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Pediatrics: pharmacokinetics and dose calculation

Abstract

The pediatrics has various pharmacodynamic, physiological and pharmacokinetic properties as well as growth rate in comparison with adults. Gastric pH is neutral at birth but falls to pH 1-3 within twenty four to forty eight hours after birth. At birth, the blood-brain barrier is still not fully mature and medicinal products perhaps obtain access to the central nervous system with sequence toxicity. Plasma protein attaching of compounds is dependent on the amount of present attaching proteins, the number of available binding sites, the affinity constant of the medicine for the protein(s), and the availability of pathophysiological conditions or endogenous compounds that perhaps change the medicine-protein attaching interaction. Total body water, explained as percentage of body weight, reduces with age, from comparatively 80% in newborns to 60% by 1 year of age. Reversibly, body fat accelerates with age, from one percent to two percent in a preterm neonate to ten percent to fifteen percent in a term neonate and 20 to 25% in a 1-year-old. First-pass metabolism of zidovudine was decrease in the first 14 days of life. At birth, renal blood flow is only 5 to 6% of cardiac output, 15 to 25% by one year of age and reaches adult values after two years of age. Children's dosage depends on factors such as their age and weight, their health status, their respiratory system, and the stage of development of their body systems for drugs metabolism (e.g., liver enzymes) and elimination (e.g., kidneys). Young's rule can be applied quickly approach a situation in which the patients weight is unknown; this rule cannot be used for newborns and consideration must be made for growth variability in growth at any given age. A young's rule for calculating the dose of medicine correct for a child by adding twelve to the child's age, dividing the sum by the child's age, then dividing the adult dose by the figure obtained, as it expressed beneath: (age in years / age (years) + 12)) × adult dose.

Keywords: dose calculation, pediatrics, pharmacokinetics, young's rule

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Gudisa Bereda
Department of Pharmacy, Negelle Health Science College, Ethiopia

Correspondence: Gudisa Bereda, Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia, Tel +251919622717/+251913118492; Email gudisabareda95@gmail.com

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Abbreviations: AAG, α1-acid glycoprotein; ADEs, adverse drug events; ADRs, adverse drug reactions; BBB, blood brain barrier; BSA, body surface area; BW, body water; CYP450, cytochrome P450; FDA, food and drug administration; GFR, glomerular infiltration rate; PEML, pediatric essential medicine list; VD, volume of distribution; WHO, world health organization

Introduction

The difference in medications pharmacokinetics & pharmacodynamics are demonstrated in pediatric affect the selection of medicine, dose, dosage form & dosing interval. There is complex and error prone procedure of drugs use in children because of many steps is required in calculating, verifying, preparing, and administering doses.[1] Thereupon, all children prescriptions & drug orders must be checked for its applicable dose, route, & prevalence with a children's dosing reference. Children should not be treated as "miniature men and women. The spectrum prolongs from the extremely little preterm newborn child less than a year to the adolescent due to the premature physiological process, which interferes with medicine pharmacokinetics (absorption, distribution, metabolism and excretion), the fast body advancement combined with the administration of medicine doses depending on body weight, and the often usage of unlicensed medications.[2–5] Pediatric, specifically little pediatric, perhaps incapable to explain their sensations and complaints, a high proportion drugs used are off-label and unlicensed, multiple meagerly evaluated phytotherapeutic, ayurvedic, anthroposophic, traditional and homeopathic drugs are popular because they are perceived as "soft" and less toxic drugs by several parents, care providers, and even health professionals, there is unreasonable usage of drugs, e.g. anti-ineffective, clinical trials are dearth and experience and skills in observing adverse drug reactions and adverse drug events are inadequate, a children essential medicine list, has yet to be advanced, important drugs preparations and administration devices for, pediatric are absent.[1,6,7] The children population is collected of a number of extremely distinctive subpopulations. The Food and Drug Administration (FDA) Guidance (1998) breaks down this population into the following groups as neonates (birth to one month), infants (one month to two years), developing children (two-twelve years), and adolescents (twelve-sixteen years) because these groups are vary in terms of physical size, body composition, physiology, and biochemistry.[8] Growth and development appear instantaneously during the first two yrs of life. Body weight typically doubles by six months of age and triples by the 1st year of life. During infancy and childhood proportions of body water, fat, and protein can be continuously altered.[8–10] The concentration of a medicine gained after a single dose depending on its Vd, which in turn depending on the volume of plasma and tissue and on the fractions of unbound medicine in plasma and tissue. After many dosing the mean steady state concentrations consider the dose and dosage interval, clearance, and bioavailability. Total clearance is depending on the aggregation of the partial metabolic and renal clearances. Certain pharmacokinetic parameters such as clearance, Vd and bioavailability are age-related; this influences the dose and dosage interval necessitated to sustain therapeutic concentrations.[11]

Pediatric pharmacokinetics

Pharmacokinetics (ADME) of pediatric are described in turn below as follows:

Absorption

In the GIT, different anatomic and physiological age-related alters have been resulted to affect medication absorption.[12] Factors affecting the absorption of pediatric pharmacokinetics are explained below:

Gastric potential hydrogen is neutral at birth but falls to pH from one to three within twenty four to forty eight hrs after birth; then the potential hydrogen spontaneously returns to neutral again by eight to ten day and latterly decreases very slowly, reaching adult values only after two yrs of age. A pediatric less than a month and young child less than a year has higher potential hydrogen; which act as a protective effect on acid-labile medicines such as ampicillin, benzyl penicillin, erythromycin or amoxycillin are greater effectively absorbed when orally administered in a pediatric less than a month and a child less than a year than in the adult and perhaps at least partially responsible for the further bioavailability of beta-lactam antibiotics. Pediatrics PH slowly decreases again accordingly to reach adult values. In immature child less than a year, who looks like to have little or no free acid during the 1st fourteen days of life the PH is not altered. The dissolution and absorption of medications can influence by gastric acid differences. The bioavailability or absorption of orally administered weak acids, such as phenytoin, acetaminophen, and phenobarbital, perhaps decreased in a child less than a year and young pediatric owing to accelerated ionization under achlorhydric situations. The bioavailability of the enteral preparation of phenytoin is seventy five percent in a pediatric less than a month and a pediatric less than a year up to 4 months analogized with nearly complete absorption in adults. Moreover reflux of gastric contents retrograde into the esophagus is extremely frequent during the 1st yr of life. Basic medications are absorbed instantaneously in a child than in adults. Developmental alters in absorptive surfaces, particularly the GIT, can affect the rate and extent of the bioavailability of a medication and also, physiopathological factors such as shock can cause hypoxia and hypoperfusion and thereupon decrease the absorption of medications.[13,14]

Gastric emptying and intestinal motility are significant predictors for the rate of medicine absorption in the small intestine, the considerable site of medicine absorption. Gastric emptying is biphasic in normal adults, a fast (ten to twenty minutes) in 1st phase is followed by an exponentially slower phase. Gastric emptying is slow and linear in the preterm child less than one year. Pediatric gastric emptying approaches adult values within the 1st 6 to 8 months of life and it would be anticipated that medications perhaps have an ameliorated absorption rate in young child less than one year child, owing to extended contact with the gastrointestinal mucosa mucosa 2ndry to slow gastric emptying. During the neonatal period gastric emptying time is extended relative to that of the adult; this perhaps partially account for delayed absorption and incomplete absorption in a child less than a month and small a child less than a year for orally administered phenobarbital, digoxin, amoxacillin, rifampin and chloramphenicol and sulfonamides.[8,15]

Intestinal transit time is extended in a pediatric < 1 month because of declined motility and peristalsis, but occurs to be decreased in older pediatric < 1 year as a result of accelerated intestinal motility and it appears to be accountable, together with other factors, for the incomplete absorption of certain sustained release preparations, as has been extensively observed for theophylline.[16]

Premature secretion and activity of bile and pancreatic fluid influences to injured fat digestion in a child less than one month and a child less than one year in the 1st few months. The absorption of fat-soluble vitamins (vitamin D and E) is decreased in a child less than one month, likely because of the insufficient bile salt pool in the ileum. After a few months, the child less than one year is able of effectively absorbing fat-soluble compounds because of a postnatal maturation of bile salt.[17]

Premature intestinal mucosa is described by less intestinal motility and proteolytic enzymatic activity, declined IgA synthesis and more intestinal permeability; potential outcomes of these explanations are an anomalous bacterial colonization of the superior GIT, an inadequate protein digestion, less defensive capacity and more absorption of proteins, immunoglobulins, carbohydrates, bacteria, virus, and toxins.[18]

Premature transport systems

Gabapentin is absorbed through an L-amino acid transporter in the GI mucosa and is excreted by the kidney as unchanged medication and its absorption technique is saturable; thereupon its bioavailability is dose dependent, due to renal clearance reaches adult levels at one to two yrs of age, and because gabapentin is not protein bound, the high oral clearance resulted is owing to declined bioavailability sequencing from premature activity of the L-amino acid transporter, which limits absorption.[19]

Variable microbial colonization

During fetal life, the GIT is sterile. From birth, microbial colonization appears and bacteria are detected within four to eight hrs. The digestive tract colonization affects the bile salts metabolism and GI motility. The types of bacteria that colonize the digestive tract of the full-term a child less than one month are vary based on whether the a child less than one month takes maternal or artificial milk. The bioavailability of certain medications is affected by the metabolism (hydrolysis and reductions) by the intestinal microflora, which is varying in a child less than one year, pediatric and adults.[17,20,21]

Distribution

Next to absorption, a medicine is distributed to different body compartments according to its physiochemical properties, such as molecular size, ionization constant, and relative aqueous and lipid solubility. Many of the procedures included in the distribution of medications are clearly vary in a child less than one month and a pediatric < 1 year when compared to adults. Factors involving ppb and water partitioning are continuously fluctuating through-out the 1st yrs of life, thus influencing the distribution of medications. Independent route of administration, once the medicine enters the blood stream, it distributes through-out the vascular system and to different areas of the body. A medications distribution describes are concluded by the parameter, apparent volume of distribution which is the ratio of the amount of medicine in the body to the correlated to plasma concentration. Volume of distribution of a medications is clinically significant because it controls the value of a loading dose, and along with a medicines clearance, it determines a medications $t1/_2$. A large volume of distribution; which the plasma concentration is relatively small for a rendered amount of medicine in the body shows extensive medicine distribution to the tissues. A small volume of distribution; which the plasma concentration is somewhat high for a given amount of medicine in the body notifies less extensive distribution from the plasma, and perhaps revealed that a medication is highly bound to plasma proteins, a process that prevents the distribution of medicine from the plasma. A medications volume of distribution is ascertained by tissue binding, ppb, and the physiochemical properties of the medicine, such as lipid and water solubility, which impact the body compartments that a medication can access. Total body water, explained as percentage of body weight, reduces with age, from approximately eighty percent in newborns to sixty percent by one yr of age. Oppositely, body fat elevates with age, from one percent to two percent in a preterm a child less than one month to ten percent to fifteen percent in a term a child less than one month and twenty

percent to twenty five percent in a one-year-old. Highly water-soluble compounds, such as gentamicin, have higher Vd in a child less than one month compared to adults. For instance gentamicin's Vd is around 0.5 L/kg in a child less than one month, compared to 0.25 to 0.3 L/kg in adults, eventually a larger mg/kg loading dose perhaps required to achieve desired therapeutic concentrations in a child less than one month. Lipophilic medications, such as diazepam, tend to have smaller Vd in a child less than one year than in older pediatric and adults.[20,23]

Membrane permeability

The BBB at birth is still immature and medicinal products perhaps increase access to the CNS with sequence toxicity; this neonatal greater permeability in turn permits certain medicines with low penetration capacity to achieve higher concentrations in brain than those reached in pediatric or adults, as it has been explained with amphotericin B.[10]

Plasma protein binding

Plasma protein binding (ppb) of compounds is dependent on the amount of present binding proteins, the number of present binding sites, the affinity constant of the medicine for the protein(s), and the availability of pathophysiological situations or endogenous compounds that perhaps change the medicine-protein binding interaction.[17] A reduced ppb is due not only to the decrement of the total amount of plasma proteins, but also to the lowered binding affinity and the more concentrations of endogenous competing substrates. In theory decreased protein binding perhaps sequence in an accelerated distribution of medications from the plasma to the rest of the body, which perhaps correlated with an accelerated volume of distribution.[8,11] Generally, acidic medicines chiefly bind to albumin, whereas basic medicines bind to globulins, α1-acid glycoprotein and lipoproteins. Commonly, the unbound fraction is higher in a child less than one month and a pediatric < 1 year for many reasons: 1st, the concentration of binding proteins perhaps decreased. Furthermore, these proteins are qualitatively varying and usually have lower binding capacities, particularly in a child less than one month. Additionally, physiological and pathological enhances in bilirubin and free fatty acid plasma concentrations frequently available in the neonatal period. An accelerated concentration of non-esterified fatty acids decrease medication binding, and also appears by the elevated levels of bilirubin and different endogenous substances competitively binding to albumin.[17,18].

Body water

In very young child less than one year, the total body water is high (eighty to ninety percent of the body weight) while fat content is low (ten to fifteen percent of body weight). The amount of total body water declines to fifty five to sixty percent by adulthood. The extracellular water content is about forty five percent in a pediatric < 1 month and particularly large in a pediatric < 1 year with LBWs, compared with twenty percent in adulthood; these changes will sequence in somewhat higher Vd of water-soluble medicines in children population than in adulthood, such as gentamicin (0.5-1.2 l/kg in a pediatric < 1 month and a pediatric < 1 year and 0.2-0.3 l/kg in adults), linezolid, phenobarbital or propofol, and identical or lower for fat-soluble medications such as diazepam.[23]

Metabolism

The initial intention of medication metabolism is to convert medications into more water soluble substances to facilitate their excretion; this technique appears initially in liver hepatocytes to secrete metabolites that are inactive and somewhat non-toxic; although, metabolites perhaps sometimes the source of toxic outcomes. However the kidney, intestine, lung, and skin are also able of biotransformation, the liver is quantitatively the most significant organ for medicine metabolism. The capacity to metabolize biliary acids is reached by 4 yrs but the metabolism of medicines is unusual. Pediatric of 2 yrs have a bacteria in the intestine capable to metabolize digoxin, although, it is not continue until adolescence when adult levels are reached. Medication metabolism mechanisms can be categorized into phase I, including structural alteration of the medicine molecule, and phase II reactions, enclosing of conjugation with varying frequent more water-soluble moiety. The initial intention of metabolism is to reduce lipophilicity and accelerate renal excretion of the molecule. Phase I reactions can be oxidation, reduction and hydrolysis and also frequent sequences in the introduction of a functional group. Oxidative reactions are the common indispensable and often, though not importantly, cytochrome P450-dependent. Phase II metabolism includes the conjugation of a functional group on the molecule (parent medicine or Phase I metabolites) with hydrophilic endogenous substrates (e.g. glucuronidation, sulfation, acetylation). Both phase I and II metabolic enzymes at birth perhaps premature. The varying capacity to metabolize medications in pediatric perhaps result in higher or lower medicine plasma levels than those reached in adults.[24] The preponderance of Phase I medication reactions are mediated by the cytochrome P450 enzymes, a super family of many hemeproteins. The specific families or enzymes that are of greatest significance in the metabolism of medications are CYP3A4/7, 2C9, 2C19, 2D6, 1A2, 2E1, and 2B6. Other than CYPs, the flavin-containing monooxygenase (FMO) enzymes are also significant for the oxidative metabolism of a broad variety of therapeutic medicine, involving nicotine, clozapine, sulindac sulfide, and ranitidine. Concisely, CYP3A7 is the initial isoenzyme explained during the prenatal period and it diminishes instantaneously after birth and is barely measurable in adults. The expression of CYP2E1 and CYP2D6 commence to accelerate at the time of birth. The expression of CYP3A4, 2C9, and 2C19 appears during the 1st weeks of life. The expression of CYP1A2, the last enzyme to advance, is available by one to three months of life. All the isoenzyme activities are identical in one to two yrs of age to those of adults. The elimination of a medicine is quantified clinically using the parameter clearance, which is a measure of the body's capability to remove medicine from the plasma. The developmental alterations demonstrated in the enzymatic systems have been assisted by the age-related alterations in the clearance in many medicines, as well as alterations in the metabolic ratios of probe substrates to their metabolites in vivo. For instance, the acceleration of the expression of CYP2D6 was correlated with enhance in dextromethorphan O-demethylation, which was determined using the urinary ratio of dextromethorphan to dextorphan.[8,12–15]

CYP3A

Is the most predominant cytochrome in the human liver and the intestinal tract, which responsible for approximately thirty to forty percent of total hepatic cytochrome. Likely crucial for the metabolism of steroid hormones of maternal, placental or fetal adrenal origin and for metabolizing more than fifty percent of the medicines, involving ciclosporin, tracrolimus, cisapride, midazolam, fentanyl, lidocaine, nifedipine, indinavir, and verapamil CYP3A levels advance at an early stage. CYP3A4 is the considerable CYP expressed in adult liver, whereas CYP3A7 is the considerable CYP expressed in the fetal liver. CYP3A5 is more frequently expressed in pediatric and teens and it reduces to twenty to thirty percent in adults. The activity of CYP3A4

is extremely weak or absent in the fetus and commences to accelerate after birth to reach thirty to forty percent of the adult activity after 1 month.[25] First-pass metabolism of zidovudine was reducing in the 1st fourteen days of life. The bioavailability of oral zidovudine differed from eighty nine percent in a child less than one year younger than fifteen days to a mean of sixty one percent in older a child less than one year.[26]

Excretion

Excretion of medications by the kidneys is dependent on three techniques such as glomerular filtration, tubular excretion and tubular reabsorption. The amount of gastric acid excreted per kg of body weight during the age of 3 years is consistent to that of excreted in adults, thus reaching the identical potential hydrogen values. In the 1st step of excretion the free medicine in the plasma (the protein bound component is too large) is filtered across the glomerular membrane into the renal tubule. The tubule transporter systems in the renal tubular membrane perhaps increase medicine excretion by rendering the passage of medications from the plasma into the tubule. In the distal part of the renal tubule, lipophilic medicines perhaps reabsorbed by passive diffusion from the tubule back into the blood. For medicines that are chiefly excreted by glomerular filtration (e.g. aminoglycosides), primary dose adjustments can be made by either enhancing the dosing interval or lowering the dose. Tubular secretion, determined by the renal clearance of p-aminohippurate (a substrate of renal OAT), is decreased at birth to approximately twenty percent to thirty percent of adult capacity but matures by fifteen months of age. Tubular reabsorption is the last renal work to mature and does not reach adult levels until two yrs of age; this delay in the advancement of tubular functions perhaps have variable outcome on certain medications clearance for which tubular secretion or reabsorption is significant in adults. For instance, digoxin, which undergoes certain active production, has a observed average renal clearance of 1.92, 3.94, and 5.20 L/hr/1.73 m^2 in full term a child less than one year less than one week of age, three-month-old a child less than one year, and pediatric of 1.5 years of old, respectively. Additionally, for medications primarily eliminated by kidney, immature renal clearance techniques sequence in the inefficient elimination of medications and prolongation of their $t1/_{2.}$[8,16] Renal blood flow at birth is only five to six percent of cardiac output, fifteen to twenty five percent by 1 yr of age and reaches adult values after 2 yrs of age.[28] However during the neonatal period the elimination of multiple medications that are excreted in urine in unchanged form is restricted by the immaturity of glomerular filtration and renal tubular generation, an identical or greater rate of elimination from plasma than in adults has been demonsterated in late infancy and/or in childhood for multiple medications involving as digoxin, phenytoin, carbamazepine, levetiracetam, diazoxide, clindamycin, cimetidine, chlorpheniramine and cetirizine.[27,28] Terminally, a child less than one year urinary pH values are additionally lower than adult values. Urinary PHs perhaps affects the reabsorption of weak organic acids and bases, and differences in renal medication elimination perhaps reflect the discrepancy in urinary pH values.

Pediatric dose calculation

Pediatrics' dosage based on factors such as their age and weight, their health status, their respiratory system, and the stage of advancement of their body systems for medications metabolism (e.g., liver enzymes) and elimination (e.g., kidneys). Newborns are not able of fully advancing these biological functions and systems. The children's has varying pharmacodynamic, physiological and pharmacokinetic properties as well as growth rate in comparison with adults; that's why dose calculation is essential in order to achieve the optimal therapeutic consequences to the patient.[28] Ascertaining the correct adjustment of the drug dosage is a complex challenge, as physicians must also consider aspects such as metabolic, physiological and weight differences among individuals and the polarity of medications. Additionally, acceleration in the generation of a number of the medications could secrete another challenges regarding toxicology. Age, weight, body surface, metabolism and height are parameters considered for children dose calculation. The formulas in pediatric dose calculation vary depending on nature involving age, body weight and surface areas, involve: age is directly proportional to the dose of a medication escalation with age except geriatrics, children needs fewer doses compared to adult, and geriatrics. For a child less than one year the best formula is Fried and Clark, however clinically dose calculation for pediatric has multiple formulas discovered by many scientists, about age, weight and surface area medications formulas given below.[28,29] (Table)

Table 1 Different formulas proposed by different scientists for child dose calculation

Name	Formulas	Importance
1) Age base:		
Young rules	Age in years / age + 12 × Adult dose	Can be applied quickly approach a situation in which the patients weight is unknown and easy to remember because young refers to age
Dilling rules	Age in years / 20 × adult dose	It is the simplest and easiest and formula for child dose calculation
Bastedo rules	Age (years) + 3/30 × adult dose	It is one of the child dose calculation formula as an optional
Fried's (Solomon) rule	[age (months)/150] × adult dose	Commonly used for neonates
Crowling rules	Age at next birth (years) / 24 × adult dose or age (years) + 1/24 × adult dose	the most safe and accurate techniques of pediatric dosage calculation
Webster rule	Age (years) +1 /Age (years)+7 · adult dose	Commonly used in older children
2) Weight base:		
Clark rules	Weight (kg)/ 70 × adult dose or weight(pounds)/150* adult dose	It is best when the calculation is not possible from age, also more commonly used
Modified weight rule	Weight kg/ 50kg *Adult dose	It is no need conversion between weight and pounds
Majid rules	adult dose /70 (Adult weight) × weight (kg)	Restrain conversion pounds to weight
3) Body surface area base:		
B.S.A Mosteller formula	√Weight (kg) × height (cm) /3600; Body Surface Area of child/ Adult S.A (1.73m²) × adult dose	It is best when calculation is not possible by body weight and it is the more accurate and used in chemotherapeutic agents

A pediatric reference volume (Vp) was calculated for each of four subpopulations such as neonates (zero to one months), infant (one to twenty four months), pediatric (2 to 12 yrs), and adolescents (12 to 16 yrs). For each subpopulation, the volume was calculated depending on body surface area, relative to the adult volume of 250 ml and adult BSA of 1.73m2. Subpopulation BSA was calculated from: BSA (m2) √Weight × height /3600. World Health Organization model formulary for pediatric, World Health Organization model prescribing information: medications used in parasitic diseases and, conversely, via common clinical equations such as Fried's rule (in neonates), Clark's rule (in infants and pediatric) and body surface area method (in all groups). Body weight typically doubles by six months of age and triples by the first yr of life. Body surface area (BSA) doubles during the first yr.[30]

Age based pediatric dosage calculation

Young's rule can be applied quickly approach a situation in which the patients weight is unknown; due to this young's rule cannot be used for newborns and consideration must be made for growth variability at any given age.

A young's rule for calculating the dose of medicine for a pediatric by adding twelve to the pediatrics age, dividing the sum by the pediatrics age, then dividing the adult dose by the number acquired, as it expressed beneath:

Young's rule = Age in years / age + 12 × Adult dose

Example: A seven year old pediatric patient is admitted to hospital. The dispenser is tasked with determining what dose of the medicine prescribed by the physician. If the adult dose is 100mg and the child weighs forty kilogram, what dose should the child is administered by using young's rule?

Answer: Child dosage=7yrs/7yrs+12yrs*100mg=7yrs/19yrs*100mg =37mg of medicine

Dilling rule is the easiest and simplest formula for child dose calculation; it expressed as beneath:

Dilling rule = Age in years / 20 × adult dose

Example: A seven year old pediatric patient is admitted to hospital. The dispenser is tasked with determining what dose of the medicine prescribed by the physician. If the adult dose is 100mg and the child weighs forty kilogram, what dose should the child is administered by using young's rule?

Answer: Child dosage=7 yrs/20 yrs*100mg=35 mg of medicine.

Bastedo rule is a little used age based formula for calculating the pediatric dose of a drug. Its formula as expressed beneath:

Bastedo rule = Age (years) + 3/30 × adult dose

Example: A seven year old pediatric patient is admitted to hospital. The dispenser is tasked with determining what dose of the medicine prescribed by the physician. If the adult dose is 100mg and the child weighs forty kilogram, what dose should the child is administered by using young's rule?

Answer: Child dosage=7yrs+3/30yrs*100mg=10yrs/30yrs*100mg =33mg of medicine

Fried's (Solomon) rule is acceptable for children patients who are < 1 yr of age and by which formula is modified to be used in infants and is method of estimating the dose of drug for a pediatric by dividing the pediatrics age in months by 150 and multiplying the result by the adult dose, as expressed beneath:

Fried's (Solomon) rule = Age (months)/150 × adult dose

Example: A physician orders diphenhydramine 50mg oral administration every six hours PRN for pediatric patient who admitted to the hospital. Calculate the dose for a four yr old child using Fried's rule?

Answer: the child is four years old, therefore, 4years*12months/1year= 48 months, then; Pediatric dose= age (months)/150 × adult dose =48months*50mg/150months =2400mg/150=16mg of diphenhydramine.

Crowling rules is a method for calculation of pediatric drug dosage in which the age of the child at the next birthday is divided by twenty four. However, the most safe and accurate methods of pediatric dose calculation involve the weight and BSA. Cowlings rule expressed as beneath:

Crowling rules = (Age in yrs+1)/ 24 × adult dose or age at next birth (yrs) / 24 × adult dose

Example 1: A seven year old pediatric patient is admitted to hospital. The dispenser is tasked with determining what dose of the medicine prescribed by the physician. If the adult dose is 100mg and the child weighs forty kilogram, what dose should the child is administered by using young's rule?

Answer: Child dosage=7yrs+1/24yrs*100mg=8yrs/24yrs*100mg =33mg of medicine

2. If a physician prescribes 500mg of ampicillin for an adult, then how many milligrams of ampicillin would the physician prescribe for a fifteen-year-old child by using cowling's rule?

Answer: Child's dosage= D (a+1)/24; where; d= child's dosage; D= adult's dosage: a=age of child in years; d=D (a+1)/24=500mg (15yrs+ 1yr)/24yrs=500(16yrs)/24yrs=800mg/24=333mg of ampicillin

3. If a physician uses cowling's rule to prescribe 250 mg of a medicine to a child, and the physician would be prescribe 1g to an adult, then how old is the child?

Answer: d=D (a+1yr)/24yrs; 250mg=1000mg (a+1yr)/24yrs; 250mg=1000mg(a)+1000mg/24yrs; 250mg/1=1000mg(a)+1000mg/24yr; By using cross multiplication; 250mg*24yrs= 1(1000mg(a)+1000mg); 6000mg=1000mga+1000mg; By using subtraction in both sides; subtract 1000; 6000mg-1000mg=1000mga+1000mg-1000mg; 5000mg=1000mga; age of a child=5 years old or child dose = age at next birth (yrs) / 24 × adult dose; 250mg= age at next birth (yrs)/24*1000mg; 250mg*24= age at next birth (yrs) *1000mg; 6000mg=1000mg age at next birth (yrs); then age at next birth (yrs) of the child is 6years old; finally the current age of child is subtracting 1 from the age at next birth (yrs); 6years-1=5years old.

Webster (modified young's rule) will approximate the area rule ($m^{2/3}$) relationship until ages eleven and twelve. For older pediatric; Clark's rule would be appropriate because Webster's rule overestimates the dosage in eleven and twelve age group: Webster formula as expressed beneath:

Webster (modified young's rule) = Age (year) +1 /Age (year) +7 *adult dose

Example: A seven year old pediatric patient is admitted to hospital. The dispenser is tasked with determining what dose of the medicine prescribed by the physician. If the adult dose is 100mg and the child weighs forty kilogram, what dose should the child is administered by using young's rule?

Answer: Child dosage=7yrs+1/7yrs+7yrs*100mg=8yrs/14yrs*100mg =57mg of medicine.

For a seven year old pediatric patient is admitted to hospital. The dispenser is tasked with determining what dose of the medicine prescribed by the physician. If the adult dose is 100mg and the child weighs forty kilogram, the child dose is range from 33mg to 57 mg of medicine. By using young's rule, Dilling rule, Bastedo rule, Crowling rules, Webster rule the child dose is 37mg, 35mg, 33mg, 33mg, and 57mg respectively. The average (mean) child dose of the above five ages based child dose calculation rule are 39mg of medicine.

Weight based pediatric dosage calculation

Clark's rule equation can be characterized as the weight of the patients in pounds divided by the average standard weight of 150 pounds (68kg) multiplied by the adult dose of a drug equals the pediatric medication dose. Its formula as expressed beneath:

Clark's rule = weight (pounds)/150* adult dose

Example 1: If an adult dose of medications calls for 30mg and the child weighs 30 Ibs, what is the child dose?

Answer: Child dose=30Ibs/150Ibs*30mg=6mg of medicine

2. Using Clark's rule, what is the dose for a twelve yr old male who weighs 35kg, if the average adult dose is 500mg?

Answer: 1st convert kg to pounds; 1kg=2.2Ibs; 35kg=77Ibs; Child dose=77Ibs/150Ibs*500mg=257mg of drug.

BSA based pediatric dosage calculation

B.S.A Mosteller formula is for dose calculation with the basal surface area method and for referenced doses expressed in mg/kg; the similar resources were used as for calculating the reference volume. The average adult is considered to have a BSA of 1.73 m^2. A useful equation for the calculation of dose based on BSA is:

B.S.A Mosteller formula = Body surface area of child (m2)/ Adult S.A (1.73m^2) × adult dose

Example 1: If the adult dose of a drug is 100 mg, calculate the approximate dose for a child with a BSA of 0.83 m^2? $Child\ 's\ dose = 0.83m^2/\ 1.73m^2\ x\ 100mg = 47.97mg\ or\ 48mg$ of drug.

2. If the adult dose of a drug is 75 mg, what would be the dose for a child weighing 40 lb. and measuring 32 inch in height using the BSA nomogram?

First calculate BSA of child based on given weight and height; then convert pounds to kg and inch to centimeter; 1kg=2.2Ib; 40 $Ib\ x$ Kg/ 2.2Ib=18.18kg; and 1 inch=2.54 cm; 32inch x 2.54cm/ 1inch=81.28cm.

BSA of children =√Weight (kg) × height (cm) /3600=√18.18kg*81.28cm/3600 =√1477.7/3600=√0.4=0.6m^2

Child dose=0.6m^2/ 1.73m^2 × 75mg=0.35*75mg=26mg of medicine

Conclusion

The difference in medications pharmacokinetics & pharmacodynamics demonstrated in pediatric affect the selection of medicine, dose, dosage form & dosing interval. The bioavailability of the enteral preparation of phenytoin is seventy five percent in a child less than a month and a child less than a year up to 4 months analogized with nearly complete absorption in adults. In very young child less than one year, the total body water is high (eighty to ninety percent of the body weight) while fat content is low (ten to fifteen percent of body weight). The bioavailability of oral zidovudine differed from eighty nine percent in a child less than one year younger than fifteen days to a mean of sixty one percent in older a child less than one year. There are different formulas compared for 12 yrs pediatric. Ascertaining the right adjustment of the drug dosage is a complex challenge, as physicians must also consider aspects such as metabolic, physiological and weight differences among individuals and the polarity of medications. Young's rule can be applied quickly approach a situation in which the patients weight is unknown. Young's rule expressed as: Age in years / age + 12 × Adult dose.

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Data Sources

Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, sceilo and Cochrane database. Search terms included: pediatric pharmacokinetics and dose calculation.

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Conflicts of interests

The author declares no conflicts of interest.

References

1. Bereda G. Evaluation of patients pharmaceutical care needs unmet and associated factors in pediatric ward of mettu karl referral hospital, south western oromia, Ethiopia: a prospective observational study, 2021. *Ann Pediatr Child Health*. 2021;9(7):1254.
2. Milap C, Taketomo C. pediatrics. IN: Joseph T, et al. Pharmacotherapy a pathophysiology approach.9th edition. Newyork.
3. Rinke M, Bundy G, Velasquez A, et al. Intervention to reduce pediatric medication errors: A systematic Review. *Pediatric*. 2013;134(2):338–360.
4. Holtkamp K, Wallraff BP, Wuller S. Methylphenidate-related growth impairment. *J Child Adolesc Psychopharmacol*. 2002;12(1):55–61.
5. Rodieux F, Wilbaux M, van den Anker JN, et al. Effect of kidney function on drug kinetics and dosing in neonates, infants, and children. *Clin Pharmacokinet*. 2015;54:1183–1204.
6. Seearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol*. 2003;112(5):973–980.
7. Seale C, Chaplin R, Lelliott P, et al. Sharing decisions in consultations involving anti-psychotic medication: a qualitative study of psychiatrists' experiences. *Social Sci Med*. 2006;62(11):2861–2873.
8. H Lu, et al. Developmental Pharmacokinetics in Pediatric Populations. *J Pediatr Pharmacol Ther*. 2014;19(4):262–276.
9. Yaffe S, Estabrook RWE, Bouxsein P, et al. Rational therapeutics for infants and children: workshop summary [online]. Washington, DC: National Academy Press; 2000.
10. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology–drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157–1167.

11. McNamara PJ, Alcorn J. Protein binding predictions in infants. *AAPS Pharm Sci*. 2002;4(1):E4.

12. Stevens JC, Marsh SA, Zaya MJ, et al. Developmental changes in human liver CYP2D6 expression. *Drug Metab Dispos*. 2008;36(8):1587–1593.

13. Phillips IR, Shephard EA. Flavin-containing monooxygenases: mutations, disease and drug response. *Trends Pharmacol Sci*. 2008;29(6):294–301.

14. Hines RN. Ontogeny of human hepatic cytochromes P450. *J Biochem Mol Toxicol*. 2007;21(4):169–175.

15. Koukouritaki SB, Manro JR, Marsh SA, et al. Developmental expression of human hepatic CYP2C9 and CYP2C19. *J Pharmacol Exp Ther*. 2004;308(3):965–974.

16. Chen N, Aleksa K, Woodland C, et al. Ontogeny of drug elimination by the human kidney. *Pediatr Nephrol*. 2006;21(2):160–168.

17. Fernandez E et al. Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults. *Pharmaceutics*. 2011;3(1):53–72.

18. Bartelink IH, Rademaker CM, Schobben AF, et al. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet*. 2006;45(11):1077-1097.

19. Strolin Benedetti M, Whomsley R, Baltes EL. Differences in absorption, distribution, metabolism and excretion of xenobiotics between the paediatric and adult populations. *Expert Opin Drug Meta Toxicol*. 2005;1(3):447–471.

20. Anderson GD, Lynn AM. Optimizing pediatric dosing: A developmental pharmacologic approach. *Pharmacotherapy*. 2009;29(6):680–690.

21. Saavedra I, Quinones L, Saavedra M, et al. Farmacocinetica de medicamentos de uso pediatrico, vision actual. *Rev Chil Pediatr*. 2008;79(3):249–258.

22. Ayrton A, Morgan P. Role of transport proteins in drug absorption, distribution and excretion. *Xenobiotica*. 2001;31(8-9):469–497.

23. Strolin Benedetti M, Baltes EL. Drug metabolism and disposition in children. *Fundam. Clin. Pharmacol*. 2003;17(3):281–299.

24. Benedetti MS, Whomsley R, Canning M. Drug metabolism in the paediatric population and in the elderly. *Drug Discov Today.* 2007;12(15-16):599–610.

25. Aman MG, Vinks AA, Remmerie B, et al. Plasma pharmacokinetic characteristics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. *Clin Ther*. 2007;29(7):1476–1486.

26. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr*. 2003;142(1):47–52.

27. Patsalos PN. Clinical pharmacokinetics of levetiracetam. *Clin Pharmacokinet*. 2004;43(11):707–724.

28. Majid Khan, Muhammad Riaz. Comparative study between various pediatrics dose calculation formulas: a case study of 12 years child for paracetamol. *International Journal of Research Granthaalayah.* 2020;8(3):304–308.

29. Majid Khan, Asaf Khan. Concepts of General Pharmacology and Clinical Approaches, Lambert Academic Publisher LAP, 2020.

30. Delmoral-Sanchez JM et al. Classification of WHO essential oral medicines for children applying a provisional pediatric biopharmaceutics classification system. *Pharmaceutics*. 2019;11(11):567.