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Drug Dosing in Obese Children: A Systematic Review of Current Pharmacokinetic Data

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Abstract

IMPORTANCE—Obesity affects nearly one sixth of U.S. children and results in alterations to body composition and physiology that can affect drug disposition, possibly leading to therapeutic failure or toxicity. The depth of available literature regarding obesity's effect on drug safety, pharmacokinetics (PK) and dosing in obese children is unknown.

OBJECTIVE—To perform a systematic literature review describing the current evidence of the effect of obesity on drug disposition in children.

EVIDENCE REVIEW—We searched the Medline, Cochrane, and Embase databases (January 1970–December 2012) and included studies if they contained clearance, volume of distribution, or drug concentration data in obese children (age ≤18 years). We compared exposure and weight-normalized volume of distribution and clearance between obese and non-obese children. We

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explored the relationship between drug physicochemical properties and clearance and volume of distribution.

FINDINGS—Twenty studies met inclusion criteria and contained pharmacokinetic data for 21 drugs. The median number of obese children studied per drug was 10 (range 1–112), ages ranged from 0–29 years. Dosing schema varied and were based on a fixed dose (n=6, 29%), body weight (n=10, 48%), and body surface area (n=4, 19%). Clinically significant pharmacokinetic alterations were observed in obese children for 65% (11/17) of studied drugs. Pharmacokinetic alterations resulted in substantial differences in exposure between obese and non-obese children for 38% (5/13) of drugs. We found no association between drug lipophilicity or Biopharmaceutical Drug Disposition Classification System class and changes in volume of distribution or clearance due to obesity.

CONCLUSIONS AND RELEVANCE—Consensus is lacking on the most appropriate weight-based dosing strategy. Prospective pharmacokinetic trials in obese children are needed to ensure therapeutic efficacy and enhance drug safety.

The prevalence of childhood obesity has stabilized at epidemic proportions. Nearly 1 out of every 6 children or adolescents living in the U.S. has a body mass index (BMI) for age and sex above the 95th percentile and is considered obese.[1] Obese children experience increased rates and severity of multiple disease states, require more frequent and more complex medical interventions,[2–7] and use significantly more prescription medications than their non-obese peers.[8]

Relatively little is known about the impact of childhood obesity on drug pharmacokinetics (PK). Obesity demonstrates important alterations in physiology such as changes in tissue composition, increased circulating blood volume and cardiac output, altered regional flow distribution, and impaired liver and kidney function.[9–11] All of these physiologic alterations can affect PK parameters including drug absorption, volume of distribution (V), metabolism, and elimination.[12–14] Furthermore, physiochemical properties of a drug, such as lipid solubility or relative protein binding, might have differential effects on drug PK in obese versus non-obese children.[14] To account for these physiologic and pharmacologic factors, some clinicians adjust weight-based dosing using various metrics of body size, such as ideal body weight (IBW). However, these dosing strategies are largely based on theoretical considerations or extrapolated from studies in adults.[15] Currently, there is no comprehensive, evidence-based understanding of the impact of childhood obesity on drug PK.

To better understand the current evidence base, we performed a systematic review of published PK studies conducted over the preceding 4 decades in obese children and adolescents. We addressed the question of whether critical obesity-related physiologic parameters change drug PK in children and evaluated the impact on PK of important drug physiochemical properties including lipophilicity (logP) and Biopharmaceutical Drug Disposition Classification System (BDDCS) class, a classification based on drug permeability and solubility.[16]

METHODS

Study Identification

We performed a systematic literature review using the Medline, Cochrane, and Embase databases (January 1970–December 2012). The search strategy was defined in collaboration with librarians at Duke University Medical Center Library and the National Library of Medicine. Search terms included: pharmacokinetics, pharmacodynamics, PK/PD, medication, dosing, dose, dosage, overweight, obesity, and obese. Exact search strategies are displayed in Supplemental eTables 1 and 2. There were no language restrictions. We identified additional studies through pertinent review of article bibliographies and conference abstracts.

Study Selection

We compiled the final search results into a single library using Endnote X5 (Thomson Reuters, San Francisco, CA). We independently reviewed study abstracts for inclusion in the final analysis (M.G. and K.B.). If an abstract lacked sufficient detail, the full article was reviewed. We included studies if they contained any PK data for obese children (ages 2–18 years) including clearance (CL), V, area under the curve, half-life, or drug concentration data. Articles with only pharmacodynamics results were not included. Because definitions of obesity and overweight have varied over the years, we included all studies in which the authors used an accepted definition of obesity, regardless of the criteria used. Studies that included both obese and overweight children in the same analysis group were also included but are clearly identified.[17–23] The different phases of systematic review are displayed in a flowchart, as described by the PRISMA 2009 statement[24] (Figure 1).

Data Extraction

We extracted dosing and PK data and information regarding the body weight measurement used for dosing. Total body measurement (TBM) was defined as the actual total body weight or body surface area (BSA) of the child. IBW was defined as the weight at the 50th percentile of a weight for height on a sex-adjusted growth curve. Adjusted body measurement was defined as any measurement that relied on scaling between ideal and total body weight (e.g., IBW + 40%*[total body weight – IBW]) or adjusted BSA. We extracted TBM-normalized CL (ml/min/kg) or V (L/kg) values when they were reported or calculated TBM-normalized values by dividing CL and V with weights reported in the original source (individual or study mean weight values). Whenever possible, data were included for children only. We did not extract pharmacodynamics or safety data, as most studies did not report these data and were not powered to do so.

Comparison of PK Data in Obese and Non-Obese Control Children

We qualified exposure to the studied drug in obese children as sub-therapeutic, therapeutic, or supra-therapeutic based on target ranges provided in the original source (e.g., a target trough level or area under the curve). We compared exposure and weight-normalized PK parameters in obese children to non-obese controls within each study when available and expressed values in obese children as a percentage (%) of controls. To evaluate the

association between changes in CL or V and the drug's physicochemical properties, we plotted the ratio of CL in obese children to CL in control children, and the ratio of V in these 2 populations against the drug's logP and BDDCS class. V and CL were normalized to actual body weight—either total body weight or BSA, depending on the weight metric used to dose the respective drug.

RESULTS

We identified 1888 unique publications, of which 1868 (99%) were excluded because they did not describe PK of an exogenous drug, they did not contain any PK data, or they did not include overweight or obese children (Figure 1). The remaining 20 publications contained PK data for 21 drugs, including 7 anti-neoplastic drugs, 4 anticonvulsants, 4 antibiotics, 3 analgesic/anesthetic drugs, 2 respiratory stimulants, and 1 immunosuppressant (Table 1). Six out of 21 (29%) drugs were not studied in a formal prospective PK trial (gentamicin[29]; vancomycin[17,18,30]; valproic acid[19]; divalproex sodium[20]; busulfan[21]; and cyclosporine[36]). PK data for these studies were collected following drug administration per standard of care, frequently with sparse sampling.

Study Population

Study definitions of obesity and overweight varied. The majority of studies used the currently accepted Centers for Disease Control and Prevention definition for children of BMI percentile ≥95% for obesity and ≥85% for overweight (18/21 drugs). Other definitions included IBW percentile ≥125% and ≥115% (2/21), weight-for-height percentile ≥75% (1/21), and absolute BMI ≥ 25 (1/21). Thirteen out of 20 (65%) studies described PK parameters for obese children separately versus combining obese and overweight children in 1 analysis group. The median number of obese children studied per drug was 10 (range 1–112 subjects), with 12/21 (57%) studies including ≤10 obese children. Patient ages ranged from 0–29 years (1 study described PK in children and adults together).[19]

Studied Dosing Schedules and Exposure

Dosing schema showed considerable variability. Drugs were dosed using a fixed dose (n=6, 29%), based on body weight (n=10, 48%) or BSA (n=4, 19%), or based on body weight in 1 study and BSA in another study (n=1, 5%). When drugs were dosed by body weight or BSA, the body weight measurement used for dosing was as follows: TBM (n=7, 33%), adjusted body measurement (n=5, 24%), or both (n=3, 14%). No drug was dosed based on IBW (Table 2).

Exposure data in obese children were available for 17 drugs, and a non-obese control comparison group was available for 13 of these drugs (Table 2). Compared with controls, obese children demonstrated meaningful differences in exposure for 5/13 drugs (38%), including 4/5 with increased exposure in the obese patients. Dosing by TBM demonstrated sub- or supra-therapeutic exposures for 4/10 drugs, while dosing strategies using various adjusted body measurement strategies resulted in appropriate exposures for 8/8 drugs (Table 2).

Pharmacokinetic Changes Due to Obesity

PK parameters were compared between obese and non-obese controls for 17 drugs, a slightly different set from the drugs with PK data (Table 3). As compared with controls, clinically significant PK alterations were seen in obese children for 11/17 (65%) of studied drugs, including decreased V (range 65–89% of controls) for 8 drugs, increased V (113%, 166%) for 2 drugs, decreased CL (range 30–84%) for 5 drugs, and increased CL (222%) for 1 drug (Table 3).

Figure 2 shows the ratios of V and CL for drugs with different logP and BDDCS class. A ratio of 1 indicates that weight-normalized V or CL were identical between obese and non-obese children, <1 indicates that obese children had a smaller V or CL, and >1 indicates that V or CL were higher in obese children. We did not identify any relationship between measured logP or BDDCS class and change in V or CL due to obesity.

DISCUSSION

This is the first systematic review of PK studies conducted in obese children. Despite a comprehensive review strategy, we identified only 20 studies (evaluating 21 drugs) performed over the preceding 4 decades. Many of these studies identified important obesity-related changes in drug PK. However, the majority included small numbers of children, and 29% were conducted using therapeutic drug monitoring data and not as part of a formal PK trial. Also, many of the drugs that we highlight are not commonly prescribed agents.[41,42] We found no data for several important drug classes for which obesity-related toxic overdosing or sub-therapeutic under-dosing have been previously described in adults, including acute care, cardiovascular, anesthetic agents, and contraception (including emergency contraception).[43-50] For contraception, the lack of PK data in obese female adolescents is particularly concerning as evidenced by recent studies in obese female adults suggesting that higher doses are required to achieve therapeutic exposure and certain emergency contraceptive agents are less effective.[49,50]

Considering the prevalence and tremendous public health impact of childhood obesity, the relative paucity of drug PK data is concerning. Kendrick and colleagues completed the only prior review of PK studies in obese children (published in 2010), identifying just 10 drugs with available PK data. They concluded that clinicians may need to extrapolate from adult data while considering the effects of growth and development on PK.[51] However, subsequent analyses have identified that simple extrapolation from studies in obese adults may give false predictions of CL and other PK values.[15] These observed differences between obese children and adults might be explained by maturational differences in expression and activity of enzymatic pathways and/or drug transporters, by differences in elimination pathways, or by as yet unexplained differences in drug metabolism.[15] Regardless, important differences exist and highlight the need for conducting PK studies specifically in obese children.

In the clinical setting, health care providers sometimes empirically adjust dosing in obese children based on perceived differences in PK (e.g., dosing by IBW). In the small number of obese children described in this systematic review, the PK differences we identified in obese

children (CL was different in 6/15 drugs and V in 10/11 drugs) were not predicted by drug logP, and no relationship between BDDCS class and PK changes was observed. Given the paucity of systematic data investigating the impact of logP and BDDCS class in obese children, these drug characteristics should still be investigated in future studies.[12,52] However, it is also possible that V and CL in obese children are affected by drug-specific factors other than logP or BDDCS class. Possible factors include route of absorption, metabolic pathway, and route of elimination. A recent study in obese adults reached a similar conclusion.[14]

Given the noted overweight-related alterations in drug exposure and PK, it would seem that optimal dosing regimens should be adjusted to account for obesity-related factors. Traditionally, a variety of adjustment methods have been proposed, including dosing regimens based on IBW, TBM, BSA, various adjusted body measurement formulae, or more complex physiologically based formulae, such as the ratio between V and body weight.[14] In our analysis, there was little consistency in which adjustment methods were used. Evaluating exposure levels in obese children by dosing strategy, we found that dosing based on TBM resulted in inappropriate exposure for 4/10 drugs. When combined with the 8 drugs for which dosing using an adjusted body measurement achieved appropriate exposure, approximately two thirds of drugs in this review would result in inappropriate exposure if dosed by TBM. However, we cannot predict which drugs should be dosed by total or adjusted body measurement and which adjustment method to use to convert from total to adjusted body measurement.

The main limitations of our analysis are small study sizes, an overall small number of studied drugs, and the heterogeneity in study population and study design for the various PK studies that we identified. To maximize the power of this review, notwithstanding inconsistent weight categorizations and a small number of available studies, we reviewed all studies in obese children. Thirty-five percent included overweight as well as obese children, which may have caused underestimation of the effects of obesity. Many of the analyzed PK studies used sparse sampling strategies (e.g., therapeutic drug monitoring data) that limit the ability to analyze drug PK in a specific age group. For these reasons, we are cautious in drawing conclusions and avoid making specific dosing recommendations. Because the data are so sparse, we are collaborating with the National Institute of Child Health and Human Development in a systematic review of acute care and commonly used drugs to develop a PK database in obese children, normal weight children, and obese adults. Data generated from this review will be used to make dosing recommendations for obese children when possible and identify priority drugs in need of study in this population.

For future PK studies in obese children, we recommend including drugs of different therapeutic drug classes. Drug class prioritizing should be based on drug utilization, medical need, and expected PK alterations in obesity (based on adult studies).[53] Based on our review of current PK studies in obese children, we recommend that future PK studies in children: 1) describe inclusion criteria, including the definitions of obesity (preferably age- and sex-adjusted BMI %), age, clinical diagnosis, and co-morbidities; 2) describe demographics of both obese and control subjects including age, weight, height, BMI, BMI %, diagnosis, and kidney and liver function; 3) provide detailed PK parameters including CL and V estimates

by BMI group (>85%, >95%, >97%); and 4) report safety outcomes and, if possible, pharmacodynamic outcomes.

In conclusion, this systematic review describes PK changes due to obesity in children. We found that an evidence base is broadly lacking. Of the existing data, many of the studies were small PK studies or were conducted for drugs that are infrequently prescribed (e.g., anti-neoplastic drugs). The studies demonstrated considerable variability in weight-based dosing strategies, criteria for obesity, and type of PK analysis. We identified important but unpredictable differences in drug CL and V in obese children for two thirds of drugs. Furthermore, our analysis demonstrates that dosing based on TBM is often sub-optimal, as approximately two thirds of drugs studied demonstrated sub- or supra-therapeutic exposure when dosed using TBM. Therefore, given the increasing societal obesity-related morbidity and medical expenditure in children, there is an urgent need for formal PK studies in obese children to develop evidence-based dosing guidelines. With dedicated PK studies, we can determine PK parameters and use them to explore different dosing regimens using modeling and simulation. We have provided recommendations for the critical components of these future PK studies to standardize design and improve granularity of future structured reviews.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX: The Pediatric Trials Network Administrative Core Committee

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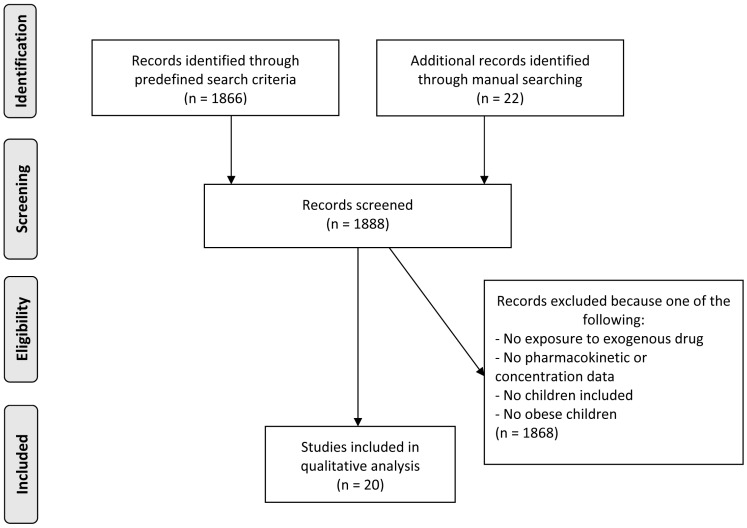
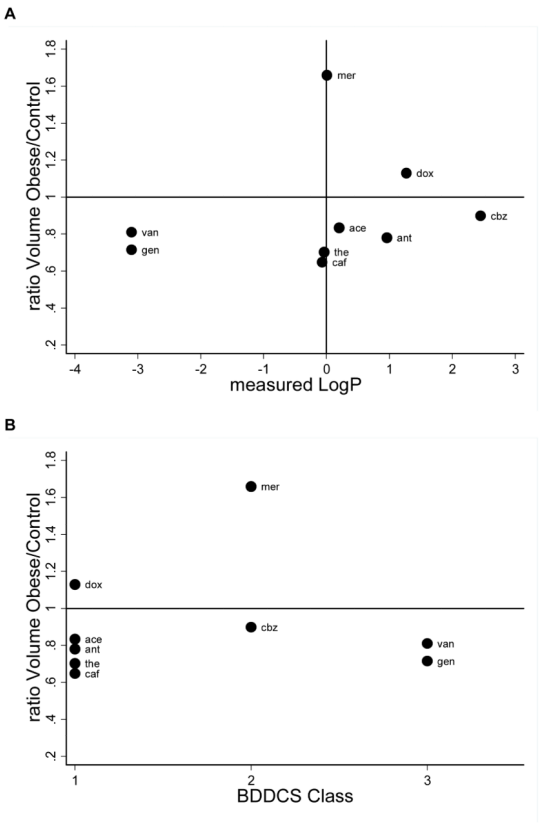


Figure 1.
Study Outline of Systematic Literature Search and Inclusion of Identified Articles



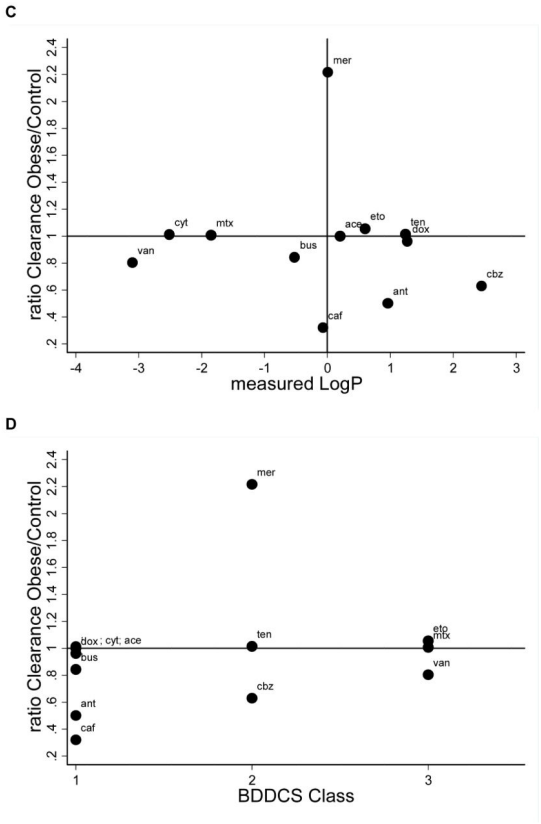


Figure 2. Relationship Between Obesity-Related Changes in Pk and Drug Physicochemical Properties

V and CL ratios plotted by measured logP and BDDCS class. Ratios displayed as obese/controls. CL and V are weight-normalized (e.g., V in L/kg). If authors did not report weight-normalized values (antipyrine, carbamazepine, and caffeine), then weight-normalized parameters were calculated by dividing reported values by individual or study mean weight values. **A**: V by measured logP; **B**: V by BDDCS class; **C**: CL by measured logP; **D**: CL by BDDCS class. V, volume of distribution; Cl, clearance; logP, lipophilicity; BDDCS, Biopharmaceutical Drug Disposition Classification System; ace, acetaminophen; ant, antipyrine; caf, caffeine; cbz, carbamazepine; dox, doxorubicin; eto, etoposide; gen, gentamicin; mer, mercaptopurine; mtx, methotrexate; ten, teniposide; the, theophylline; tob, tobramycin; van, vancomycin.

Table 1

Pharmacokinetic Studies in Obese Children

Drug	N	Mean age, years (SD or range)	Definition of obesity
Analgesics/anesthetics			
Acetaminophen[25]	12	15 (2)	BMI ≥ 95%ile
Antipyrine[26]	3	17 (0)	BMI ≥ 95%ile
Propofol[27]	20	16 (2)	BMI ≥ 95%ile
Antibiotics			
Cefazolin[28]	5	7 (3)	BMI ≥ 95%ile
Gentamicin[29]	25	10 (4)	BMI ≥ 95%ile
Tobramycin[28]	5	7 (3)	BMI ≥ 95%ile
Vancomycin[17,18,30]	112	(0.2, 18)	BMI ≥ 85%[17,18], ≥ 95%ile[30]
Anticonvulsants			
Carbamazepine[31,19]	9	(15, 29)	BMI ≥ 95%ile[31], BMI ≥ 25 (study mean 30)[19]
Divalproex sodium[20]	5	9 (5, 14)	> 115% IBW[a]
Midazolam[32]	-	-	BMI ≥ 95%ile
Valproic acid[19]	5	21 (15, 29)	BMI ≥ 25 (study mean 27)
Antineoplastics			
Busulfan[21]	22	7 (6)	BMI ≥ 85%ile
Cytarabine[33]	10	9 (2, 18)	BMI ≥ 95%ile
Doxorubicin[34,35]	4	(9, 16)	BMI ≥ 95%ile
Etoposide[33,35]	25	9 (2, 18)	BMI ≥ 95%ile
Mercaptopurine[22]	9	7 (4)	75% W/H
Methotrexate[33]	41	9 (2, 18)	BMI ≥ 95%ile
Teniposide[33]	10	9 (2, 18)	BMI ≥ 95%ile
Immunosuppressants			
Cyclosporine[36]	30 + 72	15 (4)	BMI ≥ 95% + BMI ≥ 85%ile
Respiratory stimulants			
Caffeine[37]	3	17 (0)	BMI ≥ 95%ile
Theophylline[23]	9	-	>125% IBW

BMI %, age- and sex-specific BMI percentile (≥85th considered overweight, ≥95th considered obese)[38]; % IBW, percentile of ideal body weight (>120% considered overweight)[39]; BMI ≥ 25 (considered moderate obesity)[40]; % W/H, percentile of weight for height.[38]

[a]For divalproex sodium, the authors did not stratify based on obesity, but found an empiric difference in PK for children less than and greater than 115% IBW.

Table 2

Drug Exposure in Obese Children by Dosing Method

Drug	Dosed per	Body weight measurement	Exposure in obesity	Obese vs. control
Mercaptopurine[22]	m^2	TBM	Subtherapeutic	↓
Vancomycin[17,18,30]	kg	TBM	Subtherapeutic[17,30]	↔ [17,30]
		TBM	Therapeutic[18]	↑ [18]
Teniposide[33]	kg	TBM	Therapeutic	↔ [a]
Methotrexate[33]	m^2	TBM	Therapeutic	↔ [a]
Cytarabine[33]	m^2	TBM	Therapeutic	↔ [a]
Theophylline[23]	kg	TBM	Not available	Not available
Busulfan[21]	kg	TBM[b]	Supratherapeutic	↑ (124%)
Divalproex sodium[20]	kg	TBM	Supratherapeutic	↑ (156%)
		ABM	Therapeutic	↔
Doxorubicin[34,35]	kg[34]	TBM	Therapeutic	Not available
	m^2 [35]	ABM	Therapeutic	Not available
Etoposide[33,35]	m^2 [33]	TBM	Therapeutic	↔ [a]
	m^2 [35]	ABM	Therapeutic	Not available
Tobramycin[28]	kg	ABM	Therapeutic	Not available
Cefazolin[28]	kg	ABM	Therapeutic	Not available
Gentamicin[29]	kg	ABM	Therapeutic	↔
Cyclosporine[36]	kg	ABM	Therapeutic	↔
Propofol[27]	kg	ABM	Therapeutic	Not available
Acetaminophen[25]	Fixed dose[c]	n/a	Therapeutic	↑ (135%)
Carbamazepine[19,31]	Fixed dose	n/a	Therapeutic[19]	↔ [19]
Valproic acid[19]	Fixed dose	n/a	Therapeutic	↔
Antipyrine[26]	Fixed dose	n/a	Not available	Not available
Midazolam[32]	Fixed dose	n/a	Not available	Not available
Caffeine[37]	Fixed dose	n/a	Not available	Not available

TBM, total body measurement; ABM, adjusted body measurement; ↑, increased in comparison to controls; ↓, decreased in comparison to controls; ↔, equal to controls; (%), % of controls.

[a] Comparison of exposure between obese and control subjects based on clinical outcomes (overall survival, event-free survival, and cumulative incidence of relapse).[33]

[b] Test dose used for PK comparison.[21]

[c] Acetaminophen single-dose regimen: 5 mg/kg, maximum 325 mg, the mean dose administered was 3.6 mg/kg (SD 0.8).[25]

Table 3

Observed PK Changes in Obese Children

Drug	Volume of distribution[a]	Clearance[a]
Analgesics/anesthetics		
Acetaminophen[25]	↓ (83%)	↔
Antipyrine[26]	↓ (76%)	↓ (50%)
Antibiotics		
Cefazolin[28]	↔	↔
Gentamicin[29]	↓ (71%) [b]	
Tobramycin[28]	↓ (75%) [b]	↔
Vancomycin[17]	↓ (81%)	↓ (80%)
Anticonvulsants		
Carbamazepine[31]	↓ (89%)	↓ (63%)
Midazolam[32]		↔
Antineoplastics		
Busulfan[21]	↓ (84%) [b]	
Cytarabine[33]		↔
Doxorubicin[34,35]	↑ (113%)	↔
Etoposide[35]		↔
Mercaptopurine[22]	↑ (166%) [b]	↑ (222%) [b]
Methotrexate[33]		↔
Teniposide[33]		↔
Respiratory stimulants		
Caffeine[37]	↓ (65%)	↓ (30%)
Theophylline[23]	↓ (69%) [b]	

V and CL are expressed as a percentage of mean values in non-obese controls. ↑, increased in comparison to controls; ↓, decreased in comparison to controls; ↔, equal to control.

[a] PK parameters are weight-normalized (e.g., volume of distribution in L/kg). If authors did not report weight-normalized values (antipyrine, carbamazepine, caffeine, and mercaptopurine), then weight-normalized parameters were calculated by dividing reported values by individual or study mean weight values.

[b] Significant difference found in cited study.