

Louisiana Drug Utilization Review (LADUR) Education

Pediatric Drug Dosing

By: Ahmad Khalil, Pharm.D. and C. David Matthews, Pharm.D.

ISSUES...

- The medical community and the pharmaceutical industry must plan to provide pharmaceutical care to the pediatric population.
 - Clinicians need to incorporate racial, cultural, socioeconomic, developmental and physiologic differences resulting from growth and maturation when making plans for pharmaceutical care of this population.

If we look at the report from the US Census Bureau, it shows that there were 68 million children living in the USA in 1995. This percentage makes pediatrics about 25% of the United States population. Twenty million of these children were under the age of 5 years. Over the next few decades this percentage is not likely to change substantially. The medical community and the pharmaceutical industry need to make plans to provide pharmaceutical care for this large population segment based on these figures.

Although less than a quarter (25%) of currently available drugs carry an approved Food and Drug Administration (FDA) indication for use in pediatric populations, more than three quarters of them have been used for patients younger than 18 years of age. Pediatric health care providers find themselves forced to use drugs off-label (without FDA approval) in pediatric patients. These pediatric practitioners often rely on case reports, personal experience, small clinical trials, and case series for information regarding pediatric pharmacotherapy acceptability and pediatric dosing.

As we enter the 21st century, pediatric pharmacotherapy embarks on a period of considerable growth. The information age has benefited pediatric practice as a specialty. In the past, there has been little attention paid to this important segment of our patient population. This has previously resulted in a lack of information to guide the health care professional in making competent decisions in pediatric pharmacotherapy.

The pediatric clinician encounters several limitations of information in pediatric pharmacotherapy. Some of which include small numbers on patients with rare diseases, small size studies, and huge inter-patient variability among this population. Previously, the FDA did not require pediatric data about new drugs.

Recently, more readily available computer technology has eased the access of the pediatric clinician to pediatric information by facilitating rapid scanning of all available information published over the years. Regulatory agencies have also helped. For example, the FDA is now requiring pediatric labeling for many new medications. All of these advances have resulted in a greater wealth of information on pharmacotherapy for the pediatric population.

With ages of pediatric patients ranging from 23-24 weeks gestation up to young adolescents, the diversity of the pediatric population presents a huge challenge to the neonatal clinician. One particularly problematic segment of the pediatric population includes premature neonates. The physiology, pharmacokinetics, and the pharmacodynamics of medications are highly variable among the patient groups in this age span. In order to simplify this variation as much as possible, the age of the pediatric patient has been described by placing them into groups that describe trends in development and maturation. These arbitrary groupings do not always recognize the real differences in growing children.

These groupings are as follows: preterm newborn (a baby who did not complete 36 weeks in gestation), term newborn (a baby who had 36 weeks or more of gestation), neonate (a baby who is less than 1 month old), infant (a baby who is less than 1 year old but older than 1 month), child (a person who is 1 to 11 years of age), and adolescent (a person who is 12 to 16 years of age).

Clinicians need to incorporate racial, cultural, socioeconomic, developmental, and physiologic differences resulting from growth and maturation when making plans for pharmaceutical care of this population.

Pharmacokinetic Differences

Huge variabilities in pharmacokinetics and pharmacodynamics are observed among the pediatric populations. Body size, proportion, organ development and function affect the pharmacokinetic behavior of many drugs. In addition, variability of maturation within the pediatric population imposes an extra challenge to the pediatric health care provider. Age and weight are the two maturation endpoints used in clinical decisions for dosage calculation. They can properly be used as general guides in patients; however, they should be considered only as rough indicators.

Absorption

Gastrointestinal (GI) absorption of drugs is greatly affected in the first two years of life. Gastric acid production is transiently decreased, which results in basic drugs having better absorption in the newborn and acidic drugs having reduced absorption. The transit time is prolonged in the GI tract, with gastric emptying time changing to a value that is closer to an adult by the end of the first week of life. However, the emptying time for the entire intestinal tract takes up to 6 months to mature and reach adult values. Similarly gastric acid production takes up to 3 years to mature to adult levels. Neonates have a smaller gut surface area

and more erratic gastric blood flow which may reduce the absorption of drugs that undergo passive absorption. The enzymes of digestion, such as bile acid and pancreatic enzymes, are also lacking at birth and may affect the absorption of acid sensitive agents. All of these variables make it difficult to predict how the GI absorption of a certain drug will be affected. That is why clinical experience, actual absorption, and clinical studies are important sources of information for the rational dosing of young pediatric patients.

Studies are sorely lacking on the drug-dosing of the neonate subject. However, one of the best studied areas is the use of anticonvulsants in the neonatal population. Phenobarbital is found to be well absorbed which is the reason it is considered the first line therapy for neonatal seizures. Phenytoin is the second drug of choice. The maintenance dose of phenytoin in neonates should be 20 mg/kg/day to account for the reduced GI absorption in neonates. As the baby is growing and maturing, doses should be monitored and may need to be changed regularly for several weeks due to increasing patient weight and gradually improving absorption from the GI tract.

Due to concerns that some oral medications which are hypertonic in nature may cause damage to the GI, it was suggested that premature neonates should be able to receive at least one-half of their total daily fluid intake by the enteral route before starting oral medications. This serves as an end point for maturation of the GI function and, at the same time, dilutes the drug so that it can be better tolerated.

Infants and neonates have limited muscle mass and/or fat stores, and their blood circulation is not always mature. All of these factors limit absorption by the intramuscular and subcutaneous routes. However, this variability loses clinical significance by the end of the first month of life. The volume of injection to be injected intramuscularly is limited in infants and neonates to 0.5 ml per dose in the lateral aspect of the thigh; grade school age should not be given more than 1 ml intramuscularly. Children more than 11 years can receive up to 5 ml per dose.

Percutaneous absorption of drugs is magnified in neonates and infants. This is a direct result of thinner, more hydrated stratum, corneum and greater skin surface area to body size ratio. This high absorption capacity results in potential toxicities from different cleaning and antiseptic agents such as povidone iodine which is used as a topical disinfectant. Povidone iodine has been shown to cause thyroid dysfunction in several infants being prepped for surgery. Another example of toxicity is suppression of the pituitary-hypothalamus-adrenal axis after prolonged use of topical steroid containing creams for diaper rash. Thus topical application of hydrocortisone for diaper rash should be limited to no longer than 2 weeks and only with creams containing 0.5% cortisone or less. This mode of absorption is so effective that it was considered for use as a route of administration for therapeutic agents in premature neonates to treat apnea using topical theophylline or caffeine. However, this was not practical as this route was found

too variable and erratic for routine use in such patients.

Rectal administration of drugs is a valuable route for pediatric patients. It has a predictable absorption for important medications that may be needed in times when oral administration is contraindicated or not practical. Oral preparations of valproic acid, carbamazepine, and some benzodiazepines can be given rectally in seizing or vomiting patients with a high degree of success.

Distribution:

Growth and maturation from infancy to adulthood changes many factors that affect distribution. These factors are water content, fat content, hemodynamics, plasma protein concentration, organ size, and tissue perfusion. Perhaps the best examples for discussion about the differences in pediatric distribution are the aminoglycosides. Gentamicin has been extensively studied in the pediatric population. The volume of distribution in adults is 0.2-0.3 L/kg while it is about 0.5-0.7 L/kg in the premature neonate. It is about 0.4 L/kg in children falling into the age range of 1-5 years. This is probably due to changes in body water content through life. This also may infer that highly water-soluble substances may have higher volumes of distribution in premature neonates and young infants.

Metabolism:

The liver is the primary site for most metabolic activities. Growth and maturation changes affect the liver as an organ by changing the blood circulation to the liver and the hepatic enzyme systems themselves. During the last few years, there was a lot of research examining the cytochrome (CYP) P450 enzyme system. Various researchers have shown the different CYP enzyme systems mature at different rates from gestation up to early childhood ages.

There are two types of drug metabolism that occur in the liver. Type one reactions include oxidation, reduction, hydroxylation, and hydrolysis. Type II reactions include conjugation that converts compounds to more soluble forms. The total CYP content in the fetal liver is estimated to be half that of the adult. The CYP 1A family has been extensively studied because of its activity on theophylline and caffeine metabolism in mature and premature neonates. It has been found that the activity of CYP1A2 is almost nonexistent in the neonate, and this explains the very long half-life of caffeine and theophylline in this group of patients. CYP matures by 4-6 months of age and, by that time, it may exceed the activity of that of adults on a mg per kg basis. This CYP1A2 then starts to decline to adult values around puberty.

CYP 2D6, CYP 2C19, and CYP 2C8 are severely depressed during the neonatal stage. The most important class in drug metabolism is the CYP 3A enzymes. Neonates predominantly have CYP 3A5 and CYP 3A7 which are similar to CYP 3A4, but they have a relatively minor role in the adult liver. CYP 3A4 is not highly expressed in neonates.

The alcohol dehydrogenase enzyme is also suppressed during premature and mature neonate stages. This directly impacts the ability to administer benzyl alcohol for these babies. Neonates have less than 5% of alcohol dehydrogenase adult activity, and administration of benzyl alcohol containing preparations has resulted in many acidosis cases and gasping baby syndromes. Therefore, the FDA recommends using preservative free products for neonates.

Gray baby syndrome has been caused by administration of chloramphenicol within the recommended dosage range. This has been shown to be due to the deficiency of glucouronidation in neonates and infants. Although they are immature during the infancy and neonate stages, phase II reactions, mainly conjugation, mature during childhood.

Elimination:

In neonates and infants, glomerular filtration rate, tubular secretion, and the ability to reabsorb substances are all reduced. This results in impaired drug and metabolite elimination. The glomerular filtration rate starts dramatic maturation at the gestational age of 35 weeks. Premature neonates experience GFR improvement at birth, but it is less than that seen in term neonates. Renal elimination of medication stays immature during the first week of life; however, by the end of the first week, doses should be adjusted to match improving renal function. For example, the ampicillin dose in the first week of life is 50 mg/kg every 12 hours, but after the first week, it should be adjusted to 50 mg every 8 hours.

The renal function parameters used in adult dosing of renally excreted medications are not as useful in neonates and infants. A premature infant's serum creatinine is reflective more of fluid status than of renal function. For older children, the serum creatinine is useful for renal function evaluation; however, the traditional adult renal status calculation equations are not useful. Several equations have been developed to estimate renal function of the pediatric population based on serum creatinine values which are easily obtainable. The Traub and Johnson equation is the most widely used:

$$\text{CrCl (ml/min/1.73 m}^2\text{)} = (0.48) (\text{Ht})/\text{S Cr}$$

CrCl = creatinine clearance Ht = height in centimeters S Cr = serum creatinine.

Renal function steadily matures in the first year of life, and at the end of this period, total function actually exceeds that of adults. At this age, many drugs may need to be dosed more frequently than the standard adult frequency of administration due to the greater renal function of children older than one year. A clear example of this phenomenon is gentamycin administration in leukemia patients, which should properly be dosed every 6 hours to optimize therapy.

Pharmacodynamic differences in pediatric population:

There has been little work done on the drug receptor differences in pediatrics.

Based on animal studies, it has been suggested that receptor function begins to develop in the fetal stage and matures to full function long after birth. More research in this area is warranted.

In summary, pediatric pharmacotherapy presents a lot of challenges to health care providers. We have primarily discussed dosing issues in this article; however, there are many other factors that need to be addressed. Tailoring the therapy for children according to their developmental stage, as well as chronological age, will include selecting the appropriate dosage regimen, the availability of dosage forms, the fluid volumes in neonates, and the development of new delivery devices used for application. Age specific ways to prevent medication errors and enhance compliance of pediatric patients are both significant problems that must be further addressed as we move forward in pediatric therapy. The limited amount of information about existing drugs in pediatric populations presents another challenge for the health care provider; however, with the recent changes in FDA requirements, this body of information is growing in pediatric pharmacotherapy. The great need to prevent pharmaceutical misadventures in pediatric patients presents opportunities for pharmacists to participate in the provision of pharmaceutical care for pediatrics.

References

1. Stewart CF, Hampton EM. Effect of maturation on drug disposition in pediatric patients. *Clinical Pharmacy* 6:548-64, 1987
2. Hakkola J, Tanaka E, Pelkonen O. Developmental expression of cytochrome P450 enzymes in human liver. *Pharmacology and Toxicology* 82:209-17, 1998
3. Murphy JE, Austin ML, Frye RF. Evaluation of Gentamicin pharmacokinetics and dosing protocols on 195 neonates. *American Journal of Health System Pharmacists* 55:2280-8, 1998
4. Nahata MC. Pediatrics. In Dipiro JT, Talbert RL, Yee GC et al., eds. *Pharmacotherapy: A Pathophysiologic approach*. 4th edition. Stamford, Connecticut; Appleton&Lange, 1999:44-51