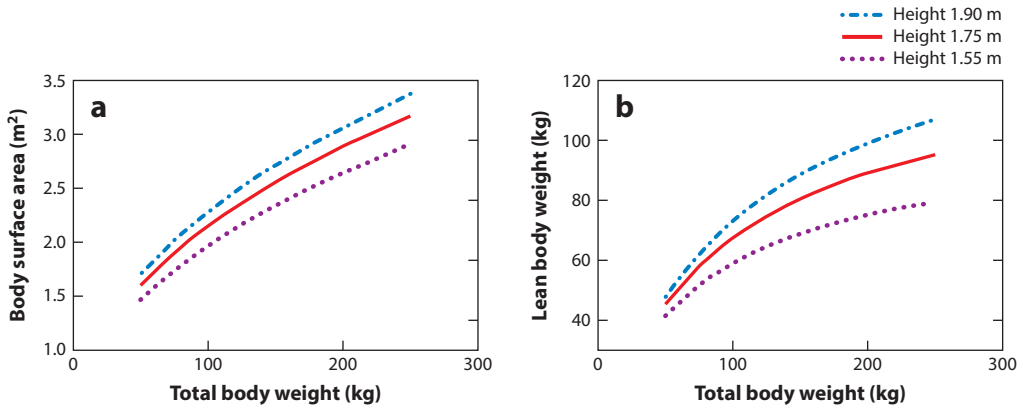

Figure 1

Body surface area (68) (*a*) and lean body weight (73) (*b*) versus total body weight for males of various heights.

weight in any way (56). Adjusted body weight is an empirical, IBW-based metric with different correction factors (0.14–0.98) that was developed after the discovery that IBW was a suboptimal parameter for drug dosing in obese subjects (66), but very little evidence supports using this as a guide for dosing (67).

Body surface area (BSA) is mainly used for dosing of anticancer drugs, a practice that has a historical rather than scientific basis. BSA can be calculated using the equations by Du Bois & Du Bois (68) or Mosteller (69). The equations are based on the theory of Euclidean geometry and account for height and weight (66). Remarkably, recent reports have shown that there is no evidence to reduce the dose or dose capping when BSA-adjusted doses are used in obese or morbidly obese cancer patients (70, 71). These results may be explained by the nonlinear relation of BSA with total body weight (**Figure 1**), reducing the absolute increase in dose in relation to the increase in body weight.

Because of the drawbacks of the previous measures, researchers have proposed using lean body weight (LBW) as a measure of body composition (72). Information on body weight as well as height and gender are required to calculate LBW (**Figure 1**). LBW represents the weight of bones, muscles, tendons, and organs without body fat (i.e., fat-free mass). The most recent LBW equation, proposed by Janmahasatian et al. (73), provided good predictions of the fat-free mass as measured with bioelectrical impedance analysis or dual-energy X-ray absorptiometry. The exact value of LBW as a predictor for dosing remains to be established. In this respect, it is important to note that in pharmacometric studies, this parameter was not always identified as the best predictor (67, 74, 75). Peters et al. (76) proposed a new formula to calculate LBW in children. However, researchers have very limited experience with this measure as a predictor for dosing drugs in obese children (77).

In general, actual body weight should be used with caution as a body-size descriptor in obesity because its value is influenced by factors such as age, sex, height, muscle mass, and obesity. Nevertheless, nonlinear functions of total body weight (TBW) show good performance as predictors of clearance in several pharmacokinetic studies covering wide ranges in body weight (74, 75, 78). Similarly, in a large study on the variation in clearance and volume of distribution of 12 different drugs, total body weight appeared to be a consistent and reliable size descriptor for the prediction of these parameters in the obese (79).

THE INFLUENCE OF OBESITY ON ORAL BIOAVAILABILITY AND ABSORPTION RATE

Only six studies have directly compared the oral bioavailability and absorption rate of drugs between obese and nonobese subjects on the basis of both oral and intravenous administration (80–85). For propranolol, clearance (CL) after an intravenous dose was not different between six obese (136 ± 36 kg) and six control (67 ± 5 kg) subjects. However, oral clearance (CL/F) was lower in obese patients, indicating that the bioavailability (F) of propranolol was slightly higher for obese subjects ($35 \pm 4\%$ versus $27 \pm 2\%$, $P > 0.05$) (80). In the discussion of their article, the authors point out that the slightly higher bioavailability reported for propranolol may also be applicable for triazolam (80, 86). Unfortunately, in the study on triazolam, there were no observations after intravenous administration (86), which makes it impossible to draw conclusions on an eventual difference in absolute bioavailability. For midazolam, no difference in bioavailability was found between normal-weight volunteers (66 ± 2 kg, $n = 20$) and obese volunteers (117 ± 8 kg, $n = 20$) ($40 \pm 3\%$ versus $42 \pm 4\%$, $P > 0.05$, respectively), nor was a difference found in time of maximum concentration (T_{max}) or maximum concentration (C_{max}) itself (81). Similarly, no difference in bioavailability or oral absorption rate was found for trazodone, cyclosporine, dexfenfluramine, and moxifloxacin between obese and nonobese subjects (82–85).

In view of the limited number of studies on oral absorption, we most recently studied midazolam bioavailability in 20 morbidly obese patients [mean body weight 144 kg (112–186 kg) and mean BMI 47 kg/m^2 (40–68 kg/m^2)] and 12 healthy volunteers [mean body weight 76 kg (63–93 kg) and mean BMI 22 kg/m^2 (19–26 kg/m^2)] (**http://clinicaltrials.gov/show/NCT01519726**). For this study, a semisimultaneous oral and intravenous administration design was chosen in which morbidly obese patients received 7.5 mg of midazolam orally followed by a 5-mg intravenous bolus dose after 159 ± 67 min. Healthy volunteers received 2-mg oral and 1-mg intravenous midazolam separated by 150 min. This study design allowed for the characterization of both clearance and bioavailability in a single pharmacokinetic study. Results of this study show an increased bioavailability ($60 \pm 13\%$ versus $28 \pm 7\%$, $P < 0.01$) and a lower oral absorption rate ($0.057 \pm 14\%$ min^{-1} versus $0.13 \pm 5\%$ min^{-1}, $P < 0.01$), but no influence of obesity on systemic clearance in morbidly obese patients compared to healthy volunteers (87). Dose simulations of the final population pharmacokinetic model showed that after a 7.5-mg oral midazolam, C_{max} is only slightly lower, whereas T_{max} is increased for morbidly obese patients (**Figure 2*a***).

The significant difference in oral bioavailability reported in this study (87) may result from the larger body weights of the subjects compared to the previous study by Greenblatt et al. (81), who reported no difference in bioavailability (mean body weight of 144 kg versus 117 kg). The observed higher bioavailability could be explained by an increased splanchnic blood flow (19), which may lead to reduced contact between midazolam and intracellular CYP3A enzymes in the gut wall. Also, the increase in bioavailability may be explained by increased paracellular absorption through the gut wall, or a combination of both (51, 52, 88, 89). The higher midazolam bioavailability found in morbidly obese patients, however, does not seem to result in higher C_{max} values (**Figure 2*a***); this may be explained by the higher volume of distribution (87) which was also reported by Greenblatt et al. (81). The lower absorption rate (and therefore increased T_{max}) in morbidly obese patients may be the result of the difference in midazolam formulation, as healthy volunteers received an oral solution and morbidly obese patients a tablet. As midazolam effectiveness is determined by the initial midazolam concentrations after an oral dose, this study suggests that the net result of the alterations in the different pharmacokinetic parameters is that no adjustments in oral midazolam dose seem necessary for obese individuals. However, a different conclusion should be drawn for

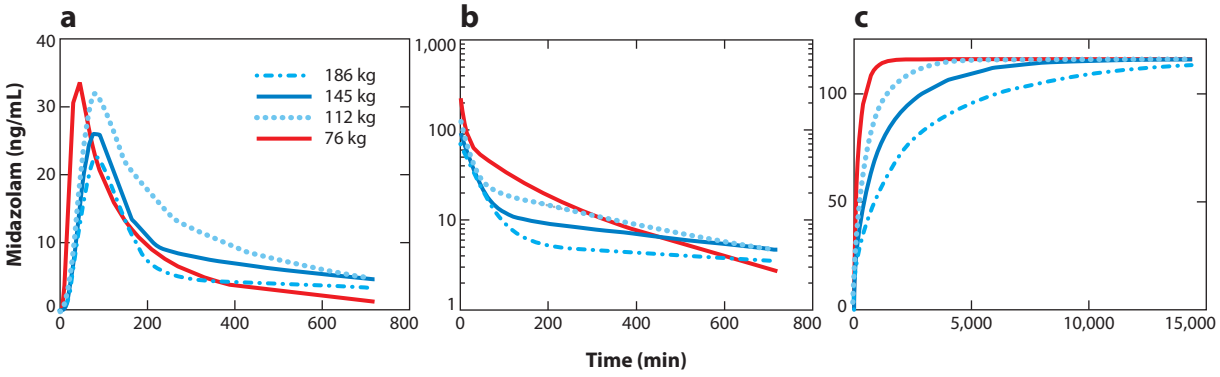

Figure 2

Population-predicted midazolam concentrations over time in three typical morbidly obese patients (112, 145, and 186 kg) and one healthy volunteer (76 kg) after (*a*) a 7.5-mg oral dose (linear scale), (*b*) a 5-mg intravenous bolus dose (logarithmic scale) and (*c*) a 2.5-mg/h continuous infusion. Figure adapted from Reference 87 with permission.

intravenous administration, given the substantially increased volumes of distribution of midazolam in morbidly obese patients (**Figure 2*b*,*c***) (81, 87).

In conclusion, there is limited information on the influence of obesity on drug pharmacokinetics after oral administration despite the fact that most drugs are given orally. From the very small number of studies on drug absorption identified in this review, it seems that drug absorption is rather unaltered. However, this may be a premature conclusion warranting further systematic evaluations on drug absorption (90). Given the reported accelerated gastric emptying of solids (47–50), increased splanchnic blood flow (19), and increased gut permeability (51, 52) in obese subjects, changes in absorption rate and oral bioavailability cannot be excluded. The recent study on midazolam oral and intravenous pharmacokinetics in both morbidly obese patients and healthy volunteers confirms some of these anticipated changes (87). The design of this study may be used as an example to study drug absorption because both oral and intravenous administration were evaluated within each individual. Investigators analyzing results on drug absorption from a study without data after intravenous administration risk being unable to distinguish between the influence of obesity on clearance and bioavailability (or between volume of distribution and bioavailability). Finally, the consequences of altered absorption rate and oral bioavailability should each be evaluated for their clinical relevance and impact on drug dosing in the obese population.

THE INFLUENCE OF OBESITY ON DRUG DISTRIBUTION

Volume of distribution is an important parameter that is often substantially altered in obese patients (79, 90–92). It is particularly important to characterize changes in volume of distribution when a rapid onset of the effect is needed as the peak concentration after single-dose administration is largely determined by the volume of distribution. The same applies for the time to reach steady state and an eventual loading dose as part of a continued or repeated administration scheme. A rapid onset of effect may be clinically relevant in anesthesia, for anticoagulation, and for antimicrobial drug effects.

In general, drug distribution depends on the physicochemical properties of the drug, such as molecular weight, lipid solubility, and protein binding, as well as the properties of the biological system (91, 93). The latter properties may differ between subjects (obese subjects versus healthy

volunteers). In obese subjects, changes in volume of distribution may be expected to result from increased blood volume, increased cardiac output and blood flow, increased LBW, increased adipose tissue and reduced tissue perfusion (19–22, 91, 92), with only a limited influence of changes in blood proteins (i.e., albumin, alpha-1-acid glycoprotein) (23, 94).

From the available evidence, the values of the volume of distribution appear highly variable in obese individuals and more difficult to predict than the values of clearance (79, 90). While intuitively more influence of obesity on lipophilic drugs than on hydrophilic drugs may be expected (93), Jain et al. (90) concluded, on the basis of an overview of the ratios of volume of distribution of various drugs in obese versus nonobese individuals, that changes in volume of distribution cannot be predicted on the basis of lipophilicity alone. More specifically, they showed that, for lipophilic drugs, the values for volume of distribution normalized with body weight may be increased, unchanged, or reduced (90). Also, in our experience, volume of distribution is difficult to predict. For instance, no influence of obesity on the peripheral volumes of distribution of propofol was observed, despite the high lipophilicity of the drug (75, 77, 78). For hydrophilic drugs, unchanged or decreased ratios of volume of distribution normalized with body weight were observed, but the magnitude of the effect of obesity was smaller than for lipophilic drugs (90).

Similarly, Mahmood (79) concluded, on the basis of a study on the pharmacokinetics of 12 different drugs, that predictions of volume of distribution in the obese from the values in normal-weight subjects were less accurate than predictions of clearance. Although total body weight appeared to be a more consistent and reliable size descriptor than other size descriptors for the prediction of volume of distribution (79), as was suggested before (56), linear scaling of volume of distribution with body weight was reported to lead to overprediction of volume of distribution in the obese for many drugs. Instead, prediction of volume of distribution by an allometric model on the basis of total body weight was more accurate. However, for the 12 drugs studied, the exponents of allometric functions were found to vary widely (0.27–2.459), illustrating the variability of changes in volume of distribution as a result of total body weight (79). As the allometric models were built on data from normal-weight subjects, Mahmood concluded that inclusion of data from the obese into these allometric models could lead to better predictions (79).

The relative impact of the obesity-related changes in volume of distribution with respect to adjusting the dose in obese individuals is illustrated below in three examples.

Example 1: Cefazolin

In a clinical microdialysis study, cefazolin concentrations in subcutaneous adipose tissue and in plasma were evaluated in morbidly obese and nonobese patients (74). Previously, no influence of morbid obesity was found on protein binding or on trough concentrations of cefazolin, whereas a modest influence of obesity was found on cefazolin peak concentrations upon an intravenous bolus administration (94). The results of the microdialysis study show that cefazolin penetration into the subcutaneous tissue over 4 h after dosing in obese patients was reduced by 30% on average (**Figure 3**).

These results were explained by reduced distribution of cefazolin to the subcutaneous tissue, which was found to depend on body weight, while there was no evidence for an increased peripheral volume of distribution represented by the subcutaneous tissue compartment (74). Instead, the value of the central volume of distribution was found to depend on body weight, and there was no influence of weight on clearance. Because time above the minimal inhibitory concentration at the target site is relevant for cefazolin prophylaxis, these findings have important consequences for the dosing regimen, particularly for the heaviest patients (74). In this respect, it is also important to take into account that obesity is an independent risk factor for postoperative surgical site infection (7, 8, 95).

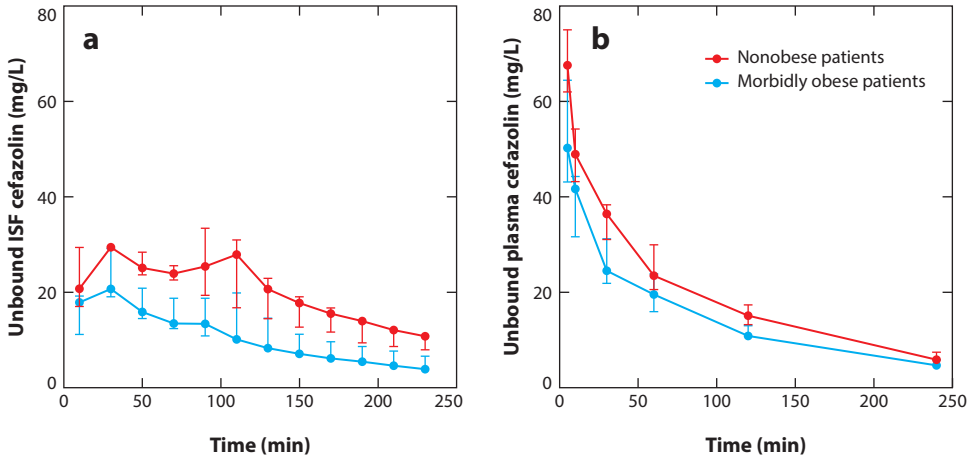

Figure 3

Concentrations of (*a*) subcutaneous interstitial space fluid (ISF) cefazolin and (*b*) unbound plasma cefazolin in morbidly obese (*blue*, $n = 7$ for panel *a* and $n = 8$ for panel *b*) and nonobese (*red*, $n = 7$ for both panels) patients. Figure adapted from Reference 74 with permission.

Example 2: Nadroparin

A second example concerns anti-Xa levels, which Diepstraten et al. (96) measured to evaluate the effect of nadroparin in morbidly obese patients (107–260 kg). Prophylactic ranges have been defined for anti-Xa levels 4 h after subcutaneous dosing (97, 98). Volume of distribution is therefore an essential parameter to determine the optimal dose for nadroparin. Upon subcutaneous administration, anti-Xa levels correlated best with LBW rather than BMI or total body weight, so dose adjustments on the basis of LBW are proposed (96).

An explanation for the finding that LBW should be used to dose low-molecular-weight heparins such as nadroparin could be that anti-Xa is a large, hydrophilic molecule that mainly distributes over vascular tissue and blood. Investigators have previously reported that blood volume increases with body weight in a nonlinear manner (22), which probably corresponds to LBW. Also, researchers have proposed to adjust the dose for enoxaparin, another low-molecular-weight heparin, in obese individuals on the basis of LBW (99). Optimal dosing of low-molecular-weight heparins in obese individuals is particularly important because these individuals are at increased risk for venous thrombosis embolisms (100).

Example 3: Atracurium

As a third example, we present a pharmacodynamic study on atracurium in morbidly obese patients (BMI > 40 kg/m^2, body weight 112–260 kg) (62). Patients were randomized to receive atracurium on the basis of IBW or total body weight (TBW). Dosing on the basis of IBW resulted in a predictable profile of muscle relaxation, allowing for adequate intubation conditions and recovery of muscle strength within 60 min. In the patients for whom the dose was individualized on the basis of TBW, a dose-dependent prolongation of action was shown (**Figure 4**); thus, van Kralingen et al. (62) concluded that atracurium should be dosed on IBW.

In this example, changes in both pharmacokinetics (volume of distribution, clearance) and pharmacodynamics may have contributed to these results. Similar results have previously been

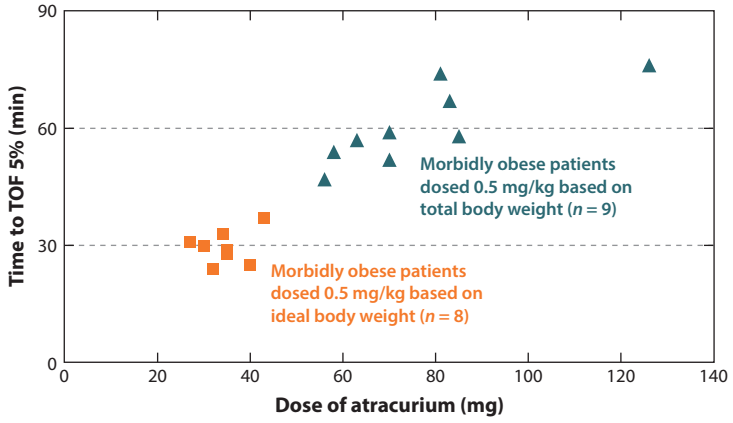

Figure 4

Effect of atracurium expressed as time to recovery of the twitch response of the neuromuscular train-of-four (TOF) to 5% versus dose for morbidly obese patients dosed 0.5 mg/kg based on ideal body weight (*orange squares*, $n = 8$) and dosed 0.5 mg/kg based on total body weight (*green triangles*, $n = 9$). Figure adapted from Reference 62 with permission.

reported for rocuronium (63, 64). Remarkably, these results have led to an IBW-based dosing advice for rocuronium in the European label, whereas in the United States, rocuronium is still advised to be dosed on total body weight (90).

From this overview, it seems that the current level of understanding of the comprehensive effect of obesity on volume of distribution is limited. Although volume of distribution often changes with obesity, the direction and magnitude is not always predictable (79, 90), despite many efforts to correlate it to physicochemical properties (17, 90–92). When no information is available, extrapolation on the basis of total body weight with an estimated allometric exponent from results in normal-weight subjects seems preferable (79).

THE INFLUENCE OF OBESITY ON DRUG METABOLISM AND EXCRETION

Typically, there is more attention for the influence of obesity on metabolic and elimination clearance than on drug distribution (79, 101–103). This may be explained by the fact that drug clearance is considered the most important pharmacokinetic parameter because it determines the maintenance dose of drugs.

A systematic review on reported clearance values of drugs in both obese and nonobese patients showed that the influence of obesity on drug metabolism and elimination differs between specific metabolic or elimination pathways (101), even though the magnitude of its influence seems relatively small compared to the influence of obesity on distribution (79). Overall, the clearance of drugs primarily metabolized through the Phase II metabolism enzyme uridine diphosphate glucuronosyltransferase is reported to increase with obesity. For drugs that are eliminated through Phase I metabolism, the changes may differ depending on the pertinent enzyme. For example, an increased CYP2E1 clearance, a lower CYP3A clearance, and a trend toward higher clearance of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 substrates have been reported (101). In agreement with these literature findings, oral clearances were successfully predicted for eight drugs that are primarily cleared by CYP3A, CYP1A2, CYP2E1, and CYP2C9 on the basis

of physiologically based pharmacokinetic modeling, in which known alterations in physiology resulting from obesity are implemented (103). More specifically, seven out of nine cases (involving eight drugs) were within 2-fold of the actual ratio of clearance in obese versus lean patients (103). Remarkably, in this study, oral clearances of the CYP3A substrates alprazolam, midazolam, triazolam, and cyclosporine in the obese were somewhat overpredicted compared to observed oral clearance values, which were expected to be lower in the obese (103). As for midazolam, similar systemic clearance and higher bioavailability in morbidly obese patients were recently reported (87); it is emphasized that oral clearance equals CL/F and that reported differences in oral clearance in the obese may result from differences in systemic clearance, bioavailability, or both. Therefore, investigators should take care to predict systemic clearance on the basis of oral data as long as limited information is available on drug absorption in the obese.

With respect to renal clearance, higher values are reported in obese individuals (35, 101). Recent results on the renally excreted antibiotic cefazolin in morbidly obese patients undergoing bariatric surgery did not identify an influence of body weight on cefazolin clearance, however (74, 94). Even though this finding may be an artifact resulting from the relatively short sampling time in the study, a lack of change in glomerular filtration rate in obese individuals without microalbuminuria has been reported before (38), emphasizing that renal clearance of drugs may not necessarily be increased.

Concerning drug clearance mediated by liver blood flow, higher values were reported for a small number of high-extraction-ratio drugs with clearance values of more than 1.5 L/min (101), which confirm early reports on increased hepatic flow in obese patients (19).

Recently, Mahmood (79) has used an allometric equation to scale the pharmacokinetics of 12 drugs that are eliminated through different routes between healthy normal-weight subjects and obese patients. The results of this study indicate that clearances of these 12 different drugs increase in a nonlinear manner with total body weight (79), confirming a previous report (56). Clearance in the obese could be predicted with accuracy from normal-weight subjects using total body weight and simple allometry if an allometric exponent was estimated within the normal-weight population (79). In addition, allometric scaling with a fixed exponent of 0.75 or 1.0 was found to be inferior to the allometric model in which the exponent was estimated. Mahmood (79) also states that obesity may not have an impact on clearance at all, as was the case for phenazone, carbamazepine, lithium, remifentanil, cefazolin, and theophylline; thus, we emphasize that allometric scaling using a fixed exponent of 0.75 or 1.0 on the basis of results from normal-weight patients should not be applied unless more data become available. This argument also applies to the proposal to scale clearance with LBW with an exponent of 2/3, independent of the drug's primary route of metabolism and elimination (102), as this approach assumes an increase in clearance with obesity, which may not be the case for all drugs (79, 104).

In conclusion, for clearance, the influence of obesity seems smaller and somewhat easier to predict compared to alterations in volume of distribution, even though many questions remain on the exact quantification (101). From the results presented here, it seems that predictions can be made on the basis of the primary pathway involved (101, 103). When no information is available, extrapolation on the basis of total body weight with an estimated allometric exponent from results in normal-weight subjects seems preferable (79).

CHARACTERIZATION OF THE INFLUENCE OF OBESITY IN CHILDREN

Despite the increasing numbers of obese and morbidly obese children, very limited pharmacokinetic and dosing information in obese children is available (105–107). A specific aspect that

investigators, regulators, and prescribers should consider when determining dosing guidelines for obese children and adolescents is that, in general pediatric practice, dosing regimens are expressed in mg/kg. This linear mg/kg-based dosing is subject to debate even in normal-weight children between 0 and 18 years (108–112), but an overdose may be anticipated if the dosing is based on mg/kg total body weight in overweight and, particularly, obese and morbidly obese children. This underscores the need to develop dedicated models for obese and morbidly obese children and adolescents (78). Performing these studies in the target population of obese individuals is even more relevant given that differences in pharmacokinetics, pharmacodynamics, or even the disease itself may exist in this population (12, 13).

In view of the limited number of pharmacokinetic studies in obese children (101, 113, 114), we present two pharmacokinetic studies in which data from overweight and obese children (and adults) of a large age range, along with their controls, are analyzed. In obese children, total body weight can be considered to be composed of both weight resulting from growth and development and weight from varying levels of obesity. This raises the question of, for instance, whether an obese 9-year-old child weighing 60 kg—in whom part of this body weight is physiological weight, i.e., body weight conforming to his age, and the other part is overweight—should receive the same dose as a normal-weight 16-year-old individual of the same weight. The distinction between physiological weight and overweight should be kept in mind when weight is studied as a covariate in children of varying ages and varying degrees of obesity.

Example 1: Propofol

For propofol, researchers performed a population pharmacokinetic meta-analysis with data from morbidly obese adults, adolescents, and children and their nonobese controls (body weight 37–184 kg, age 9–79 years) (77). In this analysis, propofol clearance was found to increase with body weight according to a power function. Age was identified and implemented as a second covariate using a bilinear function with two distinct slopes, reflecting an initial increase and, at the age of 41 years, a subsequent decrease in clearance (**Figure 5**).

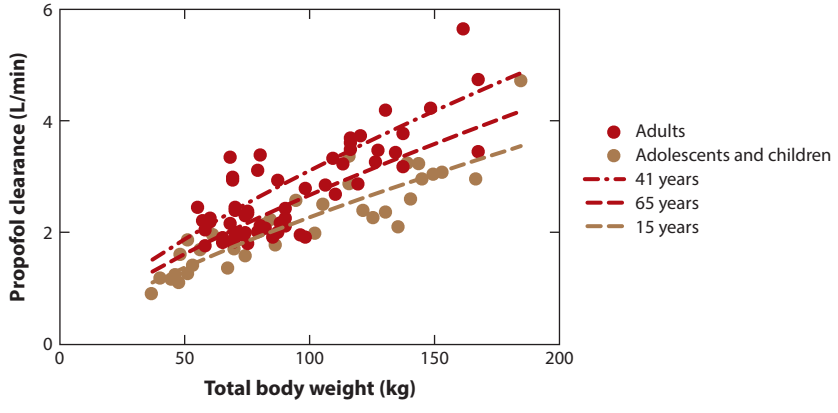

Figure 5

Individual post hoc propofol clearance estimates versus total body weight for morbidly obese adults and their nonobese controls (*red circles*) and morbidly obese adolescents and children and their nonobese controls (*brown circles*) ($n = 94$). The dashed lines indicate the population clearance values for 15, 41, and 65 years. Figure adapted from Reference 77 with permission.

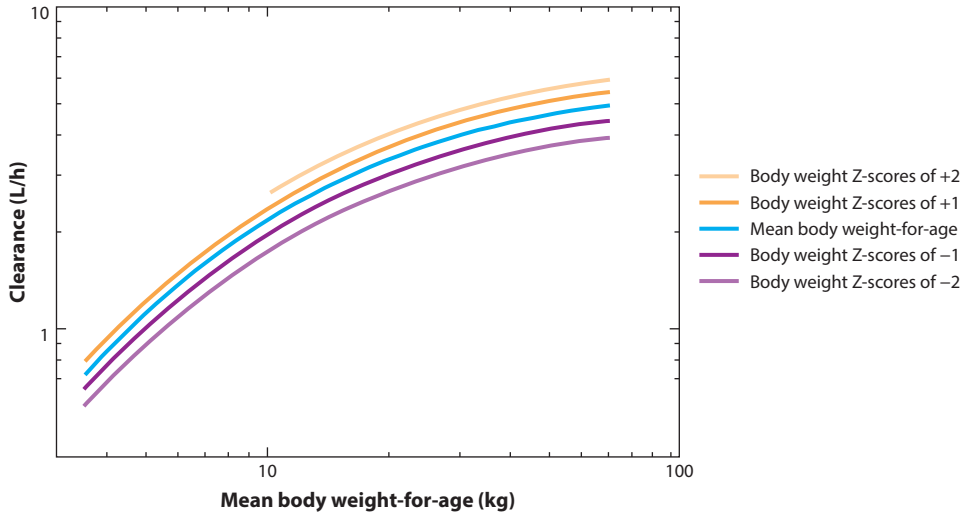

Figure 6

Busulfan clearance versus mean body weight-for-age for an exploratory model of overweight and underweight for children of all ages. In the model, a function for body weight due to growth (described using mean body weight-for-age, *blue line*) and a function for body weight due to under- and overweight (described using the body weight Z-score, *orange and purple lines*) were implemented. Orange lines represent body weight Z-scores of +1 (*dark orange*) and +2 (*light orange*), and purple lines represent body weight Z-scores of −1 (*dark purple*) and −2 (*light purple*). Figure adapted from Reference 86 with permission.

Example 2: Busulfan

In another study, investigators determined busulfan concentrations from a large population of underweight, normal-weight, and overweight children, adolescents, and adults (0.1–35 years) (115). This study used a previously derived, body weight–driven, pharmacokinetic model for busulfan in children of all ages (116). The results showed that the derived model (116) proved equally predictive in normal-weight, underweight, and overweight children (115). In addition, Bartelink et al. (115, 116) developed an exploratory model in which the body weight of each patient was considered to be composed of two parts: (*a*) physiological body weight related to growth (mean body weight-for-age) and (*b*) overweight, i.e., body weight related to under/overweight for a certain age (body weight Z-score) (**Figure 6**). Despite adequate performance of this exploratory model in which weight as a result of growth and obesity was disentangled (**Figure 6**), the model was not superior over the simple, weight-based model (115, 116).

To capture the entire developmental change in clearance across the pediatric age range, this pharmacokinetic analysis of busulfan in over- and underweight children of all ages used an advanced power function based on body weight in which the exponent was allowed to change with body weight (116, 117). This advanced power function was needed because very young infants were also included in the busulfan analysis, whereas the propofol analysis did not consider children younger than 9 years of age (77). When this function was used for busulfan, the data were adequately described, and no influence of age could be identified. In contrast, for propofol, a bilinear, age-based function with two distinct slopes was found (**Figure 5**) (77). The reason for this difference may be in part that, for the busulfan analysis, no patients above 35 years were included (115). For busulfan, these results imply that within the ranges of age and weight studied, dosing in children can be based on actual body weight, irrespective of the level of over- or underweight (115, 116).

In conclusion, although very limited pharmacokinetic and dosing information is available in obese children (105–107), we present two approaches on how to analyze data from children varying in age and degree of obesity (**Figures 5** and **6**). Future clinical studies should focus on the pharmacokinetics and pharmacodynamics of commonly used drugs in obese and morbidly obese children and adolescents to expand our knowledge in this clinically important area. Such studies should perform proper evaluations of the exact influence of weight resulting from growth, obesity, and age. As these evaluations may be complicated because of the interrelation between weight and age in different manners, they should use advanced validation frameworks, such as those described for pediatric pharmacokinetic analyses (118).

PERSPECTIVES

To predict the optimal dose for each drug in the obese, well-designed clinical studies on drug disposition in obese adults and children upon oral and intravenous administration are needed. Future research should also focus on the characterization of physiological concepts that can be used across drugs. From this overview, it is clear that for none of the parameters of bioavailability, volume of distribution, or clearance, a general covariate model with one size descriptor and one allometric exponent can be defined without paying attention to the nature of the compound involved, including the route of elimination. In this respect, physiologically based modeling principles that take into account both drug characteristics and physiological changes in the obese body are of large importance.

For obesity-related changes in clearance, a recently reported, semiphysiological approach applied in children, in which information for one drug was used to predict changes for another drug sharing the same metabolic or elimination pathway, may deserve attention. Using this approach, the maturation function for glucuronidation of morphine in young children (119, 120) was found to adequately predict the maturation in zidovudine glucuronidation in infants (121). As the physicochemical drug parameters were not found to affect this maturation profile, researchers concluded that this maturation function for glucuronidation can also be used for other substrates of this enzyme (122). This approach of between-drug predictions was also applied to renally excreted drugs in 0.5–5 kg neonates on the basis of a model derived for amikacin (123). This model has recently been extended to older children and adults (124) to obtain adequate predictions for other renally excreted drugs (125, 126).

To predict volumes of distribution in the obese, investigators need to take into account both physicochemical properties and physiological changes in the obese body. Most recently, a new covariate relation that integrates body weight and LBW as covariates, with a weighting factor depending on the physicochemical properties of the drug, was proposed to predict volume of distribution at steady state (127). Even though this approach was applied to only a limited number of obese individuals weighing below 100 kg, it deserves further exploration in the obese population, particularly because this approach to covariate modeling led to similar results as a whole-body, physiologically based pharmacokinetic model (127).

CONCLUSION

In conclusion, although studies are particularly needed on absorption and distribution of drugs in obese individuals, some insight has been gained into changes in important metabolic and elimination pathways in obesity. For obese children, investigators need to perform clinical studies for which the proposed models (77, 115) can be used to analyze the data. Future research should

focus on the characterization of physiological concepts to predict the optimal dose for each drug in the obese.

DISCLOSURE STATEMENT

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