Therapeutic Considerations in Pediatric Patients

Therapeutic Considerations in Pediatric Patients

- **Children are NOT "little adults".**
- **There are variations among pediatric age groups in:**

a. **absorption of drugs from the gastrointestinal tract, intramuscular injection sites, and skin, especially in premature infants.**
b. **the rate and extent of organ function development.**
c. **distribution, metabolism, and elimination of drugs.**

Therapeutic Considerations in Pediatric Patients

- **The pediatric drug-use process is complex and error prone because of the multiple steps required in calculating, verifying, preparing, and administering doses.**

Therapeutic Considerations in Pediatric Patients

Pediatric patients are defined as those younger than 18 (or 16) years:

1. **Premature newborn: infants born before 37 weeks of gestational age.**
2. **Neonates are those between 1 day-1 month of age**
3. **Infants are those between 1 month - 1 year.**
4. **Children are those between 1 - 11 years of age.**
5. **Adolescents are those between 12 - 16 years of age.**

Therapeutic Considerations in Pediatric Patients

- **Only ~ ¼th of marketed drugs have indications specific for use in pediatric age groups.**
- **Data on the pharmacokinetics, pharmacodynamics, efficacy, and safety of drugs in infants and children are scarce.**
- **This has led to disasters in this population, such as gray baby syndrome from chloramphenicol, phocomelia from thalidomide, and kernicterus from sulfonamide therapy.**

Therapeutic Considerations in Pediatric Patients

- Identifying an optimal dosage is a real concern.
- **Dosage regimens can NOT be extrapolated accurately from adult dose, based simply on body weight or surface area of a pediatric patients.**
- **Bioavailability, pharmacokinetics, pharmacodynamics, efficacy, and safety information which differ markedly between pediatric and adult patients, do as well differ among pediatric patients themselves, because of differences in age, organ function, and disease state.**

Therapeutic Considerations in Pediatric Patients

- **Many drugs prescribed widely for neonates, infants, and children are NOT available in suitable dosage forms.**
- **Dilution or reformulation of dosage forms intended for adult patients raises questions about the bioavailability, stability, and compatibility of these drugs.**
- **Adherence to pharmacotherapy in pediatric patients is a special challenge.**

Therapeutic Considerations in Pediatric Patients

- **The need for additional therapeutic research in pediatric patients requires ethical justification.**
- **"Investigators proposing studies", and "institutional review committees" approving human studies must assess if the risk-to-benefit ratio of each study is fair to children who are NOT in a position to voluntarily accept or reject the participation in the research.**

Drug Absorption In Pediatric Groups

Gastrointestinal Tract:

- **Factors affecting the absorption of drugs from the GIT are pH-dependent passive diffusion, and gastric emptying time.**
- **Both processes are different in premature infants compared with older children and adults.**
- **In a full-term infant, gastric pH ranges from 6-8 at birth, and declines to 1-3 within 24 hours.**
- **In contrast, gastric pH remains elevated in premature infants because of immature acid secretion process.**

Drug Absorption In Pediatric Groups

- **In premature infants, higher serum concentrations of acid-labile drugs (penicillin, ampicillin, and nafcillin), and lower serum concentrations of a weak acids (phenobarbital) can be explained by higher gastric pH.**
- **The processes of both passive and active transport may NOT be fully developed before ~ 4 months of age.**

Drug Absorption In Pediatric Groups

- **The development and expression of the efflux transporter P-glycoprotein, and the intestinal drug-metabolizing enzymes (CYP3A) and their impact on drug bioavailability in infants and children, is NOT studied very well.**
- **Gastric emptying is slow in premature infants.**
- **Thus, drugs with limited absorption in adults may be absorbed efficiently in premature infants because of prolonged contact time with gastrointestinal mucosa.**

Drug Absorption In Pediatric Groups

Intramuscular Sites:

- **Differences in relative muscle mass, poor perfusion to various muscles, peripheral vasomotor instability, and insufficient muscular contractions in premature infants compared with older children and adults can influence drug absorption from the intramuscular site.**
- **The net effect of these factors on drug absorption is difficult to predict.**

Drug Absorption In Pediatric Groups

- **Phenobarbital absorption is rapid, whereas that of diazepam may be delayed.**
- **Thus, intramuscular injection is NOT used in neonates, except in emergencies or when an IV site is inaccessible.**

Drug Absorption In Pediatric Groups

Skin:

- **Percutaneous absorption may be increased in newborns because of an under-developed stratum corneum and increased skin hydration.**
- **The relative bioavailability of topically applied drugs, including corticosteroids, may be higher in infants and young children than in adults.**

Drug Absorption In Pediatric Groups

- **The increased exposure can produce toxic effects after topical use of hexachlorophene soaps and powders, salicylic acid ointment, and rubbing alcohol.**
- **A transdermal patch formulation of methylphenidate can be used in children 6-12 years of age for treatment of attention-deficit/-hyperactivity disorder (ADHD).**

Drug Distribution In Pediatric Groups

Drug distribution is determined by:

a. **The physicochemical properties of the drug itself (pka, molecular weight, and partition coefficient).**
b. **The physiologic factors specific to the patient (extracellular and total body water, plasma protein binding of the drug, and pathologic conditions).**

- **These physiologic functions often vary in different patient populations.**

Drug Distribution In Pediatric Groups

- **Total body water is 94% in fetuses, 85% in premature infants, 78% in full-term infants, and 60% in adults.**
- **Extracellular fluid volume may account for 50% of body weight in premature infants, 35% in 4-6 month-old infants, 25% in 1-year-old children, and 19% in adults.**
- **This is reflected on the volume of distribution of gentamicin of 0.48 L/kg in neonates and 0.20 L/kg in adults.**

Drug Distribution In Pediatric Groups

- **Binding of drugs to plasma proteins is decreased in newborn infants because of: decreased plasma protein concentration, lower binding capacity of protein, decreased affinity of proteins for drug binding, and competition for certain binding sites by endogenous compounds such as bilirubin.**
- **This affects free concentration of highly protein bound drugs (phenobarbital, salicylates, and phenytoin, ..).**

Drug Distribution In Pediatric Groups

- **The decrease in plasma protein binding of drugs can increase their apparent volumes of distribution, leading to the need for higher loading doses to achieve a therapeutic serum concentration (phenobarbital and phenytoin).**
- **Pharmacologic and toxic effects are related directly to the concentration of free drug in the body.**

Drug Distribution In Pediatric Groups

- **Increased mortality from the development of kernicterus secondary to displacement of bilirubin from albumin and other serum proteins by sulfonamides in neonates is well documented.**

Drug Distribution In Pediatric Groups

- **The amount of body fat is substantially lower in neonates than in adults, which may affect drug therapy.**
- **Certain highly lipid-soluble drugs are distributed less widely in infants than in adults.**
- **The apparent volume of distribution of diazepam ranges from 1.4-1.8 L/kg in neonates and from 2.2 to 2.6 L/kg in adults.**

Drug Metabolism In Pediatric Groups

- **Drug metabolism is substantially slower in infants than in older children and adults.**
- **There are differences in the maturation of various pathways of metabolism in infants.**
- **The sulfation pathway is well developed, but the glucuronidation pathway is undeveloped in infants.**

Drug Metabolism In Pediatric Groups

- **Acetaminophen metabolism by glucuronidation is impaired in infants compared with adults, but it is partly compensated for by the sulfation pathway.**
- **Chloramphenicol-induced gray baby syndrome in newborn infants is caused by decreased metabolism by glucuronosyltransferases to the inactive glucuronide metabolite.**
- **The full development of glucuronosyltransferases may take several months to 1 year after birth.**

Drug Metabolism In Pediatric Groups

- **Metabolism of drugs by oxidation is impaired in newborn infants (theophylline, phenobarbital, and phenytoin)**
- **CYP2C9 (phenobarbital and phenytoin) surpasses adult values by 2 weeks of age.**
- **CYP1A2 (theophylline) is NOT fully developed for several months.**
- **Theophylline clearance in children 1 to 9 years of age exceeds that in infants and adults.**

Drug Metabolism In Pediatric Groups

- **Premature infants receiving theophylline for treatment of apnea, metabolise it to caffeine, in contrast to older children and adults.**
- **Because of decreased metabolism, daily doses of drugs such as theophylline, phenobarbital, phenytoin, and diazepam should be decreased in premature infants.**

Drug Metabolism In Pediatric Groups

- **6-Mercaptopurine (6-MP), a drug commonly used in pediatric leukemias, undergoes metabolism by thiopurine S-methyltransferase (TPMT).**
- **There is an inherited deficiency of TPMT in 6-11% of patients.**
- **Children homozygous for the variant alleles require 6-MP dose reduction of ~ 90%, while heterozygotic children need a dose reduction of approximately 50% compared to patients with NO TPMT deficiency.**

Drug Excretion In Pediatric Groups

- **Drugs and their metabolites may be eliminated by the kidney.**
- **The glomerular filtration rate (GFR) may be as low as 0.6-0.8 mL/min/1.73 m^2 in preterm infants and approximately 2-4 mL/min/1.73 m^2 in term infants.**
- **The processes of glomerular filtration, tubular secretion, and tubular reabsorption determine the efficiency of renal excretion.**

Drug Excretion In Pediatric Groups

- **These processes may NOT develop fully for several weeks to 1 year after birth.**
- **Premature infants require a lower daily dose of drugs eliminated by the kidney during the first week of life.**
- **The dosage requirement then increases with age.**

Drug Efficacy And Toxicity In Pediatric Groups

- **Factors related to drug efficacy and toxicity should be considered in planning pediatric pharmacotherapy.**

1. **The maintenance dose of digoxin is higher in infants than in adults, because of a lower binding affinity of digoxin to its receptors in the myocardium.**
2. **Insulin requirements are highest during adolescence because of the individual's rapid growth.**

Drug Efficacy And Toxicity In Pediatric Groups

3. **Promethazine is contraindicated in children younger than 2 years because of the risk of severe respiratory depression.**
4. **Codeine toxicity and death have been reported after tonsillectomy and adenoidectomy in children who were ultrarapid metabolizers (Codeine is metabolized to morphine) and should NOT be used in these patients.**

Drug Efficacy And Toxicity In Pediatric Groups

5. **Propylene glycol, which is added to many injectable drugs (phenytoin, phenobarbital, digoxin, lorazepam, vitamin D, hydralazine, acetaminophen, diphenhydramine, furosemide, ibuprofen, and prednisone) to increase their stability, can cause hyperosmolality in infants.**

Drug Efficacy And Toxicity In Pediatric Groups

8. **Benzyl alcohol should not be used as preservative in pediatric formulation because it has been associated with severe morbidity and mortality in premature infants (metabolic acidosis, seizures, neurologic deterioration, gasping respirations, hepatic and renal abnormalities, cardiovascular collapse).**

Drug Efficacy And Toxicity In Pediatric Groups

7. **Safety of excipients have NOT been determined for infants and children.**
8. **Antihistamines, decongestants, antitussives, and expectorants used for common cold should NOT be used in children younger than 4 years of age because of lack of evidence for efficacy and safety.**

Drug Efficacy And Toxicity In Pediatric Groups

9. **Tetracyclines are contraindicated for use in pregnant women, nursing mothers, and children younger than 8 years because they can cause dental staining and defects in enamelization of deciduous and permanent teeth, as well as a decrease in bone growth.**

Drug Efficacy And Toxicity In Pediatric Groups

10. **Fluoroquinolones (ciprofloxacin) are generally NOT recommended for pediatric patients or pregnant women because the may affect the development of cartilage of weight-bearing joints, in addition to, arthropathy, tendonitis and tendon rupture in certain patients.**

Factors Affecting Pediatric Therapy

Hepatic Disease:

- **Studies on the influence of hepatic disease on dosage requirements have NOT been performed in pediatric patients.**
- **Routine hepatic function tests (serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase, and bilirubin levels) may NOT correlate with drug pharmacokinetics.**

Factors Affecting Pediatric Therapy

- **Because of a lack of specific data on dosage adjustment in hepatic disease, drug therapy should be monitored closely in pediatric patients to avoid potential toxicity from excessive doses, particularly for drugs with narrow therapeutic indices.**

Factors Affecting Pediatric Therapy

Renal Disease:

- **Renal failure decreases the dosage requirement of drugs eliminated by the kidneys.**
- **Dosage adjustments in pediatric patients are based largely on data obtained in adults.**
- **For many important drugs, such as aminoglycoside antibiotics, renal clearance is directly proportional to the GFR, as measured by creatinine clearance.**

Factors Affecting Pediatric Therapy

- **GFR can be estimated using the Schwartz formula, which takes into account serum creatinine concentration and the patient's height, gender, and age:**

  $$GFR = K \times L/S_{Cr}$$

  where GFR is expressed in mL/min/1.73 m^2 of BSA, K = age-specific constant of proportionality, L = child's length in centimeters, and S_{Cr} = serum creatinine concentration in mg/dL.

- **Schwartz formula over-estimates GFR.**

Factors Affecting Pediatric Therapy

Age	*k*
<1 year of age, low-birth-weight infant	0.33
<1 year of age, full-term infant	0.45
2-12 year-old child	0.55
13-21 year-old female	0.55
13-21 year-old male	0.7

Factors Affecting Pediatric Therapy

- **The formula may NOT provide an accurate estimation of GFR in patients with rapidly changing serum creatinine concentrations in:**

a. **critical care setting**
b. **infants younger than 1 week**
c. **patients with obesity, malnutrition, or muscle wasting.**

- ***Factors that interfere with serum creatinine measurement also may cause errors in estimation of GFR.***

Factors Affecting Pediatric Therapy

- **Serum drug concentrations should be monitored for drugs with narrow therapeutic index and eliminated largely by the kidneys (vancomycin and aminoglycosides, ..) to optimize therapy in pediatric patients with renal dysfunction.**
- **For drugs with wide therapeutic ranges (penicillins and cephalosporins), dosage adjustment may be necessary only in patients with moderate to severe renal failure.**

Factors Affecting Pediatric Therapy

Cystic Fibrosis:

- **Increased doses of certain drugs (gentamicin, tobramycin, netilmicin, amikacin, dicloxacillin, cloxacillin, azlocillin, piperacillin, and theophylline) are required because of higher clearance values (cause unknown).**
- **The apparent volume of distribution of certain drugs also may be altered in cystic fibrosis.**

Factors Affecting Pediatric Therapy

Obesity:

- **Children and adolescents are classified as being overweight or obese according to body mass index (BMI) percentile:**

a. **Overweight children: BMI percentile > 85th - <95th.**

b. **Obese children: BMI percentile of > the 95th percentile.**

Factors Affecting Pediatric Therapy

- **Like adults, obese children are at risk for metabolic complications and the development of co-morbid conditions, including high blood pressure, high cholesterol (low HDL-cholesterol and high LDL-cholesterol), type 2 diabetes mellitus, nonalcoholic fatty liver disease, polycystic ovary disorder, cholecystitis, gastroesophageal reflux disease, and obstructive sleep apnea.**

Factors Affecting Pediatric Therapy

- **Obesity can impair the antileukemia efficacy of first-line chemotherapeutic agents and accelerate leukemia progression:**

1. **Adipocytes attract acute lymphoblastic leukemia (ALL) cells decreasing their exposure to anticancer drugs.**
2. **Adipocytes secrete asparagine, glutamine, and fatty acids that contribute to the survival of leukemia cells.**

- **High rates of life-threatening or fatal complications to chemotherapy have been reported with obese children and adolescents.**

Factors Affecting Pediatric Therapy

- **Obese children have a higher volume of distribution (V_D) for lipophilic drugs, and a lower V_D for hydrophilic medications compared with normal-weight children.**
- **Depending on drug distribution, dosing in children may be according to "actual body weight" or "ideal body weight", or by using a correction factor for body weight.**

Factors Affecting Pediatric Therapy

- **Correction factors are 0.3 for β-lactams, 0.45 for ciprofloxacin, and 0.4 for aminoglycosides, using the following formula:**

  [(Actual body weight - Ideal body weight) x Correction factor] + [Ideal body weight]

Factors Affecting Pediatric Therapy

- **Vancomycin distributes into total body water and other tissues and is eliminated primarily by glomerular filtration.**
- **Vancomycin is empirically dosed using actual body weight in overweight and obese children.**
- **Every-8-hour dosing is used initially; the frequency can be increased to every-6-hour dosing for complicated infections using serum concentration monitoring to individualize the dose.**

Pediatric Dosage Forms & Compliance

- Many drugs prepared for children are in the form of elixirs or suspensions.
- **Elixirs** are alcoholic solutions in which the drug molecules are dissolved and evenly distributed.
- No shaking is required.
- Unless some of the vehicle has evaporated, the first dose from the bottle and the last dose should contain equivalent amounts of drug.

Pediatric Dosage Forms & Compliance

- **Suspensions contain undissolved particles of drug that must be distributed throughout the vehicle by shaking.**
- **If shaking is NOT thorough each time a dose is given, the first doses from the bottle may contain less drug than the last doses.**
- **This results in less than the expected plasma concentration or effect of the drug early in the course of therapy.**
- **Toxicity may occur late in the course of therapy.**

Pediatric Dosage Forms & Compliance

- **It is essential that the prescriber provides proper instructions to patient or parents on the use of dosage form.**
- **Adherence to therapy may be more difficult to achieve in pediatric practice, since it involves NOT only the parent's, but also practical matters such as measuring errors, spilling, and spitting out.**

Pediatric Dosage Forms & Compliance

- **The measured volume of “teaspoons” ranges from 2.5 to 7.8 mL.**
- **The parents should use a calibrated spoon or syringe, to improve the accuracy of dose measurements and simplify administration of drugs to children.**
- **Parents should be told what to do if the child has spelled part of the dose.**

Pediatric Dosage Forms & Compliance

- **The parents must be told what to do if the infant is sleeping at the scheduled time of the dose.**
- **Parents should have an explanation why an antibiotic use should continue for 10-14 days, even when the child improves after 4-5 days.**
- **Practical and convenient dosage forms and dosing schedules should be chosen to the extent possible.**
- **Adherence is better with easy dosing schedules.**

Pediatric Dosage Forms & Compliance

- **Depending on their ability to comprehend, children should be given some responsibility for their own health care and for taking medications.**
- **Instructions should utilize appropriate terms understandable by both the child and the parents.**
- **Possible adverse effects and drug interactions with over-the-counter medicines or foods should be discussed.**

Pediatric Dosage Forms & Compliance

- **Because many pediatric doses are calculated using body weight, major dosing errors may result from incorrect calculations.**
- **Tenfold errors due to incorrect placement of the decimal point have been described.**
- **Thus, avoid writing the dose as .1 mL because this can be mistaken by 1 mL, a 10-fold error. We should write 0.1 mL**
- **Avoid writhing a dose as 1.0 mL since this can be mistaken by 10 mL, again a 10-fold error. We should write 1 mL**

Pediatric Drug Dosage

- **For the majority of drugs, there are NO reliable pediatric dose information, because drugs are generally NOT evaluated in pediatric patients.**
- **Drugs approved for use in children have recommended pediatric doses, stated as mg/Kg.**

Pediatric Drug Dosage

- **In the absence of pediatric dose recommendations, an approximation can be made by several methods based on age, weight, or surface area.**
- **These rules are NOT precise and should NOT be used if a pediatric dose is provided (based on studies in pediatric patients).**
- **When pediatric doses are calculated by any method, they should never exceed the adult dose.**

Pediatric Drug Dosage

1. **Surface Area, Age, & Weight:**

- **Calculations of dosage based on age or weight are conservative and tend to underestimate the required dose.**
- **Doses based on surface area are more likely to be adequate.**

Child dose=

$$\frac{\text{Body surface area in } m^2 \text{ of child} \times \text{adult dose}}{1.73}$$

TABLE 59–6 Determination of drug dosage from surface area.[1]

Weight		Approximate Age	Surface Area (m^2)	Percent of Adult Dose
(kg)	(lb)			
3	6.6	Newborn	0.2	12
6	13.2	3 months	0.3	18
10	22	1 year	0.45	28
20	44	5.5 years	0.8	48
30	66	9 years	1	60
40	88	12 years	1.3	78
50	110	14 years	1.5	90
60	132	Adult	1.7	102
70	154	Adult	1.76	103

[1]For example, if adult dose is 1 mg/kg, dose for 3-month-old infant would be 0.18 mg/kg or 1.1 mg total.

Pediatric Drug Dosage

- **Age (Young's rule):**

$$Dose = \text{Adult dose} \times \frac{\text{Age (years)}}{\text{Age} + 12}$$

- **Weight (somewhat more precise is Clark's rule):**

$$Dose = \text{Adult dose} \times \frac{\text{Weight (kg)}}{70}$$