REVIEW ARTICLES

Antimicrobial Dosing in Obese Patients

Rebecca Wurtz, Gail Itokazu, and Keith Rodvold

From the Department of Medicine, Evanston Hospital, Evanston; and the Department of Medicine, Northwestern University Medical School, Cook County Hospital, and University of Illinois at Chicago College of Pharmacy, Chicago, Illinois

Although the dose of some drugs is commonly adjusted for weight, weight-related dosage adjustments are rarely made for most antimicrobials. We reviewed the English-language literature on antimicrobial pharmacokinetics and dosing in obesity. Although there are many potential pharmacokinetic consequences of obesity, the actual effect on the pharmacokinetics and clinical efficacy of most antimicrobials is unknown. Since ~30% of adipose is water, an empirical approach is use of the Devine formula to calculate ideal body weight (IBW), to which is added a dosing weight correction factor (DWCF) of 0.3 times the difference between actual body weight (ABW) and IBW (IBW + 0.3 × [ABW-IBW]) to arrive at a weight on which to base dosage of hydrophilic antibiotics. No studies confirm this approach for β-lactam drugs. Clinical studies suggest a DWCF of ~0.40 for aminoglycosides and 0.45 for quinolones. Final dosage adjustments for antimicrobials with a narrow toxic-therapeutic window should be based on serum concentrations.

Although the dose of some medications—including cancer chemotherapeutic agents, anesthetics, and more recently heparin [1–9]—is commonly adjusted for weight, weight-related dosage adjustments for antimicrobials are rarely made. Distribution, metabolism, and clearance of many drugs are altered by physiological changes associated with obesity (table 1). Are antimicrobial pharmacokinetics altered in obese patients? Should their antimicrobial dose be increased? If so, should the adjustment be based on actual body weight (ABW) or on a percentage of ABW? After treating several patients who weighed 200% or more of their ideal body weights (IBWs), we reviewed the English-language literature for information on antimicrobial pharmacokinetics and dosing in obesity in an attempt to optimize antimicrobial management.

Methods

We used three computerized MEDLINE search programs (Silver Platter, OVID, and Grateful Med) and the International Pharmaceutical Abstracts to identify articles in the English-language literature from 1966 to 1996, using specific antimicrobial names and the subject headings and key words *pharmacokinetics, obesity,* and *morbid obesity* as cross-references. We also retrieved references cited in articles identified by the computer search and in pharmacokinetics textbooks.

Received 2 April 1996; revised 7 January 1997.

Reprints or correspondence: Dr. Rebecca Wurtz, Evanston Hospital, 2650 Ridge Avenue, Evanston, Illinois 60201.

Clinical Infectious Diseases 1997; 25:112–8

1058–4838/97/2501–0017$03.00

Ideal Body Weight, Obesity, Body Surface Area, and Body Mass Index

Equations to calculate IBWs for men and women are given in table 2 (curiously, the equations mix metric and standard measures) [10–12]. The commonly used Devine formula [10] defines IBW for men as 50 kg plus 2.3 times the height in inches over 60 inches; for women, a base weight of 45 kg is used instead. While there are only a handful of definitions of IBW [10–13], there are many definitions of obesity [8, 14]; one frequently used definition is body fat contents of 25% and ⩾30% of ABW for men and women, respectively [8]. A common definition of morbid or extreme obesity is weight exceeding 200% of IBW [8].

Body surface area (BSA) is used as the basis for calculating cancer chemotherapy doses, and some researchers have advocated the use of BSA to calculate antimicrobial dose [15–17]. One study showed that the standard formula for calculating BSA in lean subjects [18] still applies for extremely obese subjects [19]. However, with the exception of calculating acyclovir doses for children, BSA is not used in antimicrobial dosing, and no studies have demonstrated that use of BSA optimally predicts serum antimicrobial levels in obese subjects [20].

Body mass index, the weight in kilograms divided by height in meters squared, has also been advocated as a basis for calculating drug dosage, but a study by Traynor et al. [21] demonstrated that using IBW as the basis for calculating aminoglycoside dosing was as accurate as using body mass index. Abernethy and Greenblatt have shown that body mass index and percentage of IBW correlate well [2]. For clinical purposes, calculating IBW on the basis of the widely used Devine formula [10] is most convenient. In most of the pharmacokinetic studies

Table 1. Obesity-associated physiological changes with potential consequences for antimicrobial pharmacokinetics.

•Increased body mass, including both lean body mass and adipose tissue
•Increased cardiac output and blood volume
•Increased renal clearance
•Hepatic metabolic changes
•Changes in serum protein levels

cited here, the authors report either ABWs or percentages of IBWs (based on the Devine formula).

Animal Models

The disposition of drugs in obesity is studied with use of several animal models, including the genetically obese (Zucker) rat and the overfed (Sprague-Dawley) rat. Of these two, the overfed rat more closely models the changes in body composition and organ function that occur in obese humans [22, 23]. Animal models have been used to study antimicrobial disposition [24–30].

Pharmacokinetic Considerations Specific to Obesity

Obesity causes many physiological changes, some of which may negate the pharmacokinetic consequences of others; the net pharmacological significance is uncertain. There are four general considerations in evaluating pharmacokinetics in obesity: absorption, distribution, metabolism, and elimination. It is not known if absorption, whether from oral or intramuscular sites, is changed by obesity. Although hemodynamic studies performed by Alexander et al. [31] found that, compared with lean controls, obese subjects had a greater splanchnic blood flow, there is no evidence that the oral absorption of drugs is increased in obesity. A report by Cockshott et al. showed that most ''intramuscular'' injections are actually ''intralipomatous'' [32]; the kinetics of drug absorption from adipose are not known.

The volume and speed of drug distribution are influenced by many factors, including mass, blood flow to tissues, protein and tissue binding, and kinetics of elimination of drug from tissue [33, 34]. The relative importance of each of these factors varies with the physical and chemical characteristics of the drug. In assessing the distribution of drugs in obese individuals, the lipid partition coefficient, a measure of the tendency of a drug to localize in lipid tissue, is used [34]. However, lipophilic compounds do not always have larger volumes of distribution in obese patients [33].

Most antimicrobials are polar, or hydrophilic, distributing well in water but not in adipose. The water content in adipose is ~30% of that in other tissues [35]; thus, the volume of distribution for hydrophilic drugs may be only 0.30 of the volume of distribution in other tissues. Distribution of hydrophilic antimicrobials into water in adipose tissue may warrant increasing the dose in proportion to the excess in body weight, with use of a dosing weight correction factor (DWCF):

$$\text{Dosing weight} = \text{DWCF}(\text{ABW} - \text{IBW}) + \text{IBW}$$

In this equation, the DWCF is multiplied by the excess body weight (i.e., ABW − IBW), and the product is added to the IBW to arrive at a weight on which to base dosage. Use of a DWCF for a lipophilic antibiotic such as amphotericin may result in a significant underdosage, while use of ABW in dosing an antimicrobial that distributes only into water may result in a significant overdosage. Few studies have systematically assessed DWCFs.

Drugs bind to three major serum proteins: albumin, α_1-acid glycoprotein, and lipoproteins [8]. Since bound drug is generally unavailable for hepatic extraction, for metabolism, and for renal excretion, increased protein binding may result in decreased metabolism or clearance. Most antimicrobials bind to albumin [36]; albumin levels are not altered in obesity [37]. The levels of α_1-acid glycoprotein may increase in morbid obesity [27]. Morita and Yamaji [38] noted a significant positive correlation between protein binding of vancomycin and levels of α_1-acid glycoprotein.

Obese people also have increased levels of lipoproteins, triglycerides, cholesterol, and free fatty acids [7, 8, 39, 40], which bind to serum proteins such as albumin, inhibiting protein binding of drugs. In vitro studies by Suh et al. [41] found that high levels of free fatty acids significantly decreased the protein binding of cefamandole, dicloxacillin, and sulfamethoxazole and increased protein binding of benzylpenicillin, cephalothin, and cefoxitin. Amphotericin circulates bound to lipoproteins as well as other proteins [42].

Koldin et al. [30] studied the toxicity of amphotericin B in hypercholesterolemic rabbits vs. normal rabbits and concluded that there was no difference in toxicity. Amphotericin is less toxic to pig kidney cells when associated with high-density lipoproteins than when associated with low-density lipoproteins [43], and it is less toxic to mice with elevated levels of triglycerides [44]. The clinical significance of changes in protein binding by antimicrobials in obesity is unknown.

Table 2. Equations for ideal body weight (IBW) or mass.

Reference	Equation
[10]	IBW (kg) for men = 50 + (2.3 × height in inches over 60″)
	IBW (kg) for women = 45 + (2.3 × height in inches over 60″)
[11]	IBW (kg) for men = 52 + (1.9 × height in inches over 60″)
	IBW (kg) for women = 49 + (1.7 × height in inches over 60″)
[12]	Ideal body mass (kg) for children = 2.396 $e^{0.01863}$ × height in cm

Histopathologic changes in the liver (fibrosis, cirrhosis, fatty infiltration) and alterations in cytochrome activity may result from obesity and could affect hepatic drug metabolism [8, 45–49]. However, there have been no studies evaluating the consequences of obesity-associated hepatic changes specifically for antimicrobials. Phase I hepatic metabolic reactions (oxidation, reduction, hydrolysis) are substrate-dependent and are usually increased or unchanged in obesity [8]. Metronidazole, clindamycin, erythromycin, and clarithromycin are metabolized by phase I reactions [50, 51]. In contrast, metabolism of drugs by some phase II reactions (conjugation by sulfation or glucuronidation) is consistently increased in obesity [8, 52]. Zidovudine is metabolized by glucuronidation [53].

Compared with lean controls, obese patients have a higher creatinine clearance (CrCl) [24, 54]. The exact cause of the increased clearance in obese humans is unknown, although possible reasons include an increase in the number or size of nephrons [55] and an increase in blood flow (due to increased blood volume and cardiac output) to the kidney [56].

Equations used in clinical practice to estimate CrCl do not accurately predict the higher CrCl observed in obese humans [24]. In a group of 43 morbidly obese men and women, CrCl estimates that included weight as a variable were inaccurate when compared with estimates from methods using a 24-hour urine collection and serum creatinine determinations. When ABW was used, the CrCl was overestimated, and when IBW was used, the CrCl was underestimated [54]. Thus, Salazar and Corcoran proposed alternative formulas (based on animal models) for CrCl in obese subjects, to more accurately predict the elimination of drugs primarily excreted by glomerular filtration [24]. These equations require clinical confirmation.

Pharmacokinetics may be different in the extremely or morbidly obese (an ABW of ⩾200% of IBW) than in the mildly or moderately obese [8], but no comparative studies have been performed with regard to antibiotics.

In sum, although there are many potential pharmacokinetic consequences of obesity, the actual consequences for the pharmacokinetics and clinical efficacy of antimicrobials in humans are largely unknown.

Table 3. Reported adjustments of antimicrobial dosing in obesity.

Type of antimicrobial	Weight for calculating dose	Reference
β-Lactam drug	Empirical: IBW + 0.3(ABW-IBW)	. . .*
Aminoglycoside		
Gentamicin	IBW + 0.43(ABW-IBW)	[21]
Tobramycin	IBW + 0.58(ABW-IBW)	[57]
For children	IBW + 0.40(ABW-IBW)	[58]
Amikacin	IBW + 0.38(ABW-IBW)	[59]
Vancomycin	ABW	[60]
Sulfonamide	IBW†	[61]
Quinolone		
Ciprofloxacin	IBW + 0.45(ABW-IBW)	[62, 63]
Macrolide	IBW	[64]
Mycobacterial	IBW	[65] (single case report)
Antifungal		
Amphotericin	Empirical: ABW	. . .*
Flucytosine	IBW	[66] (single case report)
Fluconazole	6 mg/kg qd	[67]
Antiviral		
Acyclovir	IBW	[68]
Zidovudine	ABW	[69] (2 case reports of pregnant women)

NOTE. ABW = actual body weight; IBW = ideal body weight.
* No clinical studies confirm this approach.
† May vary for different sulfonamides.

Individual Antibiotics (Table 3)

β-Lactam drugs. In general, β-lactam drugs are protein-bound and hydrophilic and do not diffuse well into adipose. The pharmacokinetics of β-lactam drugs in obesity have not been studied systematically; most of the data reviewed here are derived from small studies or single case reports. Although an empirical DWCF of 0.30 can be suggested on the basis of the water composition of adipose, there are no clinical study data to confirm this approach. While β-lactam drugs are not associated with concentration-dependent killing, a serum or tissue concentration below an MIC might lead to antibiotic failure.

Miskowiak and colleagues looked at the absorption of oral penicillin before and after gastroplasty for morbid obesity in patients initially weighing an average of 117 kg [70]. They found that absorption was not altered by obesity or by gastroplasty; serum levels were the same before and after the surgery and were within the recommended therapeutic range for penicillin [70].

Kampmann and colleagues studied the pharmacokinetics of iv and oral ampicillin in patients who weighed an average of 131 kg before gastric bypass [71]. They found that the volume of distribution was 0.60 L/kg before surgery, compared with 0.41 L/kg in the same patients 1 year later, when the average weight was 87 kg. This suggests that ampicillin is distributed in adipose tissue to some extent. They did not report the serum concentrations.

Yuk et al. measured nafcillin serum levels in a patient with endocarditis who weighed 162 kg and concluded that there was a significant increase in the volume of distribution [72]. They suggested that a modified dosing regimen, such as 3 g every 6 hours, was needed to achieve the same drug concentration as observed in nonobese patients receiving 2 g every 4 hours.

Pories et al. [73] studied the tissue levels of cefazolin following perioperative administration of prophylactic cefazolin in obese patients weighing an average of 129 kg. They concluded that 1 g given iv 2 hours before surgery and again at induction

of anesthesia and 500 mg given every 6 hours for eight doses yielded adequate tissue levels [73]. However, Forse and colleagues [74] found that a 1-g infusion in patients weighing an average of 127.3 kg yielded serum levels below the MICs for many surgically relevant bacteria. This study was the only one that looked at the clinical outcome of adjusting the dose upward for obese patients. Surgical wound infection rates dropped from 16.5% to 5.6% when the prophylactic dose of cefazolin was increased from 1 g to 2 g for obese patients.

Mann and Buchwald studied the distribution and elimination of cefamandole during and after gastric bypass surgery in individuals weighing a mean of 230% of IBW [16]. They found that in their subjects the volume of distribution and clearance of cefamandole were higher, and they concluded that the surgical-prophylaxis dosage of cefamandole should be 2 g at induction of anesthesia and every 3 hours thereafter during prolonged procedures.

Chiba et al. [17] studied the pharmacokinetics of cefotiam in sumo wrestlers weighing 130%–220% of IBW. They found that the volume of distribution was twice that for people weighing 100% of IBW. When kinetic parameters were adjusted on the basis of BSA, the differences in volume of distribution and clearance were not significant. They concluded that the dose of cefotiam should be calculated on the basis of BSA for morbidly obese athletes.

Yost and Derendorf found that the volume of distribution of cefotaxime, a very hydrophilic drug, increased by 50% and its clearance increased by 25% in patients weighing 190%–210% of IBW [15]. Despite these changes, the authors did not believe that it was necessary to adjust the dose of cefotaxime. Brown and Sands concluded that ceftriaxone should not be given in a dosage of 1 g every 24 hours to morbidly obese patients, but they did not state the basis for this opinion [75].

Aminoglycosides. Determining the daily dose of an aminoglycoside with use of ABW may result in higher than desirable serum concentrations, while doses based on IBW may lead to subtherapeutic serum concentrations [76]. These findings are consistent with the fact that aminoglycosides are primarily distributed into extracellular fluid.

Several small studies have determined DWCFs for aminoglycosides ranging from 0.38 to 0.58 [21, 57, 59, 76–78], although Bauer et al. [76] found a wide range in DWCFs between individual patients. In these studies, obese patients weighed 125%–200% of IBW; were infected, presumed to be infected [21, 63], or uninfected [57, 59, 77–80]; and were given a single dose [78] or multiple doses of gentamicin [21, 76], tobramycin [21, 76], or amikacin [77]. Traynor et al. studied 1,708 patients (weighing an average of 150% of IBW) and calculated a DWCF of 0.43 [21]. However, given the broad range of DWCFs for individual patients [76], final dosage adjustments should be based on serum concentrations.

Although the clearance of aminoglycosides in obese humans is significantly higher than in lean controls [76], the larger volume of distribution in obese subjects (which prolongs elimination half-life) cancels out the effect of increased clearance, resulting in an elimination half-life that is similar for both obese and lean subjects. As a consequence, alteration in dosage interval is not necessary for obese individuals.

Human and animal data indicate that nephrotoxicity associated with aminoglycoside use is more common in obese subjects, perhaps because of an increased concentration of aminoglycoside in the kidneys [26, 60]. In one report, an increase was noted in the incidence of nephrotoxicity (as measured by a doubling of serum creatinine level) in mildly obese patients (with body mass indices of 27–29 kg/m^2), as compared with the incidence in control patients (whose body mass indices were 19–24 kg/m^2) [60]. More nephrotoxicity was observed in obese subjects despite the fact that their total aminoglycoside doses and duration of therapy were similar to those of the control subjects. Serum concentrations were maintained within the recommended ranges. One confounding factor, however, was the greater likelihood of obese patients to have received furosemide.

Vancomycin. Although two studies [55, 81] concluded that vancomycin doses for obese patients should be based on ABW, only one of these studies analyzed patients receiving vancomycin for therapeutic purposes [81]. Blouin et al. [55] studied six morbidly obese subjects and concluded that ABW should be used to determine vancomycin doses. Vance-Bryan and colleagues [81] studied vancomycin pharmacokinetics in 107 patients weighing 20% or more over their IBWs and also concluded that using empirical dosage regimens such as 1 g every 12 hours would produce suboptimal peak and trough vancomycin concentrations in the serum of obese patients. They recommended basing the dose on ABW and giving 20–30 mg/kg · d [81]. Nonstandard doses should be checked by measuring troughs and perhaps peaks.

Sulfonamides. Kaul and Ritschel demonstrated increased numbers of free fatty acids and decreased protein binding of sulfonamides in genetically obese Zucker rats [28, 29]. In their studies, however, the volume of distribution for various sulfonamide antibiotics depended on many factors, not simply protein binding [28]. In a study of three patients before and after intestinal bypass surgery for morbid obesity, Garrett and colleagues [61] showed that the volume of distribution for iv and oral sulfisoxazole and its N^4-acetylsulfisoxazole metabolite did not change despite weight loss of as much as 44% of total body weight. Renal clearance of sulfisoxazole was essentially constant, but that of the N^4-acetylsulfisoxazole metabolite decreased as total weight decreased. The investigators concluded that the sulfisoxazole dose should not be determined on the basis of weight.

Quinolones. Ciprofloxacin is distributed less to adipose than to other tissues [62], a circumstance suggesting that calculating a dose on the basis of ABW would overestimate the dose. Allard and colleagues studied the volume of distribution for ciprofloxacin and found that it was 23% greater in obese subjects weighing an average of 160% of their IBW than in

nonobese controls [62]. They also determined that ciprofloxacin clearance was increased. They found that maximum ciprofloxacin plasma concentrations were lower in obese subjects than in nonobese ones after a 400-mg iv infusion, but the concentrations were still within the recommended therapeutic range. Allard et al. [62] concluded that the ciprofloxacin dose should be based on IBW plus a DWCF of 0.45.

Caldwell and Nilsen [63] described a patient weighing 250 kg who had an infection requiring iv ciprofloxacin. They used the formula of Allard et al. [62] and measured peak serum ciprofloxacin level 20 minutes after completion of a 60-minute infusion on day 4 of therapy; the level was 4.2 mg/L, within the recommended therapeutic range of 0.5–5.0 mg/L.

Macrolides. Little has been written about macrolide dosing in obesity. Prince and colleagues administered 250 mg of oral erythromycin base to seven obese adults, weighing an average of 157.7 kg, prior to bariatric surgery [64]. This dose resulted in a mean peak concentration of 1.04 μg/mL, a peak concentration similar to that in nonobese adults [82].

Mycobacterial antibiotics. In a single case report of a subject weighing 190% of his IBW, Geiseler et al. noted that dosing rifampin, streptomycin, ethambutol, and pyrazinamide on the basis of IBW yielded levels in the therapeutic range [65]. Isoniazid levels were not measured.

Antifungals. Amphotericin is a highly lipophilic drug and has traditionally been dosed on a weight basis, with doses ranging from 0.5 to 1.5 mg/kg, depending on the severity of the infection. There is a single case report of an obese patient with nonmeningeal cryptococcal infection successfully treated with amphotericin B plus flucytosine, followed by oral fluconazole [66]. The dose of amphotericin was based on ABW; levels were not determined. The dose of flucytosine was based on IBW, and serum levels were maintained within the desired therapeutic range, without hematologic toxicity.

Koldin and colleagues [30], using a rabbit model made hypercholesterolemic by diet, found that there was no difference in the level of amphotericin B toxicity in comparison with that in normal rabbits. When amphotericin B was given in a mixture with human low-density lipoproteins, it was more toxic than when given without the lipoproteins, but this level of toxicity was not compared with that in rabbits given human lipoproteins alone.

Vadiei et al. [27] found that volume of distribution and clearance of amphotericin B were markedly decreased and renal toxicity increased in obese Zucker rats with hyperlipoproteinemia as compared with those in lean litter mates; they attributed this to lipoprotein binding of amphotericin B in the vascular space. Chavanet et al. found that an increase in serum triglycerides—but not cholesterol in very-low-density and low-density lipoproteins—resulted in decreased renal toxicity in a mouse model [44]. The net clinical consequence of these observations is unclear.

There is less experience with the pharmacokinetics of azoles. In a recent article comparing amphotericin and fluconazole for the treatment of candidemia, Rex et al. specified that patients being treated with fluconazole and weighing >90 kg received 6 mg/kg [67]. No rationale was given for that dose.

Antivirals. A study in which a single dose of acyclovir was administered to seven uninfected subjects weighing an average of 203% of IBW demonstrated that pharmacokinetic parameters were not significantly different from those in a normal-weight control group; the authors concluded that doses should be based on IBW [68]. Acosta and colleagues [69] found that ''standard doses'' of zidovudine (200 mg and 100 mg, respectively) yielded lower-than-expected plasma concentrations in two women weighing 142.5 kg and 128 kg; the conclusion with regard to dosing in obesity is complicated by the fact that the women were pregnant.

Children

Antibiotic dosage is routinely calculated on the basis of weight for children, although some authors believe that BSA is more appropriate [20]. Should IBW (table 2) [12] or ABW be used for obese children? For children, the difference between IBW and ABW is usually relatively small [83]. Dudley concluded that IBW is probably appropriate for most situations [83].

Koshida et al. studied the volume of distribution for tobramycin and cefazolin in a group of children with an average ABW of 161% of IBW, and they concluded that the loading dose of cefazolin should be calculated on the basis of ABW, while the initial tobramycin dose should be calculated on the basis of the IBW plus a DWCF of 0.40(ABW–IBW) [58].

Surgical Prophylaxis

Numerous studies have identified obesity as a factor in postoperative wound infections; this is usually attributed to mechanical complications, but it is possible that antibiotics do not achieve effective levels in obese patients [16, 74]. Pories et al. [73] concluded that 1 g of prophylactic cefazolin given 2 hours preoperatively and again at induction of anesthesia to morbidly obese patients before gastric bypass surgery yielded adequate antibiotic concentrations in tissue, but Forse et al. [74] suggested a dose of 2 g iv (instead of 1 g iv or im) at induction of anesthesia [73].

Mann and Buchwald studied cefamandole levels in serum, adipose tissue, and wound drainage during and after surgery in morbidly obese patients and concluded that the surgical-prophylaxis dose of cefamandole should be 2 g at induction of anesthesia and every 3 hours thereafter during prolonged procedures [16].

Conclusions

With the exception of the aminoglycosides, the net effect of the pharmacokinetic consequences of obesity has not been

rigorously studied with regard to antimicrobials. Approximately 30% of adipose is water, and an empirical approach uses the Devine formula [10] to calculate IBW and then adds a DWCF of 0.3 times the difference between ABW and IBW (IBW + 0.3 × [ABW−IBW]) to arrive at a weight on which to base dosage for hydrophilic antibiotics such as β-lactam drugs. No clinical studies have confirmed this approach.

Clinical studies suggest a DWCF of ~0.40 for aminoglycosides and ~0.45 for quinolones. Given the broad range of levels for individual patients, final dosage adjustments for antimicrobials with a narrow toxic-therapeutic window should be based on serum concentrations.

References

1. Abernethy DR, Greenblatt DJ. Pharmacokinetics of drugs in obesity. Clin Pharmacokinet **1982**; 7:108–24.
2. Abernethy DR, Greenblatt DJ. Drug disposition in obese humans. Clin Pharmacokinet **1986**; 11:199–213.
3. Cheymol G. Comparative pharmacokinetics of intravenous propranolol in obese and normal volunteers. J Clin Pharmacol **1987**; 27:874–9.
4. Cheymol G. Clinical pharmacokinetics of drugs in obesity. Clin Pharmacokinet **1993**; 25:103–14.
5. Smith TJ, Desch CE. Neutropenia-wise and pound-foolish: safe and effective chemotherapy in massively obese patients. S Med J **1991**; 84: 883–5.
6. Cox J, Penn N, Masood M, Hancock AK, Parker D. Drug overdose—a hidden hazard of obesity. J R Soc Med **1987**; 80:708–9.
7. Blouin RA, Kolpek JH, Mann HJ. Influence of obesity on drug disposition. Clin Pharm **1987**; 6:706–14.
8. Blouin RA, Chandler MH. Special pharmacokinetic considerations in the obese. In: Evan WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics: principles of therapeutic drug monitoring. 3rd ed. Spokane, Washington: Applied Therapeutics, **1992**.
9. Rashcke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a ''standard care'' nomogram: a randomized controlled trial. Ann Intern Med **1993**; 118: 874–81.
10. Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm **1974**; 8:650–5.
11. Robinson JD, Lupkiewicz SM, Palenik L, Lopez LM, Arlet M. Determination of ideal body weight for drug dosage calculations. Am J Hosp Pharm **1983**; 40:1016–9.
12. Traub SL, Kichen L. Estimating ideal body mass in children. Am J Hosp Pharm **1983**; 40:107–10.
13. Metropolitan Life Insurance Company. Metropolitan height and weight tables. Stat Bull Metropol Life Insur Co **1983**; 64:2–9.
14. Gray DS. Diagnosis and prevalence of obesity. Med Clin North Am **1989**; 73:1–13.
15. Yost RL, Derendorf H. Disposition of cefotaxime and its desacetyl metabolite in morbidly obese male and female subjects. Ther Drug Monit **1986**; 8:189–94.
16. Mann HJ, Buchwald H. Cefamandole distribution in serum, adipose tissue, and wound drainage in morbidly obese patients. Drug Intell Clin Pharm **1986**; 20:869–73.
17. Chiba K, Tsuchiya M, Kato J, Ochi K, Kawa Z, Ishizaki T. Cefotiam disposition in markedly obese athlete patients, Japanese sumo wrestlers. Antimicrob Agents Chemother **1989**; 33:1188–92.
18. DuBois D, DuBois EF. The measurement of the surface area of man. Arch Intern Med **1915**; 15:868–81.
19. Tucker GR, Alexander JK. Estimation of body surface area of extremely obese human subjects. J Appl Phys **1960**; 15:781–4.
20. Milsap RL, Hill MR, Szefer SJ. Special pharmacokinetic considerations in children. In: Evan WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics. 3rd ed. Spokane, Washington: Applied Therapeutics, **1992**.
21. Traynor AM, Nafziger AN, Bertino JS. Aminoglycoside dosing weight correction factors for patients of various body sizes. Antimicrob Agents Chemother **1995**; 39:545–8.
22. Corcoran GB, Salazar DE, Sorge CL. Pharmacokinetic characteristics of the obese overfed rat. Int J Obes **1989**; 13:69–79.
23. Shum L, Jusko WJ. Theophylline disposition in obese rats. J Pharmacol Exp Ther **1984**; 228:380–386.
24. Salazar DE, Corcoran GB. Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med **1988**; 84:1053–60.
25. Corcoran GB, Salazar DE. Obesity as a risk factor in drug-induced organ injury. IV. Increased gentamicin nephrotoxicity in the obese overfed rat. J Pharmacol Exp Ther **1989**; 248:17–22.
26. Salazar DE, Schentag JJ, Corcoran GB. Obesity as a risk factor in drug-induced organ injury. Drug Metab Dispos Biol Fate Chem **1992**; 20: 402–6.
27. Vadiei K, Lopez-Berestein G, Luke DR. Disposition and toxicity of amphotericin-B in the hyperlipidemic Zucker rat model. Int J Obes **1990**; 14:465–72.
28. Kaul S, Ritschel WA. Influence of obesity on sulfonamide disposition in Zucker rats. Eur J Drug Metab Pharmacokinet **1988**; 13:273–83.
29. Kaul S, Ritschel WA. Free fatty acids and the binding of sulfonamides in the serum of genetically obese Zucker rats. Methods Find Exp Clin Pharmacol **1987**; 9:317–20.
30. Koldin MH, Kobayashi GS, Brajtburg J, Medoff G. Effects of elevation of serum cholesterol and administration of amphotericin-B complexed to lipoproteins on amphotericin-B-induced toxicity in rabbits. Antimicrob Agents Chemother **1985**; 28:144–5.
31. Alexander JK, Dennis EW, Smith WG, Amad KH, Duncan WC, Austin RC. Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. Cardivascular Research Center Bulletin **1962–1963**; 1:39–44.
32. Cockshott WP, Thompson GT, Howlett LJ, Seeley ET. Intramuscular or intralipomatous injections? N Engl J Med **1982**; 307:356–8.
33. Bickel MH. Factors affecting the storage of drugs and other xenobiotics in adipose tissue. Adv Drug Res **1994**; 25:55–86.
34. Ritschel WA, Kaul S. Prediction of apparent volume of distribution in obesity. Methods Find Exp Clin Pharmacol **1986**; 8:239–47.
35. Gunderson K, Shen G. Total body water in obesity. Am J Clin Nutr **1966**; 19:77–83.
36. Craig WA, Suh B. Protein binding and the antimicrobial effects: methods for the determination of protein binding. In: Lorian V, ed. Antibiotics in laboratory medicine. 3rd ed. Baltimore: Williams & Wilkins, **1991**.
37. Benedek IH, Blouin RA, McNamara PJ. Serum protein binding and the role of increased α_1-acid glycoprotein in moderately obese male subjects. Br J Clin Pharmacol **1984**; 18:941–6.
38. Morita K, Yamaji A. Changes in the serum protein binding of vancomycin in patients with methicillin resistant *Staphylococcus aureus* infection: the role of serum α_1-acid glycoprotein levels. Ther Drug Monit **1995**; 17:107–12.
39. Mavrelis PG, Ammon HV, Gleysteen JJ, Komorowski RA, Charaf UK. Hepatic free fatty acids in alcoholic liver disease and morbid obesity. Hepatology **1983**; 3:226–31.
40. Wasan KM, Lopez-Berestein G. The influence of serum lipoproteins on the pharmacokinetics and pharmacodynamics of lipophilic drugs and drug carriers. Arch Med Res **1993**; 24:395–401.
41. Suh B, Craig WA, England AC, Elliott RL. Effect of free fatty acids on protein binding of antimicrobial agents. J Infect Dis **1981**; 143:609–16.
42. Brajtburg J, Elberg S, Bolard J, et al. Interaction of plasma proteins and lipoproteins with amphotericin B. J Infect Dis **1984**; 149:986–97.
43. Wasan KM, Lopez-Berestein G. The interaction of liposomal amphotericin B and serum lipoproteins within the biological milieu. J Drug Targeting **1994**; 2:373–80.

44. Chavanet P, Joly V, Rigaud D, Bolard J, Carbon C, Yeni P. Influence of diet on experimental toxicity of amphotericin B deoxycholate. Antimicrob Agents Chemother **1994**;38:963–8.
45. Andersen T, Gludd C. Liver morphology in morbid obesity: a literature study. Int J Obes **1984**;8:97–106.
46. Braillon A, Capron JP, Herve MA, Degott C, Quenum C. Liver in obesity. Gut **1985**;26:133–9.
47. Hunt CM, Westerkam WR, Stave GM, Wilson JA. Hepatic cytochrome P-4503A (CYP3A) activity in the elderly. Mech Ageing Dev **1992**;64:189–99.
48. Westphal JF, Jehl F, Vetter D. Pharmacological, toxicologic, and microbiological consideration in the choice of initial antibiotic therapy for serious infections in patients with cirrhosis of the liver. Clin Infect Dis **1994**;18:324–35.
49. Adler M, Schaffner F. Fatty liver hepatitis and cirrhosis in obese patients. Am J Med **1979**;67:811–6.
50. Westphal JF, Brogard JM. Clinical pharmacokinetics of newer antibacterial agents in liver disease. Clin Pharmacokinet **1993**;24:46–58.
51. Sturgill MC, Rapp RP. Clarithromycin: review of a new macrolide antibiotic with improved microbiologic spectrum and favorable pharmacokinetic and adverse effect profiles. Ann Pharmacother **1992**;26:1099.
52. Abernethy DR, Greenblatt DJ, Divoll M, Shader RI. Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. J Lab Clin Med **1983**;101:873–80.
53. Moore KH, Raasch RH, Brouwer KL, et al. Pharmacokinetics and bioavailability of zidovudine and its glucuronidated metabolite in patients with human immunodeficiency virus infection and hepatic disease (AIDS Clinical Trials Group Protocol 062). Antimicrob Agents Chemother **1995**;39:2732–7.
54. Dionne RE, Bauer LA, Gibson GA, Griffen WO, Blouin RA. Estimating creatinine clearance in morbidly obese patients. Am J Hosp Pharm **1981**;38:841–4.
55. Blouin RA, Bauer LA, Miller DD, Record KE, Griffin WO. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother **1982**;21:575–8.
56. Stokholm KH, Brochner-Mortenson J, Holland-Carlsen PF. Increased glomerular filtration rate and adrenocortical function in obese women. Int J Obes **1980**;4:57–63.
57. Blouin RA, Mann HJ, Griffen WO Jr, Bauer LA, Record KE. Tobramycin pharmacokinetics in morbidly obese patients. Clin Pharmacol Ther **1979**;26:508–12.
58. Koshida R, Nakashima E, Taniguichi N, Tsuji A, Benet LZ, Ichimura F. Prediction of the distribution volumes of cefazolin and tobramycin in obese children based on physiological pharmacokinetic concepts. Pharm Res **1989**;6:486–91.
59. Bauer LA, Bouin RA, Griffen WO, Record KE, Bell RM. Amikacin pharmacokinetics in morbidly obese patients. Am J Hosp Pharm **1980**;37:519–22.
60. Corcoran GB, Salazar DE, Schentag JJ. Excessive aminoglycoside nephrotoxicity in obese patients. Am J Med **1988**;85:279.
61. Garrett ER, Suverkrup RS, Eberst K, Yost RL, O'Leary JP. Surgically affected sulfisoxazole pharmacokinetics in the morbidly obese. Biopharm Drug Dispos **1981**;2:329–65.
62. Allard S, Kinzig M, Boivin G, Sorgel F, LeBel M. Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Ther **1993**;54:368–73.
63. Caldwell JB, Nilsen AK. Intravenous ciprofloxacin dosing in a morbidly obese patient. Ann Pharmacother **1994**;28:806.
64. Prince RA, Pincheira JC, Mason EE, Printen KJ. Influence of bariatric surgery on erythromycin absorption. J Clin Pharmacol **1984**;24:523–7.
65. Geiseler PJ, Manis RD, Maddux MS. Dosage of antituberculous drugs in obese patients. Am Rev Respir Dis **1985**;131:944–6.
66. Gillum JG, Johnson M, Lavoie S, Venitz J. Flucytosine dosing in an obese patient with extrameningeal cryptococcal infection. Pharmacotherapy **1995**;15:251–3.
67. Rex JH, Bennett JE, Sugar A, et al. A randomized trial comparing fluconazole with amphotericin for the treatment of candidemia in patients without neutropenia. N Engl J Med **1994**;331:1325–30.
68. Davis RL, Quenzer RW, Weller S, Blum R. Acyclovir pharmacokinetics in morbid obesity [abstract 765]. In: Programs and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society for Microbiology, **1991**.
69. Acosta EP, Schwebke K, Henry K, Fletcher CV. Disposition of zidovudine in obese pregnant women with human immunodeficiency virus type 1 infection. J Infect Dis **1996**;174:673.
70. Miskowiak J, Andersen B, Nielsen VG. Absorption of oral pencillin before and after gastroplasty for morbid obesity. Pharmacology **1985**;31:115–20.
71. Kampmann JP, Klein H, Lumholtz B, Molholm JE. Ampicillin and prophylthiouracil pharmacokinetics in intestinal bypass patients followed up to one year after operation. Clin Pharmacokinet **1984**;9:168–76.
72. Yuk J, Nightingale CH, Sweeney K, Levitz RE, Quintiliani R. Pharmacokinetics of nafcillin in obesity. J Infect Dis **1988**;157:1088–9.
73. Pories WJ, van Rij AM, Burlingham BT, Fulghum RS, Meelheim D. Prophylactic cefazolin in gastric bypass surgery. Surgery **1981**;90:426–32.
74. Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. Surgery **1989**;106:750–7.
75. Brown RB, Sands M. One-gram intravenous ceftriaxone use in a large teaching hospital. Curr Ther Res **1989**;46:285–91.
76. Bauer LA, Edwards WAD, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur J Clin Pharmacol **1983**;24:643–7.
77. Blouin RA, Brouwer KL, Record KE, Griffen WO, Plezia PM, John W. Amikacin pharmacokinetics in morbidly obese patients undergoing gastric-bypass surgery. Clin Pharmacokinet **1985**;4:70–2.
78. Korsager S. Administration of gentamicin to obese patients. Int J Clin Pharmacol Ther Toxicol **1980**;18:549–53.
79. Schwartz SN, Pazin GJ, Lyon JA, Ho M, Pasculle AW. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. J Infect Dis **1978**;138:499–505.
80. Sketris I, Lesar T, Zaske DE, Cipolle RJ. Effect of obesity on gentamicin pharmacokinetics. J Clin Pharmacol **1982**;21:288–93.
81. Vance-Bryan K, Guay DR, Gilliland SS, Rodvold KA, Rotschafer JC. Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a bayesian forecasting technique. Antimicrob Agents Chemother **1993**;37:436–40.
82. Griffith RS, Black HR. A comparison of blood levels after oral administration of erythromycin and eythromycin estolate. Antibiot Chemother **1962**;12:398–403.
83. Dudley MN. Antibiotic dosing in obese children. Pediatr Infect Dis J **1993**;12:420.