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Review Article

Drug Dosing in Obese Patients: A Dilemma

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Abstract

Prevalence of obesity has increased over the past few years and is still growing. Usually obesity is accompanied by co-morbid conditions which may be caused because of it too. Due to this it is not unusual for a physician to have a lot of obese patients. Now, the dosing of the drug is a major issue. The dose given for normal patients may not be accurate for obese patients and it is highly likely to worsen the condition of the patient on account of the fact that pharmacokinetic parameters of an obese individual differs from a normal person. During clinical trials, the dose is calculated for normal weight patients, but the scenario changes in obese. Due to the lack of sufficient evidence, the dose modification poses to be a threat to patients especially the ones who are on drugs with a narrow therapeutic index. Various scales have been formulated to help but more research needs to be done to get precise doses.

1. Introduction

Obesity has turned into a global epidemic which was earlier present in developed countries but has started to spread in developing countries as well [1,2]. According to WHO, 1.6 billion people are overweight out of which 400 million are obese [3].Obesity itself can lead to various metabolic, cardiovascular and/or pulmonary disorders [4].Obesity is defined by the WHO based on the BMI of a person. BMI is calculated using weight in kg and height in meter. The BMI is calculated by the following formula:

$$BMI = weight\ (kg)/height\ (m)^2$$

According to WHO, obesity is classified by the values obtained by the BMI. If a person's BMI is <18.5kg/m^2 they are considered underweight, 18.6-24.99kg/m^2 is normal and >25kg/m^2 is overweight. The overweight is again stratified into 4 classes as shown in Table 1.

Table 1: Classification of overweight based on BMI

Overweight	BMI
Pre-obesity	25 to 29.99 kg/m^2
Obesity class l	30 to 34.99 kg/m^2
Obesity class ll	35 to 39.99 kg/m^2
Obesity class lll	>40 kg/m^2

When the BMI is more than 40kg/m^2, it's known as morbid obesity [5]. Accurate dosage regimens for obese patients are still vague. The pharmacokinetics of each person varies with a change in weight. As the number of obese patients with comorbidities such as diabetes mellitus and hypertension increases, physicians will encounter more problems regarding doses as the normal dose may not show therapeutic effect. The clearance and distribution of obese patients are different from a normal person [6-10].

2. Pharmacokinetics

The pharmacokinetics of an obese person is different from a normal person. If we understand them the calculation of dose might be more accurate and easier.

2.1 Absorption:

Absorption depends on the lipophilicity of the drug. Adipose tissue does not affect the absorption. Studies show that there is no major alteration in the absorption in obese patients [11-14].

2.2 Distribution:

Lipophilic drugs show increased volume of distribution than lipophobic or hydrophilic drugs as they are distributed in the fat tissue and the lean mass. For example volume of distribution of Benzodiazepines is high [15,16]. Hence TBW should be used. According to various studies, IBW should be used in case of hydrophilic drugs because the distribution is only limited to the lean tissue. Hence the distribution of both kinds of drugs varies greatly making it more difficult to obtain the correct dose [17-19].

2.3 Metabolism:

Increased level of serum proteins changes the metabolism in obese patients that leads to different half-lives of the drug in an obese patient from a normal person [20]. An increase in phase ll metabolism is noticed. Phase l metabolism either increases or remains the same [21].

2.4 Excretion:

Liver and kidney are the most important organs for the excretion of the drug. Any change in the physiology may affect the clearance of the drug. In some cases, obesity can cause fatty liver which impairs the blood flow. That creates an impact on the clearance in the liver [22]. According to Han *et al* obese patients exhibit higher clearance than non-obese [23]. The kidney weight, renal blood flow glomerular filtration rate is higher in obese people hence clearance is high [24].

In an attempt to calculate the dosage regimen various formulae or dosing scales have been formulated. Ideally the dosing formula should consider height, weight, pharmacokinetic factors etc but so far that kind of formula doesn't yet exist yet [25]. It is mandatory that whenever medications are administered to an obese patient, especially the ones with narrow therapeutic index, he or she should be monitored closely. Some of the commonly used parameters for dose calculation include:

Body mass index (BMI): As explained before, BMI is officially used to obtain dosage regimens. According to Michael J Henley *et al* BMI is not the most appropriate dosing scalar because it does not consider adipose tissue and lean body mass separately [26].

Body Surface Area (BSA): It is calculated using height, weight and constants as [27]:

$$BSA\ (m)^2 = [(TBW)\times(\text{height in cm})/3600]^{1/2}$$

BSA is extensively used in dosing of anti-cancer agents, however its use in calculating drug dose in obese patients is still questionable [28]. Just like BMI, BSA cannot differentiate between adipose tissue and lean body mass [28].

Total Body Weight: This method is usually used for normal patients [29]. Lean body mass and fat depositions do not increase proportionally in morbidly obese patients [30]. Since majority of the blood supply is goes to regular muscles instead of adipose tissue, using this method for calculation may cause toxicity in morbidly obese patients [29].

Ideal Body Weight (IBW): Its equation is based on size which relates it to mortality of a subject. An empirical equation to estimate IBW was derived by Devine [31]:

$$IBW\ (kg) = 45.4\ kg\ (49.9\ kg\ \text{if male}) + 0.89 \times (\text{height in cm} - 152.4)$$

IBW is different from BMI and BSA because it considers gender while calculating. The use of ideal body weight is limited because it implies that patients with same height should receive the same dose and the changes occurring in the body due to obesity [29].

Lean Body Weight (LBW): It is the weight of a person devoid of all the fat mass. It does not take the weight of the adipose tissue into consideration [26].LBW (kg) = (9270 × TBW)/(A + B×BMI), where values of A and B are 6680 and 216 for males, and 8780 and 244 for females [30].

Predicted Normal Weight: It is used to predict the normal weight of an obese individual [32]. It is usually not accurate when height and weight are extreme [33].

$$\text{For males, } PNWT\ (kg) = 1.57 \times TBW - 0.0183 \times BMI \times TBW - 10.5.$$

$$\text{For females, } PNWT\ (kg) = 1.75 \times TBW - 0.0242 \times BMI \times TBW - 12.6$$

A compilation of drug list along with the formulae that can be used to calculate dosage regimens is depicted in

Table 2.

Table 2: Drugs with formulae to calculate dosage regimens

Drug	Formula
Anaesthetic	
Propofol [34-37]	Induction: IBW Induction: LBW assessed by BIA Maintenance: TBW or IBW + 0.4 excess weight
Thiopental [38,39]	7.5 mg/kg IBW TBW
Lidocaine [40]	IBW
Ketamine [41]	IBW
Anti- depressant	
Midazolam [42,43]	TBW for initial dose IBW for continuous dose
Lorazepam [44]	Loading doses should be adjusted on actual weight and maintenance doses should be adjusted on ideal body weight.
Benzodiazepine [45]	IBW
Skeletal muscle relaxants	
Vecuronium [46]	IBW
Cisatracurium[47]	TBW IBW
Rocuronium[48]	IBW
Succinylcholine [49]	TBW
Atracurium [50]	IBW or ABW
Muscle stimulants	
Neostigmine [51]	TBW
Suggamadex [52]	IBW + 40% excess weight
Analgesics	
Alfentanil [12,53,54]	IBW or corrected weight TBW
Fentanyl [55-57]	TBW Corrected weight = IBW + (0.4x excess weight) pharmacokinetic mass = 52/[1 + (196.4 9 e-0.025kg – 53.66)/100]
Sufentanil [58,59]	TBW
Remifentanil [12,60]	LBM (James equation) LBM (Janmahasatian equation)
Morphine [61]	IBW
Paracetamol [62]	IBW
Opiates [45]	IBW
Anti-viral	
Acyclovir [40]	IBW
Ganciclovir [40]	ABW
Anti-fungal	
Amphotericin B [63]	TBW
Fluconazole [64]	TBW
Flucytosine[65]	IBW
Anidulafungin[40]	Loading dose: 200 mg Maintenance dose: 100 mg
Antibiotics	
Erythromycin [66]	IBW
Daptomycin[64]	TBW
Penicillins[67]	TBW
Carbapenem[45]	TBW
Cephalosporin [45]	TBW
Ciprofloxacin [68,69]	(0.45 [TBW-IBW]) + IBW
Gentamicin [68]	(0.4 [TBW-IBW]) + IBW
Amikacin [45]	(0.4 [TBW-IBW]) + IBW
Vancomycin [68]	TBW
Tobramycin [68]	(0.4 [TBW-IBW]) + IBW

Clindamycin [70]	Maximum of 4.8g/day in divided doses
Metronidazole [71]	500mg TDS
Anti-tubercular	
Ethambutol[40]	IBW
Isoniazid [40]	IBW
Pyrazinamde[40]	IBW
Rifampin [72]	IBW
Anticoagulants	
Heparin [73,74]	ABW
Lepirudin [40]	TBW (Use actual body weight up to 110 kg)
Warfarin [75]	ABW
Enoxaparin [76]	TBW
Argatroban[77]	TBW
Anti-epileptics	
Phenytoin [78]	Dosing weight= IBW+[1.33(ABW-IBW)]
Valproic Acid [79]	IBW
Carbamazepine [45]	IBW
Cardiovascular drugs	
Procainamide [40]	IBW
Digoxin [45]	IBW
Anti- neoplastic agents	
Busulphan [80]	BSA
Cyclophosphamide [81]	Adj Body Weight= IBW+40%(TBW-IBW)
Melphalan [40]	BSA
Thiotepa[81]	Adj Body Weight= IBW+40%(TBW-IBW)
Carboplatin [81]	Adj Body Weight= IBW+40%(TBW-IBW)
Doxorubicin [11]	BSA
Topotecan [11]	BSA
Irinotecan[11]	BSA
Cisplatin [11]	BSA
Paclitaxel [11]	BSA
Docetaxel[11]	BSA
Methotrexate [82]	BSA
Miscellaneous	
Cyclosporine [83]	IBW
Theophylline [40]	IBW
Immunoglobulin [7]	Dose Determining Weight= IBW+0.4[actual body weight(kg)- IBW]
G-CSF (Filgrastim) [40]	Actual Body Weight

3. Conclusion

Various scales have been formulated to calculate drug dosing in obese population but more research needs to be done to get precise doses.

References

[1] Kelly T, Yang W, Chen CS, *et al*. Global burden of obesity in 2005 and projections to 2030. *Int J Obes* 2008; 32: 1431-37.

[2] Yach D, Stuckler D, BrownellKD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nat Med* 2006; 12: 62-6.

[3] World Health Organization. Obesity and overweight [fact sheet no. 311; online]. Available from URL: http://www.who.int/mediacentre/factsheets/fs311/en/index.html

[4] Haslam DW, James WP. Obesity. *Lance*t 2005; 366: 1197-209

[5] World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation [WHO technical report no. 894; Online]. Available from URL: http://whqlibdoc.who.int/trs/WHO_TRS_ 894.pdf

[6] Abernethy DR, Greenblatt DJ. Drug disposition in obese humans: an update. *Clin Pharmacokinet* 1986; 11: 199-213.

[7] Blouin RA, Warren GW. Pharmacokinetic considerations in obesity. *J Pharm Sci* 1999; 88:1-7.

[8] Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. *Clin Pharmacokinet* 2000; 39: 215-31.

[9] Abernethy DR, Greenblatt DJ. Pharmacokinetics of drugs in obesity. *Clin Pharmacokinet* 1982; 7: 108-24.

[10] Cheymol G. Clinical pharmacokinetics of drugs in obesity: an update. *Clin Pharmacokinet* 1993; 25: 103-14.

[11] Lee JB, Winstead PS, Cook AM. Pharmacokinetic alterations in obesity. *Orthopedics*. 2006; 29:984–988.

[12] Erstad BL. Dosing of medications in morbidly obese patients in the intensive care unit setting. *Intensive Care Med*. 2004; 30:18–31.

[13] Clin Buckley FP. Anaesthesia for the morbidly obese patient. *Can J Anaesth* 1994; 41: R94–R100

[14] Ijaz S, Yang W, Winslet MC, *et al*. Impairment of hepatic microcirculation in fatty liver. *Microcirculation* 2003; 10: 447-56.

[15] Han PY, Duffull SB, Kirkpatrick CM, *et al*. Dosing in obesity: a simple solution to a big problem. *Clin Pharmacol Ther* 2007; 82: 505-8.

[16] Bearden DT, Rodvold KA. Dosage adjustments for antibacterials in obese patients: applying clinical pharmacokinetics. *Clin Pharmacokinet* 2000; 38: 415-26.

[17] Semchuk WM, Sc M. Medication dosing guidelines in obese adults. *RQHR Pharmacy Services*. 2007.

[18] Pühringer FK, Keller C, Kleinsasser A, *et al*. Pharmacokinetics of rocuronium bromide in obese female patients. *Eur J Anaesthesiol* 1999; 16:507–10.

[19] Blouin RA, Mann HJ, Griffen WO Jr, *et al*. Tobramycin pharmacokinetics in morbidly obese patients. *Clin Pharmacol Ther* 1979; 26:508–12.

[20] Bauer LA, Blouin RA, Griffen WO Jr, *et al*. Amikacin pharmacokinetics in morbidly obese patients. *Am J Hosp Pharm* 1980; 37:519–22.

[21] Adams JP & Murphy PG. Obesity in anaesthesia and intensive care. *British Journal of Anaesthesia* 2000; 85: 91–108

[22] Jaber LA, Antal EJ, Slaughter RL, Welshman IR. The pharmacokinetics and pharmacodynamics of 12 weeks of glyburide therapy in obese diabetics. *European Journal of Clinical Pharmacology*. 1993 Dec 1; 45(5):459-63.

[23] Holford NH, Sheiner LB. Understanding the dose-effect relationship: clinical application of pharmacokinetic pharmacodynamic models. *Clin Pharmacokinet* 1981; 6:429–53.

[24] Akinnusi ME, Pineda LA, El Sohl AA. Effect of obesity on critical care morbidity and mortality: a meta-analysis. *Critical Care Medicine*, 2008; 36: p151-158.

[25] Alvarez A, Brodsky J, Lemmens HJ *et al*. Morbid obesity: perioperative management. 2nd ed. Cambridge University Press, 2010.

[26] Michael J. Hanley, Darrell R. Abernethy and David J. Greenblatt Effect of Obesity on the Pharmacokinetics of Drugs in Humans *Clin Pharmacokinet* 2010; 49 (2): 71-870312-5963/10/0002-0071

[27] Mosteller RD. Simplified calculation of body-surface area. *N Engl J Me*d 1987; 317: 1098.

[28] Field KM, Kosmider S, Jefford M, *et al*. Chemotherapy dosing strategies in the obese, elderly, and thin patient: results of a nationwide survey. *J Oncol Pract* 2008; 4: 108-13.

[29] Ingrande J, Lemmens HJ. Dose adjustment of anaesthetics in the morbidly obese. *British Journal of Anaesthesia*. 2010 Dec 1; 105(suppl 1):i16-23.

[30] Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clin Pharmacokinet* 2005; 44: 1051–65.

[31] Devine BJ. Gentamicin therapy. *Drug Intell Clin Pharm* 1974; 8: 650-5.

[32] Duffull SB, Dooley MJ, Green B, *et al*. A standard weight descriptor for dose adjustment in the obese patient. *Clin Pharmacokinet* 2004; 43: 1167-78.

[33] Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? *Br J Clin Pharmacol* 2004; 58: 119-33.

[34] Kirby. *Anaesthesia* 1987; 42:1125–1126.

[35] Ingrande. *Anesth Analg* 2011; 113:57–62.

[36] Servin. *Anesthesiology* 1993; 78:657–665.

[37] Albertin. *Br J Anaesth* 2007; 98:66–75.

[38] Buckley FP. Anaesthesia for the morbidly obese patient. *Can J Anaesth* 1994; 41: R94–R100.

[39] Jung D, Mayersohn M, Perrier D, Calkins J, Saunders R. Thiopental disposition in lean and obese patients undergoing surgery. *Anesthesiology*. 1982 Apr; 56(4):269-74.

[40] Greenblatt DJ, Ehrenberg BL, Gunderman J, Locniskar A, Scavone JM, Harmatz JS, Shader RI. Pharmacokinetic and electroencephalographic study of intravenous diazepam, midazolam, and placebo. *Clinical Pharmacology & Therapeutics.* 1989 Apr 1; 45(4):356-65.

[41] Reves JG, Fragen RJ, Vinik R, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology*, 1985; 62: 310–324.

[42] Weinstein JA, Matteo RS, Ornstein E, Schwartz AE, Goldstoff M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesthesia & Analgesia*. 1988 Dec 1; 67(12):1149-53.

[43] Kirkegaard-Nielsen H, Helbo-Hansen HS, Lindholm P, Severinsen IK, Pedersen HS. Anthropometric variables as predictors for duration of action of atracurium-induced neuromuscular block. *Anesthesia & Analgesia*. 1996 Nov 1;83(5):1076-80.

[44] Leykin Y, Pellis T, Lucca M, Lomangino G, Marzano B, Gullo A. The pharmacodynamic effects of rocuronium when dosed according to real body weight or ideal body weight in morbidly obese patients. *Anesthesia & Analgesia*. 2004 Oct 1; 99(4):1086-9.

[45] Leykin Y, Pellis T, Lucca M, Lomangino G, Marzano B, Gullo A. The pharmacodynamic effects of rocuronium when dosed according to real body weight or ideal body weight in morbidly obese patients. *Anesthesia & Analgesia.* 2004 Oct 1; 99(4):1086-9.

[46] Bentley JB, Borel JD, Vaughan RW, Gandolfi AJ. Weight, Pseudocholinesterase Activity, and Succinylcholine Requirement. *Survey of Anesthesiology*. 1983 Jun 1; 27(3):142.

[47] Kirkegaard-Nielsen H, Lindholm P, Petersen HS, Severinsen IK. Antagonism of atracurium-induced block in obese patients. *Canadian Journal of Anaesthesia.* 1998 Jan 1; 45(1):39-41.

[48] Van Lancker P, Dillemans B, Bogaert T, Mulier JP, De Kock M, Haspeslagh M. Ideal versus corrected body weight for dosage of sugammadex in morbidly obese patients. *Anaesthesia*. 2011 Aug 1; 66(8):721-5.

[49] Bentley. Anesth Analg 1983; 62:245–262.

[50] Salihoglu Z, Demiroluk S, Demirkiran O, Kose Y. Comparison of effects of remifentanil, alfentanil and fentanyl on cardiovascular responses to tracheal intubation in morbidly obese patients. *European Journal of Anaesthesiology*. 2002 Feb 1; 19(02):125-8.

[51] Maitre PO, Vozeh S, Heykants J, Thomson DA, Stanski DR. Population pharmacokinetics of alfentanil: the average dose-plasma concentration relationship and interindividual variability in patients. Anesthesiology. 1987 Jan;66(1):3-12.

[52] Bentley JB, Vaughan RW, Cork RC, Gandolfi AJ. Does Evidence of Reductive Halothane Biotransformation Correlate Halothane with Hepatic Binding of Metabolites in Obese Patients?. *Anesthesia & Analgesia*. 1981 Aug 1; 60(8):548-51.

[53] Schwartz AE, Matteo RS, Ornstein E, Young WL, Myers KJ. Pharmacokinetics of sufentanil in obese patients. *Anesthesia & Analgesia*. 1991 Dec 1; 73(6):790-3.

[54] Slepchenko G, Simon N, Goubaux B, Levron JC, Le Moing JP, Raucoules-Aimé M. Performance of target-controlled sufentanil infusion in obese patients. *The Journal of the American Society of Anesthesiologists*. 2003 Jan 1;98(1):65-73.

[55] Egan TD, Huizinga B, Gupta SK, Jaarsma RL, Sperry RJ, Yee JB, Muir KT. Remifentanil pharmacokinetics in obese versus lean patients. *The Journal of the American Society of Anesthesiologists*. 1998 Sep 1; 89(3):562-73.

[56] La Colla L, Albertin A, La Colla G, Porta A, Aldegheri G, Di Candia D, *et al*. Predictive performance of the 'Minto'remifentanil pharmacokinetic parameter set in morbidly obese patients ensuing from a new method for calculating lean body mass. *Clinical pharmacokinetics* 2010 Feb;49(2):131-9.

[57] Choi YK, Brolin RE, Wagner BK, Chou S, Etesham S, Pollak P. Efficacy and safety of patient-controlled analgesia for morbidly obese patients following gastric bypass surgery. *Obesity Surgery.* 2000 Apr 6; 10(2):154-9.

[58] Lee WH, KRAMER WG, GRANVILLE GE. The effect of obesity on acetaminophen pharmacokinetics in man. The *Journal of Clinical Pharmacology.* 1981 Jul 1; 21(7):284-7.

[59] DIC/KAUH drug dosing in obesity

[60] Garcia-Saiz M, Lopez-Gil A, Alfonso I, Boada JN, Armijo JA. Factors influencing cyclosporine blood concentration-dose ratio. *Ann Pharmacother* 2002; 36:193-199.

[61] Dvorchick BH, Damphousse D. The pharmacokinetics of Daptomycin in moderately obese, morbidly obese and matched non obese subjects. Journal of Clinical Pharmacology, 2005; 45:48-56.

[62] Cohen LG, Dibiasio A, Lisco SJ. Hurford WE. Fluconazole serum concentrations and pharmacokinetics in an obese

patients. *Pharmacother* 1997; 17:1023-1026.
[63] Ellison MJ, *et al*. Calculation of heparin dosage in morbidly obese woman. *Clin Pharmacokinet* 1989; 8:65-68.
[64] Spruill WJ, Wade WE, Huckaby WG, Leslie RB. Achievement of anticoagulation by using a weight-based heparin dosing protocol for obese and nonobese patients. *Am J Health-Sys Pharm* 2001; 58:2143-2146.
[65] Abernethy DR, Greenblatt DJ. Phenytoin disposition in obesity. Determination of loading dose. *Arch neurol* 1985; 42(5): 468-471.
[66] Wilkes L, *et al*. Phenobarbital pharmacokinetics in obesity. A case report. *Clin Pharmacokinet* 1992; 22:4814.
[67] Kendrick JG, Carr RR, Ensom MH. Pharmacokinetics and drug dosing in obese children. *The Journal of Pediatric Pharmacology and Therapeutics* 2010 Apr; 15(2):94-109.
[68] Mulla H, Johnson TN. Dosing dilemmas in obese children. Archives of disease in childhood-Education & practice edition. 2010 Aug 1; 95(4):112-7.
[69] Shibutani K, Inchiosa MA Jr, Sawada K, Bairamian M. Pharmacokinetic mass of fentanyl for postoperative analgesia in lean and obese patients. *Br J Anaesth* 2005; 95: 377–83.
[70] Brunette DD. Resuscitation of the morbidly obese patient. *The American Journal of Emergency Medicine*. 2004 Jan 31; 22(1):40-7.
[71] Richard AA *et al*. Comparison of Anti-Xa Levels in Obese and Non-Obese Pediatric Patients Receiving Treatment Doses of Enoxaparin. *J Pediatr* 2013; 162:293-6.
[72] Taylor BN, Bork SJ, Kim S, Moffett BS, Yee DL. Evaluation of weight-based dosing of unfractionated heparin in obese children. *The Journal of pediatrics*. 2013 Jul 31; 163(1):150-3.
[73] Hurewitz AN, Khan SU, Groth ML, Patrick PA, Brand DA. Dosing of unfractionated heparin in obese patients with venous thromboembolism. *Journal of general internal medicine.* 2011 May 1; 26(5):487-91.
[74] Janson B and Thursky K. Dosing of Antibiotics in Obesity. *Current Opinion Infectious Disease* 2012; 25: 634-649.
[75] Department of Health. Clinical Guidelines for immunoglobulin use. Second edition update, edited for Scotland. March 2013.
[76] Flagyl® (Metronidazole) Zentiva. Summary of Product Characteristics Accessed at www.medicines.org.uk 17th July 2013.
[77] Rice L, Hursting MJ, Baillie GM. Argatroban anticoagulation in obese versus nonobese patients: implications for treating heparin-induced thrombocytopenia. *J Clin Pharmacol* 2007; 47: 1028-34.
[78] Gibbs JP, Gooley T, Corneau B, *et al*. The impact of obesity and disease on busulfan oral clearance in adults. *Blood* 1999; 93: 4436-40.
[79] Sauer M, Rydholm N, Piatkowski J, *et al*. Nephrotoxicity due to intermediate-dose methotrexate without rescue in an obese adolescent with acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. 2002; 19:135–140.
[80] De Jonge ME, Mathoˆ t RA, van Dam SM, *et al*. Extremely high exposures in an obese patient receiving high-dose cyclophosphamide, thiotepa, and carboplatin. *Cancer Chemother Pharmacol* 2002; 50: 251-255.