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Pharmacokinetics of Antimicrobials in Obese Children

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Abstract

Introduction—Childhood obesity is common and results in substantial morbidity. The most commonly prescribed drugs in obese children are antibiotics. However, physiologic changes associated with childhood obesity can alter antibiotic pharmacokinetics and optimal body size measures to guide dosing in his population are ill defined. This combination can result in therapeutic failures or drug-related toxicities. This review summarizes pharmacokinetic information for antibiotics in obese children and implications for dosing.

Methods—We conducted a comprehensive literature search of PubMed, EMBASE, and International Pharmaceutical Abstracts to identify pharmacokinetic studies of antimicrobial agents in obese children. We included the following search terms: *obesity, pharmacokinetics, pharmacodynamics, drug toxicity, dosing, anti-infective agents, antiviral agents, and antifungal agents.*

Results—We identified four pharmacokinetic studies of antibiotics in obese children: one for cefazolin and tobramycin, one for gentamicin, and two for vancomycin. Only the cefazolin/tobramycin trial was prospective. The drugs studied differ in their tissue and body water distribution characteristics. Two of the studies (tobramycin and gentamicin) reported pharmacokinetic differences and required dosing modifications in obese children.

Discussion—The lack of pharmacokinetic studies in obese children is pronounced. The scarcity of pharmacokinetic data limits the ability to predict drug disposition using drug physicochemical properties and impedes a rational approach to selection of appropriate body size measures for dosing. Given this knowledge gap, additional trials in obese children are urgently needed and is a public health concern.

Conclusion—Pharmacokinetic studies of antimicrobials in obese children are desperately needed to guide dosing and avoid therapeutic failures or unwanted toxicities.

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Keywords

Pediatrics; obesity; antimicrobial agents; pharmacokinetics

Introduction

The World Health Organization defines obesity as body mass index (BMI)-for-age measurement > standard deviations above the reference median [1, 2]. The United States Centers for Disease Control defines obesity as BMI-for-age-and-sex >95th percentile [3]. In the United States and Europe, the prevalence of childhood obesity is 16.9% and 4–6% [4, 5]. Childhood obesity is common and associated with significant morbidity and mortality. Obese children are more likely to die prematurely or develop weight-related illnesses compared with their normal-weight peers [6, 7].

Obesity results in numerous changes to physiology and body composition that may affect drug disposition (Table 1). Pharmacokinetics (PK) can be altered in obesity through changes to volume of distribution (V) and clearance (CL), the primary determinants of drug dosing. Changes in body composition (increased fat mass per kg or per m²) in obese children may result in the need for dose adjustments using different measures of body size such as total/actual body weight (TBW), ideal body weight (IBW), adjusted body weight (ABW), or lean body weight (LBW). Poor outcomes for obese patients with certain life-threatening conditions may result from suboptimal dosing strategies; for example, suboptimal dosing of obese adult oncology patients and obese children following cardiopulmonary resuscitation may be responsible for under-dosing and reduced survival, respectively [22, 23].

Antibiotics comprise the class of medications most commonly prescribed in children [24]. Optimal dosing of these drugs in obese children is critical because such patients may be more susceptible to infection [25], and inappropriate dosing can lead to therapeutic failure, antibiotic resistance, and drug-related toxicity. This article will review the current PK information available for antibiotics in obese children and implications for dosing.

Methods

We searched PubMed, EMBASE, and International Pharmaceutical Abstracts databases for PK studies of antimicrobial agents in obese children (all years). We used combined search terms including *obesity*, *pharmacokinetics*, *pharmacodynamics*, *drug toxicity*, *dosing*, *anti-infective agents*, *antiviral agents*, and *antifungal agents*. We limited the search to children <18 years of age. We included studies if they provided PK data in obese children receiving an antimicrobial agent.

This review discusses the following body size descriptors: TBW (kg) = measured body weight; IBW (kg) = $2.3 \text{ kg} \times (\text{height (in)} - 60) + a$, where $a = 45.5 \text{ kg}$ for women and 50 kg for men; BMI (kg/m²) = $\text{TBW}/\text{height}^2$; LBW (kg) = $b \times \text{TBW} - (c \times \text{BMI} \times \text{TBW})$, where $b = 1.1$ for males and 1.07 for females, and $c = 0.0128$ for males and 0.0148 for females; ABW (kg) = $\text{IBW} + 0.4 \times (\text{TBW} - \text{IBW})$ [26–29]; and dosing weight = the weight used by the pharmacy to dispense the drug.

Results

The PubMed search strategy identified 90 articles, among which four studies of antimicrobial PK in obese children met the inclusion criteria. Searches of EMBASE and International Pharmaceutical Abstracts did not yield additional peer-reviewed articles beyond those found in PubMed. One conference abstract describing vancomycin PK in obese children was not included because insufficient study detail was provided. Drugs studied in obese children included cefazolin, tobramycin, gentamicin, and vancomycin (Table 2).

Cefazolin and tobramycin were studied prospectively in a study of five obese children 2–9 years of age (BMI >95 percentile), and serum PK results were compared with previous results from a study of six non-obese children of similar ages [30]. The dosing weight for obese participants in this study was obtained by calculating the mean of TBW and IBW, whereas non-obese participants were dosed based on TBW. Participants in both cohorts received a single 25 mg/kg dose of cefazolin by 30-minute intravenous (IV) infusion. Ten minutes after completion of the cefazolin infusion, tobramycin was infused over 30 minutes as a single 2 mg/kg dose. Cefazolin steady-state volume of distribution (V_{ss}) and CL normalized by TBW and protein-binding were not significantly different between obese and non-obese children. Tobramycin CL normalized by TBW was not significantly different between obese and non-obese children, but V_{ss} normalized by TBW was significantly lower in obese children compared with non-obese children ($p < 0.05$).

Gentamicin was studied in a retrospective cohort study in 25 obese and 25 non-obese children with a mean \pm standard deviation age of 9.9 ± 3.9 years and obese children's BMI percentile of 98 ± 1.3 [31]. Obese children received significantly lower TBW-normalized doses relative to their non-obese peers (mean 1.86 vs. 2.25 mg/kg TBW, $p < 0.01$), had significantly higher peak concentrations (8.17 ± 2.02 vs. 7.06 ± 1.52 $\mu\text{g/mL}$, $p < 0.05$), similar trough concentrations (0.95 ± 0.58 vs. 0.74 ± 0.24 $\mu\text{g/mL}$, $p = 0.11$), and decreased weight-normalized V (0.20 ± 0.05 vs. 0.28 ± 0.07 L/kg TBW, $p < 0.01$).

Two retrospective studies evaluated the PK of vancomycin in obese children. The first study included 70 obese and overweight children aged 2 to <18 years of age and mean \pm standard deviation TBW 43.4 ± 30.4 kg receiving vancomycin [32]. Dose (16.6 vs. 17.2 mg/kg TBW, $p = 0.295$) and dosing frequency were not significantly different between the obese/overweight cohort and their non-obese peers. In spite of similar TBW normalized doses, mean steady-state trough concentrations were higher in overweight or obese children compared with normal-weight children (9.6 vs. 7.4 $\mu\text{g/mL}$, $p = 0.03$), but this difference was not clinically significant as both mean troughs were within the target range defined by the study (5–15 $\mu\text{g/mL}$). Neither the proportion of therapeutic troughs (63.0% vs. 61.4%, $p = 0.825$) nor the frequency of nephrotoxicity (8.5% vs. 3.0%, $p = 0.093$) or red-man syndrome (45.7% vs. 50.6%, $p = 0.493$) differed between obese/overweight and non-obese children, respectively. The other retrospective study of IV vancomycin in 24 obese and 24 non-obese children (mean \pm standard deviation 6.8 ± 4.31 years of age and obese BMI percentile 97.3 ± 1.49) showed that obese children received lower TBW-normalized doses (not clinically significant, 14.1 vs. 14.9 mg/kg TBW/dose, $p = 0.03$) and higher, albeit not

statistically significant, steady-state serum trough vancomycin concentrations (6.9 vs. 4.8 ug/mL, $p=0.052$) [33].

Discussion

This review highlights the lack of PK and dosing information for the most commonly used drugs (antibiotics) in obese children. The lack of PK data is not only substantial overall but even more pronounced for orally administered drugs and those undergoing extensive liver biotransformation. For the four antibiotics studied thus far, no clinically relevant differences in drug distribution justify dosing modifications, suggesting that 1) there are truly no differences; 2) larger studies need to be conducted to observe a difference; or 3) children at the extreme of the obesity spectrum need to be included in clinical trials.

Obesity results in numerous changes to physiology and body composition that may affect drug disposition and dosing (Table 1). Volume of distribution (V) and clearance (CL), the primary determinants of drug dosing, may be affected differently depending on the drug's physicochemical properties and routes of metabolism and elimination [34, 35]. V may be affected by distribution of drug into tissues, which is determined by drug properties such as lipophilicity, as well as physiologic characteristics such as body composition, organ blood flows, and drug protein- and tissue-binding. Changes in body composition and organ blood flows have been documented in obese adults and children (Table 1). CL in obese individuals can be affected by weight-related changes in renal function (glomerular filtration rate and renal blood flow) [19, 36] or changes in the activity of drug-metabolizing enzymes [17]. For example, xanthine oxidase and N-acetyltransferase 2-mediated metabolism of caffeine was elevated in obese children compared with non-obese children ($p<0.05$) [17].

In the absence of data supporting dosing, body size measures are often chosen to dose drugs in obese children on the basis of drug physicochemical characteristics (e.g., lipophilicity, protein-binding), drug distribution profiles, and drug elimination pathways. Traditionally, non-obese children are dosed per kg of TBW, but other body size measures (e.g., IBW, LBW, body surface area) may better correlate with V and CL in obese children and achieve more appropriate exposure.

Due to the expected affinity of lipophilic drugs to adipose tissue, it is hypothesized that lipophilic drugs will have increased V in obese patients, resulting in the need for a higher initial dose. Conversely, hydrophilic drugs are expected to remain in the intra-vascular space, bind less to adipose tissue, and thus lower V, placing children at risk for overdose. Unfortunately, the relationship between a drug's lipophilicity and its distribution to adipose tissue is not always consistent and predictable, especially for highly lipophilic drugs. A study of five lipophilic β -blockers found greater binding to lean tissue than adipose tissue [37]. Tobramycin and gentamicin are highly and moderately lipophilic ($-\text{Log}P=5.8$ and 3.1 , respectively), but both distribute primarily in extracellular fluid, not adipose (Table 3). The distribution is consistent with the finding of decreased $V_{ss}/\text{kg TBW}$ in obese children observed for both tobramycin and gentamicin. $V_{ss}/\text{kg TBW}$ was also decreased (0.29 ± 0.13 vs. 0.33 ± 0.11 L/kg, $p = 0.05$) in a large prospective study of obese and non-obese adults who received tobramycin or gentamicin [38]. Conversely, cefazolin, a drug with low

lipophilicity (-LogP=0.6), widely distributed to tissues (Table 3). Based on lipophilicity alone, it would be reasonable to hypothesize that V/kg TBW would be decreased in obese individuals, requiring a lower initial dose per kg of TBW. Lower cefazolin V/kg TBW was seen in obese adults [39] compared with non-obese adults [40]. However, in the five obese children in the study described above, cefazolin V/kg TBW was unchanged compared with their non-obese peers. It is unclear why obesity affects V in adults but not children, but it could be related to a small sample size in the pediatric study that prevented identification of differences. Vancomycin has moderate lipophilicity (-LogP=3.1) and is distributed to total body water and tissues (Table 3). Similar to cefazolin, unchanged vancomycin V/kg TBW in children is inconsistent with reports of decreased V/kg TBW in obese adults [41, 42]. Clearly, for the drugs included in this report which were evaluated in small cohorts of children, drug lipophilicity is not predictive of drug distribution. The combination of degree of solubility and extent of metabolism (Biopharmaceutics Drug Disposition Classification System class) also did not distinguish the different distribution profiles of the drugs included in this report, as all four are highly soluble and poorly metabolized.

Studies have investigated the effect of obesity on drug binding to blood proteins or lipids. Serum albumin and total protein levels are unchanged in obesity, while the effect of obesity on alpha-1-acid glycoprotein levels is inconclusive [43–45]. However, drug-binding is influenced by more than absolute concentrations of serum proteins. Free fatty acid and triglyceride levels may affect a drug's affinity for serum proteins, and free fatty acids and triglycerides are often increased in obesity. *In vitro* studies on the effects of free fatty acid levels on protein-binding found increased albumin binding of three out of six acidic antibiotics when the ratio of free fatty acid concentration to protein concentration was >2; binding of three basic and neutral antibiotics was unchanged regardless of free fatty acid concentration [46].

Drug CL depends on clearance organ size and function. The liver and kidney are lean organs, and LBW is increased in obesity (though less than adipose as a fraction of excess weight). A study of 21 participants with normal liver and renal function found that liver volume was not a significant predictor of antipyrine clearance, while kidney volume appeared to mediate the association between LBW and creatinine clearance [47]. CL can also be affected by obesity-related changes in drug-metabolizing enzyme activity or renal function. Drugs eliminated via glomerular filtration or renal tubular-mediated processes, or that are metabolized by uridine diphosphate glucuronosyltransferase, xanthine oxidase, N-acetyltransferase, and cytochrome P450 (CYP) 2E1, have increased CL reported in obese adults; drugs metabolized by CYP3A4 have decreased CL [48]. Animal studies in obese mice suggest that increased kidney size and glomerular hypertrophy may result in increased glomerular filtration rate [49], and that lipid accumulation in the liver and induction of pro-inflammatory cytokines are possible mechanisms for alteration of drug-metabolizing enzyme expression [50, 51]. Non-alcoholic fatty liver disease is associated with obesity, and clinical studies indicate that CYP2E1 activity is increased with this condition [52, 53]. Other CYPs have not been evaluated in clinical studies of patients with non-alcoholic fatty liver disease; however, an *in vitro* human liver microsome study of drug-metabolizing enzyme activity found that progression of non-alcoholic fatty liver disease was associated with

decreasing activity of CYP1A2 and CYP2C19 and increasing activity of CYP2A6 and CYP2C9 [16].

No CL changes were observed in obese children in the studies included in this review. For cefazolin, this is inconsistent with data in obese adults. Cefazolin CL (4.2 vs. 3.9 L/h) and V (13.0 vs. 12.3 L) estimates in obese adults [39] were similar to non-obese adults [40]; thus CL/kg TBW and V/kg TBW would be likely reduced in obese adults. As was the case in the studies of obese children, aminoglycoside and vancomycin CL/kg TBW was found to be unchanged in obese adults [38, 41, 42]. One limitation to the evaluation of vancomycin PK in obese children was the large fraction of children in both groups with undetectable trough concentrations [33].

In spite of limited PK data in obese children, dosing recommendations have been suggested. The cefazolin study recommended the use of TBW for initial dosing. The tobramycin study recommended dosing by ABW in obese children, consistent with adult obesity dosing [54]. Unlike the tobramycin study, the gentamicin study recommended dose reduction as opposed to using ABW. Both methods would result in a lower absolute dose administered. Due to the lack of observed obesity effect on vancomycin PK, the two studies recommended the use of TBW for dosing of obese children, consistent with dosing recommendations in obese adults [55].

Prospective studies of antimicrobial PK in obese children are needed to provide information on optimal dosing to clinicians. Future studies should consider drug physicochemical properties in addition to elimination pathways when developing dosing regimens. As stated above, V/kg TBW of moderate to highly lipophilic drugs are more likely to be affected by obesity [56]; effects on CL/kg TBW may be dependent on pathway(s) of elimination. The use of probe drugs for specific elimination pathways would enable extrapolation of results for other substrates of that pathway. The use of modeling and simulation approaches such as physiologically based PK, which incorporates both drug and physiological information, may help to provide mechanistic insights and inform study designs in this special population [57]. As there are no reliable predictors of obesity effects on PK in children, future studies of antibiotics in obese children should be prioritized based on clinical importance and frequency of use.

Conclusion

Optimization of antimicrobial dosing in obese children is at an early stage. Most classes of antimicrobial agents have yet to be studied in this population. Physicochemical properties alone do not reliably predict drug disposition, and traditional body size measures (actual body weight) used for dosing of drugs in obese children do not account for potential changes in CL mechanisms such as drug-metabolizing enzyme activity and renal function. The few studies done to date have not shown clinically relevant differences in PK or dosing in obese children relative to their non-obese peers. Future studies should consider drug physicochemical properties, known physiologic changes in obesity, as well as drug elimination pathways.

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Table 1

Selected physiological and body composition changes reported in obese adults and children

| Adults | Children | Reference |
|--------|----------|---|
| ↑ | NS | Fat per kilogram [8] |
| ↑ | ↑ | Fat-free mass, fat mass, and mineral [8, 9] |
| ↓ | NS | Lean tissue per kilogram [8] |
| ↑↔ | ↑ | Lean body mass [10] |
| ↑ | ↑ | Extracellular water proportion [11] |
| ↑ | NS | Blood volume [12] |
| ↑ | NS | Cardiac output [13] |
| ↔ | NS | Hepatic blood flow [14] |
| ↔ | NS | Oral absorption [15] |
| ↓↑ | NS | Effect of NAFLD on hepatic metabolism [16] |
| NS | ↑ | Xanthine oxidase activity [17] |
| NS | ↔ | CYP1A2 activity [17] |
| ↑↔ | NS | Glomerular filtration rate [18, 19] |
| ↑ | NS | Renal blood flow [20, 21] |

NS=not studied, ↑=increased, ↓=decreased, ↔=unchanged, NAFLD = non-alcoholic fatty liver disease.

Table 2

Summary of pharmacokinetic studies in obese children

| Drug | Dosing | Dosing weight | Study design and sampling | Population | Ages (years) | Obesity definition | Findings in O compared with N |
|-----------------|----------|------------------------|---|----------------------|---|--|--|
| Cefazolin [30] | 25 mg/kg | Average of TBW and IBW | P, SD, I | 5 O, 6 N | Median (range) O: 8.3 (1.8–9.3) | Degree of obesity * [mean (StdDev)] O: 63% (18) | V _{ss} /TBW ↔ CL/TBW ↔ |
| Tobramycin [30] | 2 mg/kg | | | | | | V _{ss} /TBW ↓ CL/TBW ↔ |
| Gentamicin [31] | O < N | NA | R, C _{max,ss} , C _{min,ss} | 25 O, 25 N | Mean (SD) O/N: 9.9 (3.9) | O: BMI 98%ile | V/TBW ↓ C _{max,ss} ↓ Ke, t _{1/2} , C _{min,ss} ↔ |
| Vancomycin [32] | O = N | NA | R, C _{max,ss} , C _{min,ss} | 70 O or OV, 162 N | O/OV: 2 to <6: n=22 6 to <12: n=29 12 to <18: n=19 | OV: BMI >85 & <95%ile O: BMI >95%ile | O/OV: C _{min,ss} ↑ %TT ↔ |
| Vancomycin [33] | O < N | NA | R, C _{max,ss} , C _{min,ss} | 24 O, 24 N | Mean (SD) O: 6.8(4.3) | O: BMI 97%ile | t _{1/2} , C _{min,ss} ↔ |

BMI: body mass index; CL: clearance; C_{max,ss} steady state peak concentration; C_{min,ss} steady state trough concentration; I: intensive; IBW: ideal body weight; Ke: elimination rate constant; N: normal-weight; NA: not applicable; O: obese; OV: overweight; P: prospective; R: retrospective; SD: standard deviation; t_{1/2}: half-life; TBW: total body weight; TT: therapeutic trough; V: volume of distribution; V_{ss}: steady-state volume of distribution; %ile: percentile.

* Degree of obesity was estimated from height and TBW using a nomogram [30].

Table 3

Properties of drugs used in pharmacokinetic studies in obese children

| Drug | Lipophilicity | Distribution | Protein binding | Elimination |
|---------------------|----------------------|------------------------------------|------------------------|---|
| Cefazolin [30] | Low | Widely, to most tissues | 80% | Renal (60–80%) |
| Tobramycin [30] | High | Mainly extracellular fluid | 0–30% | Renal (60–85%), mainly excretion, some secretion |
| Gentamicin [31] | Intermediate | Mainly extracellular fluid | 0–30% | Renal (70–100%), mainly excretion, some secretion |
| Vancomycin [32, 33] | Intermediate | Total body water and other tissues | 30–55% | Renal (40–100%) |