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Recent Advances in Pediatric Pharmacokinetics

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A large number of significant papers were published this year in the area of pharmacokinetics. They include not only advancements in study design and interpretation, but also an increasing number of trials conducted in special patient populations, such as pediatrics. In addition to traditional pharmacokinetic and dose-ranging studies in children, some very useful review articles and thought-provoking commentaries have been written. This issue of *Pediatric Pharmacotherapy* will review some of the top pharmacokinetic papers of 2003.

Children as study subjects

As a result of the Food and Drug Administration (FDA) request for pediatric studies, the issues of trial design and subject enrollment have come to the forefront. While the traditional approach to drug studies in adults has relied heavily on the use of healthy volunteers, pediatric research has generally been restricted to patients who might benefit from treatment. This traditional view, however, is being challenged by the need to obtain more pediatric information. In a well-written commentary published in *Clinical Pharmacology and Therapeutics*, four of the leaders in pediatric pharmacokinetic research have presented both the pros and cons of enrolling healthy children in drug studies.¹ In addition, the authors address issues of informed assent in children and make suggestions for future research efforts. This article is highly recommended for anyone conducting medical research in the pediatric population.

The Bayesian approach in children

The development and refinement of techniques to conduct pharmacokinetic studies in children have also been the focus of recent interest. In an article published earlier this year, Mahmood suggests that Bayesian methodology, a technique designed to maximize the information gained from limited blood sampling, should be considered as the initial approach for pediatric

pharmacokinetic studies.² The author presents the results of a comparison of the Bayesian approach using three blood samples with traditional techniques using nine samples for two drugs in which adult and pediatric pharmacokinetic data were already available. Comparing the Bayesian (predicted) to the previously determined (observed) results for the first drug, the mean area under the curve (AUC) was 278 ± 95 in the model versus the observed mean of 298 ± 89 mcg-h/ml. The maximum concentration was 20.0 ± 4.2 in the model versus the observed value of 21.2 ± 3.9 mcg/ml, and the elimination half-life was 9.1 ± 3.1 versus 8.8 ± 2.7 hours. For the second drug, the mean AUC was 382 ± 84 in the model versus 346 ± 88 mcg-h/ml from the observed data, with a maximum concentration of 41.0 ± 9.6 versus 36.2 ± 8.7 mcg/ml, and an elimination half-life of 12.7 ± 4.3 versus 12.0 ± 3.9 hours. The mean prediction error (MPE) in AUC was 3% for the first drug, with an MPE of 2.4% in the maximum concentration and 7.2% in half-life. For the second drug, the MPE was 4.5% for AUC, 11.1% for maximum concentration, and 10.8% for half-life. An MPE value under 10% was considered as representative of good precision. Based on these results, the author concluded that the Bayesian approach with limited sampling provided parameter estimates as reliable as those obtained from more traditional techniques.

Cytochrome P450 probes

Continuing on the developments of the past decade, this year has seen several advancements in our understanding of the role of the cytochrome P450 (CYP) enzyme system in drug metabolism. Donato and Castell have recently published an extensive review of the *in vitro* work in this area, highlighting the two most commonly used methodologies: incubation with microsomes and incubation with metabolically competent (intact) cells.³ The most useful features of this review are the extensive tables of

the CYP enzyme probes currently available and the methodologies by which they can be used to establish metabolic function. In addition, the authors describe the process currently recommended for studying potential drug interactions prior to the marketing of new agents in the United States.

Cisapride

Prior to the knowledge of its association with arrhythmias, cisapride had become widely used as a prokinetic agent for infants and children with gastroesophageal reflux disease (GERD). While no longer commonly prescribed, cisapride is still useful in refractory GERD. Earlier studies suggested that the activity of CYP3A4, the enzyme responsible for cisapride metabolism, was reduced in infants. To confirm these findings, Kearns and colleagues, publishing for the Pediatric Pharmacology Research Unit Network, recently reported the results of an open-label study of cisapride in 35 infants between 28 and 54 weeks postconceptional age.⁴ All patients were given a single 0.2 mg/kg oral dose, followed by blood sampling for 24 hours.

The results of the study revealed an average time to peak of 4.4 ± 2.8 hours, with a mean peak of 29.3 ± 16.6 ng/ml. Apparent volume of distribution was 9.0 ± 7.1 L/kg with an elimination half-life of 10.7 ± 3.7 hours, and an apparent total body clearance of 0.62 ± 0.43 L/hr/kg. Stratification based on postconceptional age revealed a slower rate of elimination in the youngest patients. The authors concluded that cisapride pharmacokinetics were developmentally dependent, reflecting an increase in CYP3A4 activity within the first three months of life, and that adjusting dosing regimens to account for this effect might reduce toxicity during infancy.

Bosentan in pulmonary hypertension

One of the most significant pharmacokinetic studies published this year described the profile of a new agent, bosentan, in children with pulmonary hypertension.⁵ This study is of note not only because of the value of having another effective therapy in this difficult disease, but also because it highlights the current emphasis on studying new drugs in children. A total of 19 children were enrolled in this multicenter, open-label study. Patients were divided into groups for dosing. Children between 10 and 20 kg were given oral doses of 31.25 mg, while children between 20 and 40 kg received 62.5 mg, and children over 40 kg received a standard adult maintenance dose of 125 mg twice daily for 4 weeks. Patients could then be titrated to the most effective dose for the remainder of the 12 week

study. At the end of the study, the mean AUC was 3,496 ng·h/ml in the smallest patients, versus 5,428 and 6,124 ng·h/ml in the larger children. The maximum concentrations were 685, 1,136, and 1,200 ng/ml in the three groups, and time to maximum was 2.5, 1.0, and 1.8 hours, respectively. The elimination half-life was similar in all three groups, at 6.0, 5.6, and 5.3 hours. Examination of covariates (weight, gender, age, or use of epoprostenol) had no impact on bosentan pharmacokinetics. Overall, the parameters estimated in these pediatric patients were similar to previously published values in adults and supported the stepped dosing strategy proposed by the authors.

Clozapine disposition in children and teens

Clozapine, the first of the atypical antipsychotics, is no longer widely used because of its association with agranulocytosis, but may have a role in refractory childhood-onset schizophrenia. In this open-label study, pharmacokinetic data were evaluated in six children (9 to 16 years of age) receiving clozapine.⁶ The average dose at the time of the study was 200 mg (3.4 mg/kg/day). Unlike data in adults, serum concentrations of the active norclozapine metabolite were greater than those of the parent compound. Clinical response and the development of adverse effects were correlated with norclozapine concentrations. The authors concluded that both clozapine and norclozapine contribute significantly to the efficacy and adverse effects associated with clozapine use.

Ketoprofen

Ketoprofen is available only in an oral dosage formulation in the United States, but in other countries, it is manufactured in parenteral and rectal preparations. Like ketorolac, ketoprofen is a non-steroidal anti-inflammatory agent useful for moderate pain. In a study from Kuopio University Hospital in Finland, the pharmacokinetics of intravenous (IV) and rectal ketoprofen were evaluated in 28 children between 7 and 93 months of age.⁷ Eighteen children received an IV dose of 1 mg/kg, while 10 received a 1 mg/kg dose as a suppository. The IV dose produced peak plasma concentrations ranging from 10.5 to 22.2 mg/L, while the rectal dose produced lower concentrations (3.8 to 7.4 mg/L). Bioavailability of the rectal formulation was 73%. The volume of distribution was 0.04 to 0.1 L/kg in the IV group and 0.08 to 0.16 L/kg in the rectal group. Terminal elimination half-life was similar in the groups, with a range of 0.7 to 3 hours in the IV group and 1.2 to 2.9 hours in the rectal group. The authors concluded that both ketoprofen dosage forms produced effective concentrations.

Linezolid in infants

Linezolid is a oxazolidinone antibiotic used in treatment of drug-resistant Gram positive infections, such as vancomycin-resistant enterococci. A number of studies have been published over the past three years describing the efficacy and safety of linezolid in children, including a pharmacokinetic analysis. A recent multicenter study from the Pediatric Pharmacology Research Unit Network was conducted to extend the knowledge of linezolid kinetics to neonatal patients.⁸ Forty-two infants were enrolled in this open-label, single dose evaluation. Patients were stratified by both postnatal and gestational age. All received an IV dose of 10 mg/kg, with blood sampling over 12 hours. The mean (\pm SD) value for volume of distribution was 0.75 ± 0.19 L/kg, with a half-life of 2.8 ± 2.1 hours, and a clearance of 0.25 ± 0.12 L/hr/kg. All parameters were similar to values previously published for children and adults; however when analyzed by age, clearance was reduced in infants less than a week of age. Based on their results, the authors concluded that current pediatric dosing recommendations for linezolid (10 mg/kg IV every 8 hours) could be applied to infants over one week of age.

Single-dose omeprazole study

The pharmacokinetic profile of omeprazole, a proton pump inhibitor for GERD, was evaluated in 37 children between 2 and 16 years of age.¹⁰ Patients were given a single 10 or 20 mg dose, and serum samples were collected over 6 hours. All subjects were evaluated for the presence of functional CYP2C19 alleles, in order to assess the effect of genotype on metabolism. The mean maximum concentration was 331.1 ± 333.6 ng/ml, with a wide range of 20.8 to 885.8 ng/ml. The average elimination half-life was 2.1 ± 1.2 hours, (range 1 to 6 hours). There were no differences in clearance between patients with one or two CYP2C19 alleles. There was also no association between age and clearance. Based on these results, the authors concluded that the pharmacokinetics of omeprazole in children were similar to adults and that there was no association between genotype and clearance.

Oxcarbazepine review

Oxcarbazepine has become an important option for the management of seizures in both children and adults. A recent review published in *Clinical Pharmacokinetics* provides a thorough description of the oxcarbazepine pharmacokinetic studies conducted to date, including the trials in children.¹⁰ The authors also address oxcarbazepine drug interactions and the potential role for serum concentration monitoring.

Quinapril

The angiotensin converting enzyme (ACE) inhibitors are frequently used in the treatment of hypertension in children and adults. While it has not been previously studied in children, quinapril could be a useful alternative to captopril and enalapril and offer the advantage of once daily dosing. In a recent study of 24 children who were receiving chronic ACE inhibitor therapy, quinapril was substituted for a single 24 hour period to allow assessment of its pharmacokinetic parameters.¹¹ The patients ranged in age from 2.5 to 82 months and were given a single 0.2 mg/kg oral dose. Quinapril was rapidly converted to active quinaprilat, with peak concentrations reached in 1 to 2 hours. The mean elimination half-life was 2.3 hours, similar to values in adults. Clearance was correlated with body size (body surface area or weight) and creatinine clearance.

Sumatriptan in adolescents

The pharmacokinetic profile of sumatriptan nasal spray was recently evaluated in 16 adolescents (12 to 17 years of age).¹² Noncompartmental pharmacokinetic analysis revealed an average maximum concentration of 13.9 ng/ml (95% CI 11.0, 17.6), with an elimination half-life of 2.0 hours (1.8, 2.3). Although clearance and volume of distribution increased slightly with age, the change was not considered clinically significant. Based on their data, the authors concluded that a standard adult dose of sumatriptan nasal spray would be appropriate for adolescents.

Topiramate pharmacokinetics

In another recent study, Ferrari and colleagues evaluated the influence of dose, age, and concomitant anticonvulsants on topiramate levels.¹³ Fifty-one patients ranging in age from 3 to 30 years were enrolled in this observational study. A linear relationship was seen between dose and plasma concentrations over the range from 1.8 to 10 mg/kg. Dose-normalized plasma topiramate concentrations were positively correlated with age. Clearance was inversely related to age; the mean rate in children less than 10 years of age was almost three times as high as that of patients over 15 years of age (112 ± 82 versus 42 ± 16 ml/kg/hr). As anticipated, clearance was also more rapid in patients receiving enzyme-inducing agents. Forty-one patients were evaluated for therapeutic response. There was no significant difference in plasma topiramate concentrations between patients who had a 50% or greater reduction in seizures versus those who did not. In addition, the authors found no relationship between plasma topiramate concentrations and the development of adverse effects.

Transdermal absorption of acne products

While many topical products are available for the management of acne, relatively little is known about their absorption and distribution following application. The authors of a new review article provide a detailed background on the topical agents commonly used for acne, as well as information about their systemic absorption.¹⁴ Particular attention is given to the teratogenic risks from the retinoids and the potential for pseudomembranous colitis in patients using topical clindamycin. The article, with over 100 references, will serve as a useful teaching tool for many pediatric health care professionals.

Zidovudine in infants and children

Although the pharmacokinetic profile of zidovudine in children has been studied by several investigators, few infants have been included in these trials. As part of a multicenter pediatric trial comparing zidovudine, didanosine, and the combination of the two agents, the pharmacokinetic parameters of zidovudine were evaluated in a subset of 384 patients.¹⁵ The most significant variable affecting the pharmacokinetic parameters was age, with subjects less than 2 years of age having a reduced clearance. The authors suggested that the lower clearance in infants leads to higher zidovudine concentrations and a greater risk of hematologic adverse effects.

Summary

Clinical research in pediatric patients continues to advance, with incentives from the FDA and the pharmaceutical industry helping to facilitate many of these projects. Over the past year, several studies have been published which have helped to identify the optimal dosing of new and old drugs in children. In addition, other papers have challenged current thoughts about study design and data analysis, encouraging investigators to consider nontraditional options. It is hoped that this trend will continue, providing clinicians with more information about the medications they use in children.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 12/12/03:

1. The restriction on controlled-release oxycodone (OxyContin®) was amended to allow prescribing for Palliative Care Service patients.
2. Revisions of the drug sample and medication storage policies were approved.
3. The medication error quarterly report and medication utilization criteria for epoetin in adult intensive care patients were also presented.

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