Pediatric Pharmacotherapy

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Therapeutic Drug Monitoring in Pediatric Patients

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An Overview of Therapeutic Drug Monitoring:Why, When, and How

Therapeutic drug monitoring (TDM) provides a method for assessing medication efficacy and safety (1-5). The goal of this process is to individualize therapeutic regimens for optimal patient benefit. TDM combines a knowledge of pharmaceutics, pharmacokinetics (how the body handles the drug), and pharmacodynamics (what the drug does to the body). The science of TDM

became a part of clinical practice in the 1960's, with the publication of initial pharmacokinetic studies which linked mathematical theories to patient outcomes (1).

Although pharmacokinetic studies in children were being performed in the early 1970's, TDM was not routinely integrated into pediatric medicine until later that decade. At that time, most institutions began routine monitoring of aminoglycosides, vancomycin, and theophylline in children. Initial guidelines for patient monitoring were developed for adults, and we have continued to extrapolate much of our information from studies performed in adult patients. Research in pediatric patients has slowly accumulated, however, and suggests that some of the recommendations for adults may not be appropriate for children. For example, the therapeutic range of phenobarbital is generally considered to be 20-40 mcg/ml. This range was developed from studies in adult patients with epilepsy. We now know that neonates with seizures may require much higher serum concentrations for therapeutic effect, and a modified target range of 20-60 mcg/ml may be more appropriate (6). Knowledge of the differences in drug disposition in children, including drug absorption, distribution, metabolism, and elimination is necessary for the optimization of therapy (7).

This is not to imply that only drugs with established dose-concentration relationships are evaluated by TDM. All therapeutic regimens must undergo continual assessment for efficacy and to identify clinical signs and symptoms of toxicity. Many more medications are evaluated by a process labeled the "target-effect" strategy (2). An example of this strategy would be the relationship between inotropes and targeted blood pressure. Although there is an established dosage range for epinephrine, dobutamine and dopamine, most clinicians are aware of the large degree of interpatient variability in blood pressure response to these agents, necessitating titration to the desired effect.

Why should you use TDM?

Today, TDM plays an important part in the development of safe and effective therapeutic regimens. In addition to individualizing treatment plans, TDM can have other uses. Periodic evaluation of trough serum concentrations can help to identify problems with medication compliance. This is particularly useful in adolescent patients taking chronic medications. The request for a serum sample from the patient may also provide a time for the health care professional to reemphasize the importance of compliance with the chosen medication regimen. TDM may also be used to isolate potential problems with drug administration or identify drug interactions. A common example is the interaction of phenytoin and enteral feedings. When given together through a nasogastric tube, the phenytoin is adsorbed onto the proteins of the tube feeding, becoming unavailable for systemic absorption and resulting in a lower serum concentration. The use of pharmacokinetic analysis has also been important to identify drug-drug

interactions, such as the inhibition of hepatic cytochrome P450 enzymes by erythromycin which can result in toxic accumulation of carbamazepine.
TDM is frequently used in the investigation of drug overdoses, both to identify the substances ingested and, in some cases, determine the extent of supportive care necessary. The use of serum acetaminophen concentrations has become the standard for predicting potential hepatocellular toxicity and determining the need for the administration of N-acetylcysteine as an antidote.
Pharmacokinetic and pharmacodynamic research is important to add to our understanding of new medications, especially in infants and children. For example, knowledge of the slower elimination of theophylline in the premature neonate has led to the recommendation of an every 8-12 hour dosing interval, while in adult patients, the dosing interval is typically every 4-6 hours with the same immediaterelease products. Utilization of newer research techniques such as the non-linear mixed effect model (NONMEM) allows estimation of kinetic parameters with fewer serum samples, minimizing the amount of blood required to determine average population values (6,8).

When do you use TDM?

In an ambulatory care setting, TDM is used most frequently to assess chronic medications, such as theophylline, antiarrhythmics, anticonvulsants, and cyclosporine for children who have received organ transplants or who have auto-immune illnesses. In hospitalized children, TDM may be used for those agents, as well as antibiotics such as the aminoglycosides and vancomycin.
It is important to note that while the process of TDM for any medication is continued throughout the treatment course, the need for pharmacokinetic analysis may be only periodic. Evaluation of serum drug concentrations should not be considered routine, but should be reserved to answer specific therapeutic concerns for individual patients.

How do you use TDM?

While most clinicians are familiar with the pharmacodynamic characteristics of the therapies needed in their patient population, many are less certain of pharmacokinetic principles. Pediatric pharmacokinetic parameters for several common medications are provided in the newsletter insert. For more information on the routine monitoring of patients receiving cyclosporine, see Pediatric Pharmacotherapy Volume 1, Issue 4. A basic understanding of pharmacokinetics terminology is necessary to utilize TDM effectively. The following description of pharmacokinetic terms incorporates information specific to infants and children (9-12).
Bioavailability (F) is the percentage or amount of a drug that reaches the plasma, or central compartment. The determination of bioavailability is essential to the evaluation of interchangeable brands of a given drug (generics). Bioavailability is

affected by the dosage form, route of administration, the degree of first-pass metabolism, and patient characteristics. In infants and young children, the bioavailability of medications administered via the oral route may be different from adults due to differences in diet, gastric emptying, pH of intestinal contents, and quantitative differences in digestive enzyme activity.

Volume of distribution (Vd) is a theoretical volume into which a known drug dose distributes, resulting a given drug serum concentration. It is used to provide an estimate of the dose needed to achieve a target serum concentration. It is also used to calculate a loading dose of a drug, if necessary. The volume of distribution for water-soluble drugs is often greater in infants and young children than it is in adults. For medications at steady state and following first-order (linear) elimination, the relationship between Vd and the serum concentration may be defined by the equation below:

$$Vd = (Dose \times F)/Serum\ Concentration\ (maximum)$$

Consideration of the degree of drug bound to serum proteins is another component of pharmacokinetic analysis. Only free unbound drug is active at tissue receptor sites; however, most serum drug assays evaluate whole drug concentrations, both bound and unbound. This becomes clinically significant for highly protein-bound drugs (Table 1) when serum proteins are decreased. In the pediatric population, a decrease in drug protein binding may occur in patients with malnutrition, chronic renal failure, or in neonates, especially those with hyperbilirubinemia (12). In these children, a greater percentage of a dose may be available in the unbound (active) form in the serum. As a result, the pharmacologic effect may be greater for a given serum drug concentration. It is possible for the patient to experience symptoms of toxicity while serum drug concentrations are still within the established therapeutic range. Specific assays which determine only the free fraction are available, but due to cost, are reserved for those situations where protein binding is known to be affected. The relationship of protein binding to overall clinical effect is complex in nature. For further information, readers are encouraged to refer to the article by Kearns and Reed (3).

Table 1. Examples of Highly Protein-Bound Drugs (9)

1. Amitriptyline
2. Carbamazepine
3. Chlordiazepoxide
4. Chlorpromazine
5. Cyclosporine
6. Diazepam
7. Diazoxide
8. Imipramine
9. Methadone
10. Nafcillin
11. Nortriptyline

12. Phenytoin
13. Propranolol
14. Salicylic Acid
15. Thiopental
16. Valproic Acid
17. Warfarin

Half-life (t1/2) is the term used to define the time required for the serum concentration to diminish by 50%. In the strictest sense, this term applies to drugs that are eliminated by first-order (linear) kinetics; however, it is often used "generically" for non-linear drugs, like phenytoin, as well. Half-life is essential for determining the appropriate dosing interval of a medication. Steady state is reached when the amount of drug administered equals the amount of drug eliminated. It is achieved within four to five half-lives of a drug. As a general rule of thumb, the dosing interval of a medication should be at least two to three times the half-life.

Clearance is the intrinsic ability of the body to remove a drug. It is expressed as a volume of serum cleared per unit of time (i.e. ml/kg/min). In general, clearance is inversely proportional to age in children. Premature babies often have slower drug clearance (and a longer half-life), due to the delayed metabolism and elimination associated with the immaturity of the hepatic and renal organ systems. Clearance is determined by the volume of distribution and the half-life of a drug:

$$CL = (0.693 \times Vd)/t1/2$$

For most medications, peak and trough serum concentrations are used to determine if a patient is within a specific therapeutic range (see insert) and to calculate individual pharmacokinetic parameters. These values, volume of distribution, half-life and clearance, are compared to average population parameters based on the child's age (2,3,7). The initial dosing regimen can then be tailored to conform to an individual patient's drug disposition characteristics.

Most clinicians are familiar with the use of peak serum concentrations to monitor efficacy. For the aminoglycosides, the site of infection is used to determine the peak needed based on drug distribution and penetration (e.g. higher peaks are needed for treating pneumonia than for a urinary tract infection). Peak concentrations can also be used to evaluate adverse effects (2,3). For example, a neonate who becomes tachycardic after each theophylline dose but then does well throughout the rest of the dosing interval may have a peak concentration above the therapeutic range. Lowering the peak by giving a smaller dose more frequently may result in the same reduction in apneic episodes without the periods of tachycardia.

Trough serum concentrations are also used to evaluate both efficacy and toxicity. Nephrotoxicity has been associated with elevated trough concentrations of aminoglycosides or vancomycin given for a prolonged period. TDM of chronic medications is often based on trough serum concentrations obtained periodically

throughout treatment. For example, maintenance therapy with anticonvulsants is usually monitored with trough serum concentrations alone (9).
In summary, TDM can optimize therapeutic regimens and improve both efficacy and safety. While the pharmacodynamic aspect of TDM is often easier to comprehend in the clinical setting, an understanding of basic pharmacokinetics can provide a clinician with very useful tools to modify therapy.

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FDA News

On June 28th, the Advisory Committee on Immunization Practices (ACIP), a branch of the CDC, issued a recommendation that all children 12 to 18 months of age should be given the varicella vaccine unless they have already contracted the virus. The committee recommends that these children receive the vaccine at the same time as the MMR vaccine. In addition, children between the ages of 19

months and 13 years should be vaccinated by the time they are 13 years old, unless they have already had chicken pox.
The ACIP also voted that the federal vaccination initiative, "Vaccines for Children," should cover the costs of varicella vaccine for two target groups, those 15-18 months of age and 11-12 years of age. As a result of this pronouncement, and similar statements by the American Academy of Pediatrics, insurers are also beginning to include coverage for this new vaccine. QualChoice is currently including varicella vaccine in its routine immunization package.
At that same session, the ACIP voted to reserve the use of hepatitis A vaccine to those individuals believed to be at high risk for contracting the disease. A full report of the committee's recommendations will be published in Morbidity and Mortality Weekly Report.

Pharmacology Literature Review

Cytochrome P450 Enzymes

This brief review article describes the latest advances in our knowledge of the hepatic cytochrome P450 enzyme system, the major site of drug metabolism. Research in this area may make the results of drug interactions and adverse effects more predictable and preventable in the future. The authors provide a table of recognized substrates and inhibitors for the five major classes that have been identified. Slaughter RL et al. Recent advances: The cytochrome P450 enzymes. **Ann Pharmacother 1995;29:619-24.**

Dilution of Intravenous Medications for Neonates

The authors present the system developed at Texas Children's Hospital for diluting IV medications for use in their neonatal intensive care units. This procedure, similar to the one used at UVa, sets standard concentrations for each medication in an effort to eliminate excessive fluid administration and reduce drug wastage. Nieuwoudt CD. Dilution of intravenous medications for neonates. **Am J Health-Syst Pharm 1995;52:1320-2.**

Gentamicin in Neonates

This study is a retrospective analysis of gentamicin dosing in a large neonatal population. The records of 175 babies receiving gentamicin after delivery were examined. Based on the results of calculated pharmacokinetic parameters, the authors suggest that an initial dosing interval of 18 hours would be more appropriate for term infants than the 12 hour regimen in use at the time of the

study. Also of interest, APGAR scores failed to correlate with serum gentamicin concentrations. This observation suggests that infants with high initial scores do not always have good renal function and that preliminary evaluations of clinical status should not be used alone to determine aminoglycoside dosage regimens. Gray TM. Reevaluation of gentamicin dosing in the neonatal population. **J Pharm Tech 1995;11:105-9.**

New Drug Development

Like the article describing research with cytochrome P450 enzymes, this in-depth review focuses on one aspect of research in pharmacology. Developing new drug entities has traditionally taken large quantities of both time and money, but this process is undergoing tremendous change. Random screening of compounds has given way to structural modification and structure-based or "rational" drug design methods. The authors present a basic review of this new approach. The impact of innovations in computer technology and genetic engineering on the drug development process is also presented. Kleinberg ML, Wanke LA. New approaches and technologies in drug design and discovery. **Am J Health-Syst Pharm 1995;52:1323-36.**

Formulary Update

Dr. Anne E. Hendrick has taken over the position of Director of Drug Information Services and will serve as the secretary for the P&T committee, replacing Dr. Beth Klym. For more information about the committee, please call Dr. Hendrick at 924-2910. To utilize the services of the Drug Information Center, please call Dr. Hendrick or Dr. Dave Rogers at 924-8034.

Editors' Notes

Welcome to Our New Readers!

The editorial staff of Pediatric Pharmacotherapy would like to welcome all new members of the Children's Medical Center staff. This newsletter is provided free of charge to CMC personnel. If you are interested in submitting material for publication or serving on the editorial board, please contact Dr. Marcia Buck at the address listed below.

Reader Survey

Thank you to the readers who have returned their surveys. Many good suggestions for topics have been sent in and several of them will be incorporated into future issues. If you haven't yet returned your reader survey, please send it in by August 1st. Your feedback is very important to provide support for the continued publication of this newsletter. If you need a survey form, please call Dr. Marcia Buck at 982-0921.

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