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PHARMACOKINETIC CONSIDERATIONS IN DRUG DOSING TO PEDIATRIC OBESE PATIENTS

FARMAKOKINETIČKA RAZMATRANJA U DOZIRANJU LEKOVA PEDIJATRIJSKIM GOJAZNIM PACIJENTIMA

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Abstract

Since the incidence of obesity continues to increase globally, this source of disposition variability remains a significant issue for clinicians. The prevalence of overweight and obesechildren has increased worldwide, causing substantial concern over proper therapeutic dosing in this population. Pharmacotherapy in these patients represents a major challenge in the clinical practice, because obese patients are, often, excluded from the clinical trials. Consequently, data on drugs' pharmacokinetics (PK) in this population of patients are scarce, incomplete and/or inconclusive. It is previously observed that different degrees of obesity may change the PK profile of drug. Consequently, there is a need for the descriptors of size of the organism that best describes the changes in the composition of the organism in obese patients, and the one that best predicts key PK parameters that define dosage regimen. Changes in PK parameters of certain drugs are clinically important in the obese children and adolescent patients, requiring changes in usual dosage regimen.

INTRODUCTION

Globally, obesity has more than doubled since 1980, whereas childhood obesity tripled in the same period of time [1, 2]. In the following years, obese prevalence will increase as overweight and obese children (for 2 to 12 years) and adolescents (from 12 to 16 or 18 years) are likely to remain obese in the adulthood. Unfortunately, this suggests that health professionals will, in the near future, provide daily health-care services to the obese patients. Morbidity and mortality increase with obesity, where greater incidence of cardiovascular diseases, diabetes, hyperlipidemia, variety of cancers is observed [3, 4]. Accordingly, obese patients are multi morbid, and require multiple drug therapies.

Obese patients have significant changes in body composition that contribute to alterations in the pharmacokinetic (PK) profile of a drug. When studying PK of a drug in pediatric obese patients, at least two simultaneous factors are affecting it: patient's age and obesity [5, 6]. Ethical reasons limit the involvement of the pediatric subjects in the clinical trials, and, at the same time, obesity is neglected as a factor of variability during drug development. Additionally, existing studies are limited by the poor design and insufficient sample size [7]. Therefore, data on drugs' PK in this population of patients are scarce, incomplete and inconclusive. However, certain PK changesmaybeof a clinical importance, consequently requiring the adjustment of the drug's dosing regimen to individual patient needs [7-12]. Hence, adequate drug dosing to pediatric obese patients represents a major challenge for the health-care professionals.

ASSESSMENT OF BODY COMPOSITION IN OBESE PEDIATRIC PATIENTS

Previous studies have shown that obese children are taller, their total body weight (TBW) is increased due to increased, primarily, fat mass, and, to lesser extent increase in body water, lean mass in comparison to their normal-body-weight controls [13]. Traditionally, body fatness has been estimated from the measurements of the skin fold thickness. The accuracy of this approach is a major concern because of poor reproducibility, and the inclusion of only

few regional body sites for the measurement represents a major limitation. Consequently, height and weight-based parameters, adjusted for the age and gender, are the most practical descriptors of body size and its composition [14].

Pediatric dosing recommendations are, for the majority of medications, weight-based reflecting the use of TBW [15]. However, using obese child's TBW for calculating the dose according to the recommended milligrams per kilogram may not be justifiable, as TBW does not show proportionality with body structure. No supreme descriptor for PK-based drug dosing in obese exists. However, different body size descriptors for adults and/or pediatrics have been used in PK studies, such as: body mass index (BMI), body surface area (BSA), ideal body weight (IBW), percent of ideal body weight (%IBW), lean body weight (LBW), adjusted body weight (ABW), normal fat mass (NFM) [16-19]. In pediatric population, the assessment and the interpretation of such descriptors may be different comparing to the adults.

Body Mass Index (BMI) is the parameter used in international classification of obesity, which represents the ratio between TBW in kilograms and the square of height in meters. Unlike adult population, BMI in children and adolescents is age and gender dependent. Therefore, overweight and obesity classificationin adults does not apply to pediatric population. World Health Organization (WHO) provides the reference charts by BMI-for-age indicators for boys and girls from 5 to 19 years [1]. Hence, 23 kg/m^2 is healthy weight in adults while a 10-year-old boy with the same BMI would be in obese category since z-scores for his BMI exceeds 2 standard deviations for a median child's BMI for that age and gender, given by specific WHO growth standards [1]. It is shown that BMI represents reliable indicator of body fatness for most children and adolescents [2], however it does not measure directly fat tissue. Fat mass is mainly concentrated in abdominal region, and it represents 30-50% of children's TBW[13]. Additionally, increased hydration of lean mass due to increase in extracellular fluid was observed [13, 20]. This indicates that the use of BMI as ascalar parameter for drug dosing is limited, since patients with higher content of extracellular water may receivethe same dose as patients with increased fat content. For children under 5 years, obesity is defined if child's weight for height is greater than three standard deviations to the responding median values given by WHO growth standards [1].

Body Surface Area (BSA) takes into account person's TBW and height using specific equations [9, 21]. From the physiological point of view, this parameter may be suitable for drugs' dosing since it correlates reasonably well with basal metabolism, estimated glomerular filtration rate (eGFR), blood volume i.e. drug's PK characteristics [9]. Its use has been established for dosing many chemotherapeutic agents; though nowadays the justification of its use is questionable. Nevertheless, the equation for calculating BSA in obese patients is not well-defined. Although current recommendations for obese adults suggest using TBW for the BSA calculation when dosing cytotoxic chemotherapy drugs is BSA-based [22]. BSA does not considerate child's gender and age, and its use in drug dosing to obese pediatric patients is open for future research [9, 23]. Currently available data suggest that clearance of methotrexate, etoposide, tenipo-side, and cytarabine normalized to BSA did not differ between the weight stratified groups of patients [24].

Ideal Body Weight (IBW) is used to determine the optimal body weight according to the gender and height. Percent **Ideal Body Weight (%IBW)** quantitatively describes the TBW inrelation to IBW. Adult patients whose TBW is 30% over their IBW are considered obese, however there are no data confirming that same threshold may be acceptable in children and adolescents. Assessment of IBW for pediatrics is possible using growth charts, such as the ones proposed by WHO[1] or Center for Disease Control and Prevention [2] that consist of a series of percentile curves that illustrate the distribution of selected body measurements in pediatrics. Using IBW for drugs dosing would result in administrating the same dose to all pediatric patients same age, gender and height regardless thebody composition.

Lean Body Weight (LBW) is primarily composed of muscle, extracellular fluid, skeletal system, andvital organs. Itis a use ful parameter in adult obese patientswhen estimating PK parameters and dosage regimen, since almost in whole elimination processes (metabolism and excretion) take place within lean tissues [25]. In children, similar to adults, relationships between estimated LBM, extracellular fluid and TBW are defined. Therefore, drug dosage in children may also be based on the estimated LBM rather than TBW where proven its the use in adults [26]. It has great importance in loading and maintenance dose of some anesthetic agents [27].

Adjusted Body Weight (ABW)is introduced in order to optimize the dosage regimen of aminoglycoside antibiotics in adults, and it can be calculated as IBW+0.4(TBW-IBW) [28, 29].

PHARMACOKINETIC CHANGES IN OBESE CHILDREN AND ADOLESCENT PATIENTS

PK driven dosing is based on the PK parameters' values and target drug concentrations. These parameters adequately represent processes of drug absorption, distribution, metabolism and excretion, which are dependent on body size, maturation, and organs' functions involved in these process in pediatric patients [15, 18]. Anderson et al. illustrated that more than 80% of the observed variability in drug clearance (CL) can be explained by allometry principles and maturation process [18]. Given that overweight children tend to have earlier puberty maturation, and they are, in general, more mature [30], it emphasizes the need to take into account this factor when considering the PK changes in obese children.

Physiological/pathophysiological changes in obese patients may cause minor or major changes in the values of PK parameters that require considerations for changing the usual drug dosage regimen. Drugs' dosing based on TBW or BSA is not completely acceptable to obese patients as the structural and functional aspects of an organism are not similar in obese and non-obese pediatric patients. Structural aspects of the organism are defined by volume of distribution (Vd), while the functional is correlated with CL which reflects intrinsic capacity of the various organsand contribution of their perfusion to clear the drug [6, 12, 17]. Since data of the effect of obesity in pediatric population of patients are

scarce, extrapolations from obese adults, in spite of PK differences between pediatric and adult population, might be sometimes useful.

Minor changes in oral, subcutaneous or intramuscular drug **absorption are** observed; however the clinical importance of these variations is doubtful [31].

Distribution of drugs is affected primarily by the body composition, whereas regional blood flow, and drug affinity for tissue and plasma protein binding have minor importance[10]. The amount of fat mass normally changes throughout the childhood. As previously mentioned, the increase of TBW, absolute and relative fat content, lean mass and its hydration are observed in obese children [13, 20]. The presence of large amounts of fat can significantly affect Vd of the drug. Results of studies in adult population show that Vd is not always directly correlated with the degree of hydrophility or lipophility[11, 17]. The physiologic determinates of Vd are the actual blood volume (V_{blood}) and the volumes of the body tissues and organs ($V_{tissues}$) where drug distributes, taking into account unbound drug fraction (f), according to the following equation[29]:

$$Vd = V_{blood} + \sum \frac{f_{blood}}{f_{tissue}} \cdot V_{tissue}$$

Therefore, absolute amount of adipose tissue and the binding of drug in the tissue itself will determine how much obesity will affect drug's Vd. If the drug shows great affinity for adipose tissue, f in adipose tissue will be small, and a large amount of drug will accumulate in that tissue. Drugs with low and moderate lipophilic characteristics have limited distribution into excess fat tissue, so for hydrophilic drugs dosing on LBW or IBW might be straightforward. Vd of lipophilic drugs in obese is expected to increase due to drug's distribution into adipose tissue. However, increased TBW in obese is not accounted only for fat tissue, thus Vd of lipophilic drugs, as well, is variable in obese adults [10, 32, 33]. In addition, most drugs are not purely hydro- or lipophilic, so their distribution is rather between these extremes. Similar patterns may be also applied to obese children and adolescents. For instance, results reported by Rose et al. showed that dosing of succinylcholine, hydrophilic anesthetic drug, should be based on TBW [34], and not on LBW as previously reported [35]. In dosing succinylcholine, changes in PK parameters do not play major role, but increased pseudocholinesterase activity [34]. PK analysis performed on the measured tobramicin concentrations, confirmed, as expected, that Vd/TBW was significantly lower in obese children in comparison to non-obese children due to the physico-chemical characteristic of the drug and body composition in obesity [36, 37]. ABW was used to normalize the values of Vd in obese patients where TBW exceedsa certain percentage ofIBW [28]. Aminoglycosideantibiotics are relatively polar molecules with good water solubility. Therefore, they do not distribute in adipose tissue to any significant extent. However, in obese patients, Vd for aminoglycosides increases on account of the additional extracellular fluid contained in adipose tissue. The reason why aminoglycosides' Vd is affected by this relatively small amount of additional extracellular fluid in adipose tissue lays in its relatively small Vd of 0.26 L/kg. For other hydrosoluble drugs with larger Vd, the additional extracellular fluid in adipose tissue may not be a significant factor [29]. Then again, great number of studies confirms that changes in body composition in obese children and adolescents affect drug's extent of distribution [6, 7, 11, 12, 31]. Changes in Vd affect initial drug concentration following the administration of initial (single) dose, maximal drug concentration, and drug's half-life.

Metabolism undergoes variations in obese patients through changes in the activities of enzymes involved in I and/or II phase of metabolism [10, 38, 39]. There are limiting and not consisting results on the alteration of drugs' hepatic clearance (CL_H) in obese pediatrics [7, 31].

Excretion. Results of studies indicate non-uniform changes in the processes of glomerular filtration, tubular secretion and reabsorption, and consequently in the values of renal clearance (CL_R) of drugs in obese patients. If a drug is predominantly eliminated via kidneys, its CL_R is correlated with eGFR, which is, in pediatrics, calculated using Schwartz method [40]. However, it has not been validated in obese pediatrics. In obese adults, creatinine clearance (CL_{CR}) may be calculated using Salazar-Corcoran formula based on TBW, or Cockroft-Gault formula using LBW or IBW [41, 42]. In adolescent patients it has been showed that eGFR were significantly lower in obese and/or overweight than lean patients. A significant positive correlation was found between eGFR and BMI in obese children age7-16 years [43]. Hence, the effect of obesity on renal excretion remains open for further research.

Estimation of **initial dose (Di)** is based on value of Vd. This parameter has great importance when rapid achievement of desired levels is needed in order to attain drug effect. Vd can be expressed as an absolute value in liters or normalized to TBW or IBW. If there is a difference in the distribution coefficient values in obese patients and normal body weight, it is apparent that the drug distributes to an additional body weight. If no difference is observed, the drug shows the distribution into adipose tissue. In that scenario the calculation of Di is based on TBW. If the absolute value of Vd increases in obese individual, a distribution coefficient value is lower. This scenario indicates an incomplete distribution of the extra fat, and IBW or LBW should be used [6, 7, 10, 12, 17, 31-33]. **Maintenance dose rate** (given dose per dosing interval, Do/τ) is based on total drug's CL (sum of CL_R and CL_H). There is no consensus which body descriptor gives best prediction of CL, but it is clear that CL does not increase proportionally with TBW. According to Green and Duffull, LBW is the best descriptor of drug's CL [16].

CONCLUSIONS

PK changes in obese pediatric patients have clinical significance affecting theefficacy and safety of the medicines. In order to achieve optimal pharmacotherapy there is a needto adjust dosage regimen in obese children. Unfortunately, the results from clinical trials are lacking due to ethical reasons as well as from the fact that different stages of obesity may cause different effect of drugs' disposition. Previously published manuscripts have shown that there is no single body size descriptor, which describes the values of pharma-

co kinetic parameters in these patients. In considering the extrapolation of the results of performed studies to a specific patient, it is vital to critically appraise the study design, and ensure the whether the patient fits the characteristics of the population included in the study (e.g. age, range of BW, %IBW, BMI). Apart from PK changes, differences in PD in obese children and adolescents could be present and should be also taken into account when dosing.Therefore, healthcare professionals have to observe obesity as a complex source of variability in drug's profile, and to consider the need to adjust dosing regimen based on recommendations (if available), patient's degree of obesity, alterations in PK processes, drug dosing in obese adults, and the available results of the clinical studies in pediatrics.

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Sažetak

Obzirom da se globalno uočava kontinuiran porast incidence gojaznih osoba, gojaznost kao faktor varijabilnosti u dispoziciji leka postaje vrlo značajan aspekt razmatranja za kliničare. Prevalenca dece sa prekomernom telesnom masom i gojazne dece se povećava u svetu, dovodeći do nedoumica u pogledu pravilnog doziranja lekova u ovoj populaciji. Farmakoterapija ovih pacijenata predstavlja veliki izazov u kliničkoj praksi, jer su gojazne osobe, često isključene iz kliničkih ispitivanja. Stoga, podaci o farmakokinetici (FK) lekova u ovoj populaciji pacijenata su često oskudni, nepotpuni i/ili nisu utemeljeni na jakim dokazima. Primećeno je da različiti stepen gojaznosti može promeniti FK profil leka. Shodno tome, postoji potreba za deskriptorima veličine organizma koji najbolje opisuju promene u sastavu organizma kod gojaznih pacijenata, ali i definisati onaj koji najbolje predviđa vrednosti ključnih parametara FK koji definišu režim doziranja. Promene u FK parametrima određenih lekovakod gojazne dece i adolescenata imaju klinički značaj, što zahteva korekcije uobičajenih režima doziranja.

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