Drug Disposition and Therapy in Adolescence: The Effects of Puberty

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Puberty, a part of adolescence, is a time of rapid physical, psychological, and psychosocial changes. Variability in drug absorption, distribution, metabolism and excretion occurs due to physical and hormonal changes, as well as those of body composition. Environmental factors affecting nutrition and compliance in the pubescent individual also affect success in achieving desired pharmacologic effects while minimizing toxicities. Based on available data, pharmacologic research has been relatively inadequate in providing information about drug disposition during puberty. The majority of available studies have neglected to provide staging for pubescent adolescents or have altogether excluded this population from their investigations. However, data are available that describe the effects of puberty on the pharmacokinetics of agents such as theophylline, digoxin, carbamazepine, lamotrigine, vigabatrin and benzodiazepines.

To date, few clinically significant changes in drug disposition have been noted during puberty. However, factors such as compliance, concomitant drug use, and the potentially rebellious nature of adolescents must be taken into consideration in the medical management of the adolescent.

Keywords: drug disposition, puberty, adolescence, adolescent, pharmacokinetics

J Pediatr Pharmacol Ther 2003;8:86-96

INTRODUCTION

Puberty is a maturational and hormonal growth process dependent on biologic determinants. It is the physiological stage of becoming capable of reproduction. Although puberty and adolescence are often used interchangeably, puberty is only one aspect of adolescence. Technically speaking, puberty and adolescence are different, with puberty referring to the onset and continuation of the transition process from a child's body to an adult's body. Adolescence begins at puberty but also includes the social, psychological, cognitive, and emotional changes and extends up to the beginning of adulthood. Adolescence refers to the time period between the onset of secondary sex characteristics (e.g., puberty) and the completion of physical matu-

urity.¹ It is a period of rapid physical and psychological growth occurring during the second decade of life.²

The physical changes occurring during puberty have the potential to affect all aspects of a drug's kinetic profile.³ While differences in gastric pH and motility, drug distribution (e.g., total body water, percent lean mass, plasma protein concentrations), hepatic metabolism, and renal elimination between pediatric and adult patients are recognized, the time at which the individual makes the transition between the two domains of "child" and "adult" is hazy and often arbitrarily determined.³ The child undergoing puberty experiences not only physical changes, but also changes in emotions and socialization, as well as experimentation with smoking, alcohol, and illicit drugs.^{2,4} Behavioral changes that occur during adolescence pose added difficulties in drug management as rebellion and compliance with medication regimens become problems. Eating disorders, malnutrition, and poor dietary habits also can pose problems. The adolescent's concern regarding cos-

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metic appearance may increase. Social pressure to fit in and be the same as the group also increases. Trust issues may become a problem as adolescents begin to rebel against authority and view adults and authority figures, such as health care providers, with disdain.^{2,3} Exacerbations of chronic diseases which occur during adolescence often are considered to be due to non-compliance, but may be due to puberty-related changes in pharmacokinetic parameters (e.g., of digoxin, caffeine, and theophylline) or diseases (e.g., asthma and type 1 diabetes).^{2,5-8}

The adolescent patient is potentially at risk of therapeutic failure if changes in pharmacokinetics result in decreased therapeutic effect. Likewise, the patient may be at risk for toxicities if the physical changes of puberty increase serum drug concentrations. Because of the variability in the age at which children experience puberty, the speed at which the changes occur, and the psychosocial variability associated with adolescence, extra care in monitoring of drug therapy is required during this time period.

Despite the many rapid physical, psychological, and social changes that occur during puberty, few clinical studies have examined the effects of puberty on drug therapy. Pharmacokinetic studies tend to group adolescents with either pediatrics (where they are considered as older children) or adults (where they are considered young adults) without taking into account the individual's pubertal stage of development. One of the challenges in studying and treating diseases in children of this age group is that puberty is a very variable process in onset (commencing at a range of ages 11–15 years), duration (progressing at a variety of rates), and final outcomes (variation in height, secondary sexual characteristics, etc.).^{2,4} In order to meet the goals of drug therapy [i.e., to produce the desired pharmacological effect (efficacy) while minimizing toxicities and adverse drug reactions], drug therapy must be individualized to the specific individual and modified as needed to account for the changes occurring during puberty. When dealing with the adolescent, the psychological as well as the physiological changes occurring during this time of life must be taken into account.

The purpose of this paper is to describe general changes that occur during puberty and to review available evidence describing the effects of puberty and adolescence on the disposition

of specific drugs. The implications of puberty on drug therapy also will be discussed.

SEARCH STRATEGY

Search terms used were: puberty, adolescence, adolescent, pharmacokinetics, kinetics, drug disposition. The databases searched were: Medline (1966-2001), EMBASE (1988-2001), Healthstar (1975-2000), and Current Contents (1996-2001).

TANNER STAGES OF PUBERTY

Pubertal development was classified into stages by Tanner et. al. in 1962.⁹ The determination of the stage of puberty is determined by physical examination and based on stages of breast development and the growth of pubic hair for females and genital development and pubic hair growth in males. Stage 1 is considered very early puberty, and stages IV and V are late stages of puberty.^{1,9-11} The Tanner staging correlates with phase of development but not with chronological age. Tanner staging was created using a cohort group of European adolescents. Its utility in other ethnic groups has not been evaluated. A limitation of the Tanner staging system is that it requires subjective scoring and assessment of physical examination parameters and is therefore subject to inter-rater variability. Furthermore, Tanner staging has not been correlated quantitatively with the biochemical and hormonal changes of puberty. However, Tanner staging has been well-characterized as a method to assess the stage of sexual maturity and to predict the timing of growth spurts.¹²

PHYSICAL AND HORMONAL CHANGES OF PUBERTY

Puberty and adolescence are a time of great physical change for the individual and also for increased differentiation between females and males with the development of secondary sexual characteristics (Table). Until the age of approximately 12 years, body size for females and males is essentially the same.³ Differences between the sexes are seen at puberty.

Around the age of 7 or 8 years, due to critical body mass, the hypothalamus produces gonadotropin-releasing hormone (Gn-RH), which

increases the amount of circulating adrenal androgens. The adrenal androgens activate the hypothalamic-pituitary-gonadal axis. The hypothalamic-pituitary-gonadal axis is active during fetal development and the first few months of life to create the primary sex characteristics. It then becomes dormant until the reactivation around 10 years of age. This reactivation initiates puberty. Other pituitary hormones such as thyroid stimulating hormone and adrenocorticotrophic hormone do not rise at puberty. The hypothalamus releases follicular stimulating hormone and luteinizing hormone releasing factors, which act on the anterior pituitary to release follicular stimulating hormone and luteinizing hormone in a pulsatile fashion.¹⁰

In females, follicular stimulating and luteinizing hormones act on the ovary causing it to release estrogens and progesterones. The concentrations of both hormones increase steadily from the age of 10 years leading to an increase in estradiol and estrone. After menarche begins, progesterone concentrations increase during the second part of the menstrual cycle. Plasma concentrations of adrenal androgens DHEA and DHEA-S increase earlier, beginning at around 7 years of age. Prolactin concentrations increase in late puberty, presumably because of the effects of estrogen.^{10,11}

In males, plasma gonadotropins begin to rise from 11 years of age. Follicular stimulating hormone and luteinizing hormone act on the testes to initiate spermatogenesis and cause the production and release of androgens. Plasma testosterone increases from 12 years of age and reaches adult levels around 15 years of age. A slight increase in plasma estradiol and estrone concentrations is observed in the late stages of puberty. Plasma adrenal androgens increase at 8 years of age, 3 years before the initiation of puberty.¹⁰

Growth accelerates during puberty but at different rates and endpoints between females and males. Numerous factors influence the age of puberty and its development. Genetic or familial delays or early onset in puberty, endocrine abnormalities, nutrition and activity (e.g., sports) all play a role.⁷

Females

Signs of sexual development include enlargement of ovaries, uterus, vagina, labia, and breasts as well as growth of pubic hair. Puberty in fe-

males is associated with an increased level of active gonadotropins, which leads to follicular development in the ovary with a subsequent increase in circulating gonadal steroids.¹¹ The average age of onset of menarche in North America is 12.5 years. Although the mean age of menarche has steadily decreased over the past century in developing nations, the earliest age of menarche has remained unchanged.¹⁰ The onset of menarche tends to correspond with physical size rather than chronological age.¹⁰ Approximately 90% of menstrual cycles occurring in 12 to 14 year olds are anovular, but by 21 years of age, 60%–80% are ovular. Lean body mass increases during early puberty, peaks at menarche and then decreases in late puberty. Fat mass starts to increase in late puberty. Total body water decreases by approximately 5% by the end of puberty.²

Males

Males go through puberty at a slightly later age than females, between 11.2–15.3 years of age. Their signs of sexual development consist of increased genitalia size, increased testicular volume, and pubic hair growth. Voice changes occur as a result of androgen-induced enlargement of the larynx. A growth spurt occurs, the height velocity changes, and skeletal maturation (fusion of epiphyseal cartilages) occurs. Both growth hormones and sex steroids are responsible for growth, and it cannot occur normally in the absence of either one.²

Changes in body composition in males also occur and vary from changes in females. Lean body mass increases during early puberty and continues throughout puberty. In contrast to females, males' total body water increases by 5% by the end of puberty.²

NUTRITION

Protein-calorie malnutrition and micronutrient deficiencies may appear during periods of rapid growth in early adolescence because of poor quality diets, the development of eating disorders or the inability to keep up with the caloric demands of rapid growth.² Nutritional deficiencies can not only affect drug absorption, but may also alter drug metabolism if required cofactors are lacking. Likewise, drug distribution may be affected if malnutrition has caused plasma proteins to decrease. For instance, the free

Table. Growth Parameters That Change as a Result of Puberty

PARAMETERS	MALE	FEMALE
Age at puberty (range)	11.2–15.3 yr	10.5–15.2 yr
Skeletal growth	growth spurt: 12–16 yr longer prepubertal growth period h of 7–12 cm in height/yr at peak growth	growth spurt: 10–14 yr shorter prepubertal growth period h of 6–11 cm in height/yr at peak growth
Body composition	h total body water by 5% (61% to 65% total body water) n ECF h ICF h LBM	i total body water by 5% (61% to 54% total body water) n ECF i ICF h LBM at early stages of puberty h fat mass (2 times > males) and i LBM at later stages of puberty
Sexual characteristics	genitalia growth and development h testicular volume pubic hair growth voice changes	breast development menstruation enlargement of ovaries, uterus, vagina, labia pubic hair growth

LBM = lean body mass; TBW= total body water; ECF= extracellular fluid; ICF= intracellular fluid; ↑ = increase; ↓ = decrease; ↔ = remains constant

fraction of highly protein-bound drugs (e.g., phenytoin, valproic acid) may be increased.⁴

GENERAL CHANGES IN PHARMACOKINETICS DURING PUBERTY

Absorption

Few studies have compared absorption differences between adolescents and children or adults, it has been suggested that adolescents have slower absorption of ethosuximide, phenobarbital, diazepam, and imipramine than do children.^{4,13}

Adolescence is a high-risk period for the development of eating disorders.⁸ Eating disorders such as bulimia, during which forced vomiting and laxative abuse occur, may affect drug absorption by removing the drug from the gut before it can be absorbed adequately. Anorexia nervosa and bulimia also can affect gastric morphology, pH and motility.⁴ Females' dieting and starvation to conform to societal body images can lead to malabsorption and malnutrition. If malabsorption is present, larger doses of drug are required to achieve the same serum concentrations in those who are not malnourished.⁴

Distribution

During puberty, albumin and α -1 acid glycoprotein concentrations increase up to two fold

and their binding affinities may change because of interactions between albumin and globulins, which may alter albumin binding affinities.¹³

Once a drug has entered the systemic circulation, it is distributed to interstitial and cellular fluids. The initial phase of distribution depends upon cardiac output and regional blood flow to certain organs that are highly perfused. During the first few minutes following drug administration, the liver, heart, brain, and kidney receive most of the drug.⁴ The ratio of organ size to total body weight decreases as age increases, which may increase the amount of drug available to distribute to other tissues. The second phase of distribution is longer than the first as the drug penetrates into the remaining, less highly perfused compartments. These compartments include muscle, fat, skin, and viscera. This phase may take minutes to hours depending on the chemical properties of the drug.⁴ Body fat increases in females at the end of puberty and accounts for 25% of total body weight in females versus 12% of total body weight in males by the end of puberty.² The changes in body fat and lean body tissue may impact drug distribution in tissue, plasma protein binding, and free fraction of drug in serum.

During adolescence, height increases by approximately 25%, and weight is nearly doubled. Bone may act as a reservoir for some drugs (e.g.,

tetracyclines, and toxins such as lead). The increased rate of bone growth during adolescence may result in a larger surface area for drug absorption to the bone surface and incorporation into bone during bone production. Drugs affecting vitamin D metabolism (e.g., phenytoin and phenobarbital) may decrease bone growth during the growth spurt of puberty and potentially can lead to the development of rickets or decreased stature.⁴

Metabolism

Before puberty, drug metabolizing activity and general liver function are similar in male and female children. During puberty, the presence of higher levels of sex steroids alters both the structure, due to increasing liver size, and the function of the liver and creates differences in rates of biotransformation between males and females. Androgens in males and estrogens in females may act via pituitary growth hormone to induce, inhibit and maintain gender-specific isoenzymes. Oxidation and hydroxylation enzyme systems compete with sex steroids for substrate.¹⁴ These changes are likely to influence drug metabolism.⁴ Differences exist between the sexes for both phase I and phase II reactions. For example, males have higher clearance rates of propranolol than females in both the phase I reaction side-chain oxidation and the phase II glucuronidation.¹⁵ Evaluation of changes in metabolism during puberty is confounded by the genetic variations and fast and slow metabolizers of certain drug metabolizing enzymes. Studies performed to date have not characterized well the changes in metabolism based on puberty, nor have they accounted for pharmacogenetic factors. Major changes involve cholesterol and steroid hormone metabolizing enzymes in the liver and reproductive organs. Evidence suggests that maturation of the cytochrome P450 system occurs during puberty.²

Cytochrome P450. Cytochrome P450 (CYP) is the primary oxidative pathway of drug metabolism. It also is a major site of drug-drug, drug-nutrient, and drug-disease interactions. Changes in cytochrome P450 metabolism can have profound effects on response and toxicity due to "sub-therapeutic" and "supra-therapeutic" serum drug concentrations, respectively. The cytochrome P450 group of enzymes is subject to wide inter-patient variability due to differences

in genetics, diet, and concomitant drug therapy among patients. Data suggest that from birth to adulthood, the P450 metabolism pathways mature. In neonates and infants, P450 enzymes function at 20–70% of adult values but during growth and development, the pathways develop and mature to adult levels.¹⁶ Development of this enzyme system is isoform specific. For example, CYP3A4, a primary isoform in adults, is not found in fetal liver whereas CYP3A7 is present in all fetal livers but found in only approximately 50% of adult livers tested.³

There is little information regarding the influence of puberty on the cytochrome P450 enzyme systems. Lambert et. al. suggested there is a Tanner stage-dependent decrease in clearance of caffeine via the oxidation demethylation process of CYP1A2.¹⁷ Caffeine clearance was determined using a caffeine breath test. In their study of 62 subjects aged 3 to 20 years (all non-smokers, 36 male and 26 female), a comparison of pubertal stage and gender demonstrated significant differences in female Tanner stage 1 versus stage 5 and males Tanner stages 1,2,3, 4 versus 5. The higher Tanner stages had lower clearances ($P<0.05$). A difference also was observed in gender responses, with the lower clearance values seen at an earlier Tanner stage of puberty in females than in males.¹⁷

Acetylation. The rate of acetylation is controlled genetically with individuals such that they can be identified as having a slow or fast acetylator phenotype. There may be an age-related decrease in acetylation capacity; however, the magnitude of the change is most likely small during adolescence.¹⁸ Rey et. al.¹⁸ investigated the effect of age on isoniazid pharmacokinetics. Patients were divided into fast and slow acetylators. The majority of the patients were adults, and only 3.5% of the patients (16 of 458 patients) were under 15-years-old. No correlation was found between age and clearance in the fast acetylators, and although differences in oral clearance in the slow acetylators occurred around adolescence, the magnitude of the difference reached only 30% ($P=0.05$). There was no significant difference in half-life between the two age groups in either the slow or fast acetylator groups. The Tanner stage was not taken into account in the study.¹⁸

Glucuronidation. Acetaminophen and lorazepam are substrates for glucuronidation and have been studied in adult and pediatric popu-

lations. Glucuronidation capacity increases with increasing age. The glucuronidation of acetaminophen appears to reach adult levels in children by the age of 12 years.¹⁸ A study of lorazepam pharmacokinetics by Crom et. al. demonstrated higher lorazepam clearances in children than in adults and similar clearances in adolescents and children.¹⁹

Sulfate Conjugation. Heparin, catecholamines, steroids, terbutaline, salbutamol and acetaminophen all undergo sulfate conjugation. Sulfation appears to compensate for underdeveloped glucuronidation pathways. Sulfation capacity decreases with increasing age. However, sulfation rates have not been studied in adolescents.¹⁸

Excretion

Glomerular Filtration Rate (GFR). Glomerular filtration rate is commonly estimated by calculating creatinine clearance based on endogenous serum creatinine concentrations.^{20,21}

The estimate is used to modify dosing regimens for drugs that are cleared renally. Although the serum creatinine level varies inversely with GFR, the relationship between serum creatinine and GFR also varies during growth of children. At comparable levels of renal function, the serum creatinine concentration increases with age. Schwartz et. al. studied the relationship between length (height) and serum creatinine in 223 individuals aged 6 months to 20 years old.²¹ They gave each of the subjects a water load of 800 mL per 1.73 m² and collected 3–5 consecutive timed (20 to 30 minutes apart) urine specimens. They found no difference in the relationship between height and serum creatinine between males and females in prepubertal and postpubertal children. There appears to be no difference in GFR corrected to a body surface area of 1.73 m² between children greater than one year old and young adults.²¹

Serum creatinine concentrations vary with age, gender, diet, and muscle mass. Values of serum creatinine are lower in children and adolescents than in adults and also in females compared with males. Normal serum creatinine is 0.9 to 1.3 mg/dL in adult males and 0.6 to 1.1 mg/dL for adult females. Normal serum creatinine ranges from 0.3 to 0.7 mg/dL in children and from 0.5 to 1.0 mg/dL in adolescents.²²

Tubular Secretion. Tanner stage may corre-

late better than chronological age with a decline in apparent renal tubular clearance, which occurs during adolescence and in the later stages of pubertal development. The ratio of drug clearance to creatinine clearance decreases for some drugs (e.g., digoxin) during puberty.^{20,23}

The renal processing of uric acid changes during development. The excretion of uric acid is complicated and involves filtration, reabsorption, secretion and postsecretory reabsorption. Serum uric acid concentrations in children average 3.6 mg/dL from the third day of life until prepubertal years. Adult values are approximately twice as high as those of prepubescent children, and the levels in adult males are approximately 1.2 times those of adult females until menopause.²⁰

BODY SURFACE AREA (BSA) VERSUS WEIGHT FOR DRUG DOSING

Often the decision to use body surface area (BSA) or weight for calculating drug dosage is arbitrary. The clinical importance of differentiating between the two is significant because the proportional increase in body size from the age of 2 years to 18 years is 5.5 fold for weight, but only 3 fold for BSA. Dosing of most drugs is based on body weight (i.e., mg/kg); however, certain drugs, such as chemotherapy agents and corticosteroids for physiologic replacement, use BSA (i.e., mg/m²) for dosage calculations.²⁴ In the absence of evidence determining which method of drug dosing best predicts pharmacological effect and avoids toxicity, the clinical decision for empiric initial dosing in pubescent patients must be based on the arbitrary determination of whether the physical attributes of the adolescent more closely resemble an adult or a child. Of course, if the adolescent is at adult weight, appropriate drug dosing (i.e., maximum mg per dose or per day) should occur to prevent overdosing that might result from the use of mg/kg dosing. Basing the decision on purely the chronological age of the adolescent should be avoided because of the wide variability in physical characteristics of this age group.⁴

DRUG INTERACTIONS

Many adolescents begin experimenting with recreational drugs, alcohol, smoking, and use

over-the-counter (OTC) medications and prescription medications such as oral contraception often without their parents' knowledge.^{2,5,7} Many teens are reluctant to admit to the use of such agents, especially in front of their parents. Health care professionals need to be aware of this and take it into consideration during medication and social history taking. The inappropriate use of OTC medications, illicit drugs, or potential drug-drug interactions should also be taken into account if unexplained pharmacological effects or adverse drug reactions are occurring. For example, sedation or behavior changes from antiepileptic or other sedating medications may be enhanced if alcohol and other sedatives are being used. Likewise, a worsening of asthma may occur in an adolescent that has begun to smoke tobacco or marijuana.

ADHERENCE ISSUES

Martin et. al. evaluated the incidence of near-fatal asthma in childhood over a 3-year period.⁶ Although not rated on the Tanner scale of puberty, 53% of the subjects (n=30) were between 12 and 15 years of age. None of the patients smoked, but 32% had first degree relatives who smoked at home. Medical management was assessed, and all patients (100%) used β -agonists, 68% used an inhaled steroid and inhaled β -agonists, and none used a spacer device. Compliance was assessed by interviews with the patient, the patients' general practitioners and/or treating specialists, allied health professionals, and household or other close acquaintances, within 12 weeks of the acute asthma exacerbation. The interview consisted of using a validated illness behavior questionnaire, which asked questions regarding personal details, previous asthma symptoms and management, and circumstances surrounding the near fatal episode. Compliance was noted to be a problem in 58% of the patients. Psychosocial factors were considered to have significantly affected asthma management in 73% of the subjects. Based on denial scores, 43% were determined to have severe denial regarding their asthma and its severity. Eighty-three percent of the patients studied were judged as having preventable asthma exacerbations.

Miller studied compliance to theophylline therapy in 21 adolescent patients (12–17 years old) with chronic asthma.²⁵ The authors assessed

compliance by measuring serum theophylline concentrations in patients who self-reported compliance with their regimens and who were appropriately dosed with long-acting theophylline preparations based on literature guidelines. Serum theophylline concentrations were measured, and theophylline dosage (mg/kg/day) was calculated in patients who were purported to be compliant with their medications. Only 10% of patients were found to have serum theophylline concentrations within the desired reference range (10–20 ug/mL), and the mean serum concentration was below the desired range (mean 5.2 ± 4.2 ug/mL). Dosing was calculated to be appropriate based on literature guidelines (mean 21.5 ± 3.6 mg/kg/day). Confounders that may have attributed to decreased serum theophylline concentrations were accounted for and not thought to be contributory. No correlation was made between compliance, theophylline serum concentrations, disease control, or frequency or severity of asthma exacerbations. The author concluded that noncompliance among adolescent asthmatics is significant and that drug serum concentrations and education regarding the therapeutic actions of the medication and the necessity of compliance was important in the medical management of the adolescent with chronic diseases.²⁵

Teenagers who have an exacerbation of chronic disease during puberty are often assumed to be noncompliant. However, changes in drug distribution and clearance (i.e., metabolism and excretion) at different ages (pediatrics versus geriatrics) may not be taken into account when drug dosing adjustments are considered.²⁵ The dosage of medication used prior to the onset of puberty may become inappropriately high or low and may produce toxicity or an exacerbation or relapse of disease. Either way, teenagers are less likely to remain compliant if the medication is causing unpleasant side effects or is not controlling their symptoms. However, the adolescent may be inappropriately dosed as either a child or an adult depending on the clinician and the drug being given. Drug and dosing regimens should not be based on the chronological age of the child but rather his/her stage of pubertal development and maturity. Careful discussion with the adolescent patient regarding the importance of compliance, self-monitoring and prompt reporting of changes in disease, drug efficacy or

the development of adverse drug reactions is necessary. It is essential that the adolescent be given the feeling of control over his/her drug therapy and decision making.

DRUG-SPECIFIC PHARMACOKINETIC DIFFERENCES DURING PUBERTY

Theophylline

The bronchodilator, theophylline, has a long history of use in the management of chronic asthma in children, adolescents, and adults. Cary et. al. studied the clearance of theophylline in 70 non-smoking, asthmatic adolescents (48 outpatients and 22 hospitalized patients), 8–18 years old.²⁶ Half-life was shorter in younger patients than in older patients and correlated with Tanner developmental stage (Tanner, $r=0.42$; age, $r=0.33$; $P<0.01$). The longer half-life with increasing age was described as a relationship between lean body mass or total body weight. Volume of distribution correlated with lean body mass ($r=0.80$, $P<0.01$). Clearance was found to be correlated to a lesser extent to total body weight ($r=0.51$, $P<0.01$). The increase in half-life seen during puberty is likely related to the increase in the volume of distribution related to the stage of development and growth. The authors recommended that serum concentrations of theophylline be closely monitored in older children and adolescents and the dosage adjusted downward or the dosage interval increased appropriately during puberty to avoid toxicities or “supratherapeutic” serum concentrations of theophylline.²⁶

Digoxin

The positive inotrope, digoxin, is used in the management of heart failure, atrial fibrillation, and other supraventricular tachyarrhythmias. Linday et. al. studied the effect of puberty on the net renal tubular secretion of digoxin and correlated the ratio of digoxin clearance to creatinine clearance with both the Tanner stage of puberty and chronological age.²⁷ They examined 45 patients aged 2 months to 80 years who received digoxin for the treatment of congestive heart failure or arrhythmias. Serum creatinine was within the reference ranges for all patients. Net tubular secretion of digoxin, measured as the ratio of digoxin clearance to creatinine clearance, was lower in adults compared to children (children

1.49 ± 0.67 versus adults 0.82 ± 0.25 , $P<0.05$). The pubertal group was divided into two subgroups based on Tanner stage. The mean digoxin/creatinine clearance ratio was statistically higher ($P<0.05$) in the immature subgroup (1.45 ± 0.66) compared to the mature subgroup (0.95 ± 0.28). The decrease in net tubular secretion of digoxin from childhood to adulthood appears to correlate better with sexual maturation or the stage of puberty than with chronological age.²⁷

Anticonvulsants

Carbamazepine. Carbamazepine is a traditional anticonvulsant used to control simple or complex partial and generalized tonic-clonic seizures in adults and children. It is a challenging drug to dose as it has a narrow reference range. There is not a strong relationship between the dose and desired effect, and many factors (e.g., concomitant medications, smoking, age, co-morbid diseases, autoinduction) affect its pharmacokinetics. Clearance per kilogram body weight decreases as age increases; hence, the dose per kilogram body weight needs to be reduced accordingly.²⁸ With the sudden changes in growth and body weight during puberty, close monitoring for toxicity is essential during this period of development. Delgado Iribarugaray et. al. retrospectively studied 201 children, aged 1–14 years old, who had 387 serum carbamazepine concentrations measured.²⁹ The children had been taking carbamazepine for 1–3 years. The authors also validated the results with the prospective data of 74 children. The authors concluded that clearance increased linearly with total body weight and non-linearly with age. They took into account only total body weight and chronological age and not the developmental stages of puberty.²⁹

Lamotrigine. The anticonvulsant, lamotrigine, is used in the treatment of partial and generalized epilepsy. Battino et. al. studied the effects of age and concomitant treatment retrospectively in 106 patients with epilepsy (40 children and adolescents, 2 months to 16 years old, and 66 adults 17 to 62 years old).³⁰ No correlations between the administered lamotrigine dose and serum concentrations were found in either age group. Thirteen of the 40 children and adolescents were taking at least one enzyme-inducing anticonvulsant (e.g., carbamazepine, phenytoin, phenobarbital, mesuximide, or

primidone), 15 were taking valproic acid, and 12 were taking anticonvulsant medications not thought to affect drug metabolism (e.g., ethosuximide, vigabatrin, clobazam). The concentration to dose ratio was highest in the 9–14 year-old age group, in patients receiving lamotrigine as monotherapy. In the patient group receiving lamotrigine plus an inducer (such as carbamazepine), the 9–14 year-old group had similar concentration to dose ratios as the 14–30 year-olds. The stage of puberty was not studied. The authors concluded that patients receiving concomitant enzyme-inducing anticonvulsant drugs require a larger lamotrigine dosage, while those receiving valproic acid require a smaller lamotrigine daily dose. They also concluded that children and adolescents require larger daily doses of lamotrigine than adults to achieve serum concentrations in the desired reference range. The variability in the ratio of dose based on body weight to serum concentration make dosing based on body weight a poor predictor of serum concentrations. The authors suggest measuring serum lamotrigine concentrations at the beginning of treatment to determine the optimal dosage.^{28,30-32}

Vigabatrin. Although not available in the United States, vigabatrin is an irreversible inhibitor of GABA-transaminase, the enzyme mainly responsible for GABA catabolism in the central nervous system. The pharmacological action outlasts its presence in serum, making drug concentration monitoring of little benefit in clinical decision making. Armijo et. al. studied the influence of age and associated anticonvulsant drugs on serum vigabatrin concentrations in 179 patients (114 children, 1–14 years old, and 65 adults, 15–62 years old) with epilepsy.³³ The patients were divided into 5 age groups (<5 years, 5–9 years, 10–14 years, 15–30 years, and >30 years). Thirty-three patients (30 children and 3 adults) were taking only vigabatrin, and the rest of the patients were also taking concomitant anticonvulsants medications. Vigabatrin trough serum concentrations correlated better with dosage in mg/kg in children than in adults ($r=0.62$, children versus $r=0.17$, adults; $P<0.001$). The concentration to dose ratio appears to increase linearly from early childhood to adolescence in an age-related fashion; however, the effects of the

pubertal stage of development on drug serum concentration to dose ratio were not compared to chronological changes in the drug serum concentration to dose ratio.³³

Benzodiazepines

Although benzodiazepines are primarily used in children as anticonvulsant therapy, there is an increasing recognition of anxiety disorders in children and adolescents. Adolescents with severe chronic illnesses such as asthma may also suffer from anxiety and depression, especially if they are steroid dependent.³⁴ Alprazolam has shown efficacy in treating overanxious or avoidant disorders in children and adolescents and is used in the treatment of anxiety-triggered asthma. Devane et al. studied serum concentration monitoring of alprazolam in 6 adolescents with severe asthma.³⁴ The dosage ranged from 0.75–3.0 mg/day. Clearance was calculated for 3 of the patients (0.83–1.36 mL/min/kg) and was found to be within the range reported in adults (0.7–1.5 mL/min/kg). The authors concluded that the clearance of alprazolam was similar in adolescents and in adults when similar doses were used. The range of tolerable drug serum concentrations appears to be similar to that in adults in that it is wide and variable.³⁴

Similar results were found with lorazepam (often used as a probe substrate for determining Phase II metabolic activity), where higher lorazepam clearances were seen in children than in adults and similar clearances in adolescents and children.¹⁹ Crom et. al. studied lorazepam pharmacokinetics in 50 children and adolescents who were in complete remission from acute lymphocytic leukemia, aged 2.3–17.8 years, and compared them with a group of 10 healthy adults. Thirteen children were between 13 and 17.8 years old (i.e., adolescents). Total and unbound lorazepam clearance values, normalized to body weight, were not significantly different between children and adults. However, clearance values were smaller in all children (including the adolescents) when normalized to body surface area (i.e., total clearance 31.9 versus 40.6 mL/min/m², respectively, $P=0.036$; unbound clearance 352 versus 485 mL/min/m², respectively, $P=0.010$). Mean total clearance for the adolescents was 33.9 mL/min/m², and unbound clearance was 364 mL/min/m². Statistical analysis was not performed to compare the adolescent group to ei-

ther the children ≤ 12 years of age or adults; however, the values were similar to the children's group. The Tanner stage of development was not taken into consideration.¹⁹

CLINICAL DECISION MAKING CONSIDERATIONS

Most studies either exclude adolescents between the ages of 12 to 16 years or, if adolescents are included, do not consider the Tanner pubertal stage. Since puberty occurs at a range of ages in children, pharmacokinetic studies need to address the pubertal stage of subjects within the 11- to 16-year age range rather than their chronological age. Unfortunately, a small number of studies have done this.

Based on the available data, few clinically significant changes in drug disposition are seen during puberty. However, factors such as compliance, concomitant drug use (often not reported by the patient), and the rebellious nature of adolescents must be taken into consideration in the medical management of the adolescent. Monitoring of serum drug concentrations may be of use to assess medication adherence and appropriate dosing of medications with established desired serum concentration ranges. For medications not routinely monitored using serum concentrations, careful assessment of compliance and appropriate use of devices, such as inhalers, should be done prior to increasing the dose of medication. During puberty, a period of rapid growth, large increases in drug doses may be necessary to "keep up" with changes in body weight, height, and surface area.

Key research questions regarding changes in drug disposition during puberty and adolescence that need to be addressed include the following: 1) which changes are clinically relevant?; 2) is there a correlation with quantifiable surrogate markers?; 3) and what are the specific dosing change recommendations that should be made, based on the changing kinetic parameters?

Until further data are available, the decision as to whether to treat the adolescent as a "big child" or a "small adult" should be based on the pubertal stage and physical size of the individual and not on the chronological age.

CONFLICTS OF INTERESTS The authors declare no conflicts of interest or financial interest in any product or service mentioned in the manuscript, including grants, employment, gifts, and honoraria.

NOTE At the time the review was performed, Dr. Roxane R. Carr was a Doctoral of Pharmacy student at the University of British Columbia, Vancouver, B.C.

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