PEDIATRIC PHARMACOTHERAPY

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Advances in Pediatric Pharmacokinetics

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The past year provided a number of interesting publications in the area of pediatric pharmacokinetics. Studies were conducted that provided valuable information on drugs often used in pediatric medicine such as cyclophosphamide, ibuprofen, mycophenolate, pantoprazole, sildenafil, and voriconazole. Other papers have furthered our knowledge of the dosing and monitoring of drugs during adolescence and added to our understanding of toxicities associated with common therapies such as opioid analgesics. This issue of *Pediatric Pharmacotherapy* will provide an overview of these studies and case reports.

Antiretroviral Therapy in Adolescents

The authors of a recent review article in *Clinical Pharmacology and Therapeutics* call attention to the lack of antiretroviral dosing information in adolescents with HIV/AIDS.[1] Although several pharmacokinetic (PK) studies have been published in this age group within the last five years, there are still many drugs in this therapeutic class that have not yet been evaluated. In addition to PK and dose-ranging studies, the authors also highlight the need for studies designed to identify long-term effects of treatment during puberty, such as hyperlipidemia and the risk for cardiovascular disease. The effects of concomitant administration of other drugs often prescribed during adolescence, such as antidepressants and oral contraceptives, also need to be evaluated. While this article is primarily focused on identifying future research needs, it would also make a useful reference for health care providers caring for teens with HIV infection. An extensive table provides current pediatric and adult dosing guidelines from both the World Health Organization and the U.S. Food and Drug Administration (FDA), and provides specific information on adolescent dosing, when available.

Caffeine Pharmacokinetics in Infants

Caffeine is widely used in the treatment of apnea of prematurity. It has been suggested that caffeine may also have a neuroprotective effect in this patient population. A newly published study utilized caffeine serum concentrations from 110 infants with apnea of prematurity to develop a population pharmacokinetic model to add to our understanding of this common therapy.[2] The infants (< 30 weeks gestation) were randomized to receive a caffeine citrate dose of 5 or 20 mg/kg/day, starting 24 hours after a loading dose of 20 or 80 mg/kg. Patients on full enteral feeds received oral doses, all others were treated with intravenous (IV) caffeine. Four timed blood samples were taken from each patient to evaluate serum caffeine concentrations. The data from the samples were analyzed with non-linear mixed effects modeling (NONMEM) and fit to a one compartment model with first-order absorption.

The study demonstrated complete absorption of caffeine from the gastrointestinal tract, resulting in an estimated bioavailability of 100% and suggesting that no dosage adjustment is necessary when switching between routes of administration. The mean absorption half-life of 30 minutes was approximately twice as long as reported in adults. Clearance increased in a nonlinear manner with postnatal age, from approximately 1 mL/min/kg on the first day of life to 12 mL/min/kg at 45 days, reflecting an increased rate of N-demethylation via cytochrome P450 (CYP) 1A2. The mean elimination half-life was 101 hours.

The authors reported no significant adverse effects during the trial, and found no clear relationship between serum caffeine concentrations and response. This information, along with the finding of considerable day-to-day variability in clearance, led the authors to conclude that standard dosing methods are appropriate and that routine monitoring of caffeine concentrations is not necessary. The findings of this new study support the results of previous work with caffeine in premature infants, but also introduce new information, including data on oral bioavailability.

Cyclophosphamide Pharmacokinetics

Current dosing regimens for cyclophosphamide in the treatment of children with neuroblastoma have resulted in considerable variability in patient response. A recent study, conducted through the Children's Oncology Group, addressed this problem through development of a population pharmacokinetic model to better describe the profile of cyclophosphamide and its metabolites.[3] The model was developed with NONMEM techniques, using 196 blood samples taken from 22 children receiving IV cyclophosphamide. As anticipated, considerable interpatient variability was found in the area under the concentration-time curve (AUC) for cyclophosphamide, as well as for the hydroxycyclophosphamide (HCY) and carboxyethylphosphoramide (CEPM) metabolites. The non-inducible clearance rate of cyclophosphamide was 1.83 L/hr/m^2, with a standard error of 30.6% and a between-subject variability of 61.7%. The authors concluded that their results confirm the high rate of interpatient variability in cyclophosphamide disposition and represent a first step in designing future pharmacokinetic-based pharmacodynamic studies of cyclophosphamide in children.

Drug Metabolism During Adolescence

One of the most interesting developments in pediatric pharmacology over the past decade has been an increased appreciation for the changes in pharmacokinetics during adolescence. A recent review of the topic, published in the December 2008 issue of *Clinical Pharmacology and Therapeutics*, addresses the impact of growth and sexual maturation, as well as the changes in CYP450 enzyme function and the potential interface between these developments.[4] The authors cite a number of recent examples of clinical trials conducted in adolescents to support their hypotheses. This issue of the journal, which also includes the antiretroviral review described previously, as well as the study on growth hormone below, is an excellent resource for health care providers caring for teens.

Growth Hormone Deficiency and Metabolism

Pharmacokinetic differences have been identified in both children and adults with growth hormone deficiency (GHD) for several drugs. In a multi-center study, Kennedy and colleagues compared metabolic function in 12 children with GHD and historical controls (12 healthy controls and 12 with cystic fibrosis).[5] Comparison of molar ratios of CYP1A2, xanthine oxidase, and N-acetyltransferase 2 (NAT-2) indicated significantly lower activity in children with GHD. The difference in NAT-2 activity was correlated with patient age; once the ratio comparisons were adjusted for age, the difference between GHD patients and controls was no longer statistically significant. The age-adjusted ratios for CYP2D6 and xanthine oxidase activity were significantly lower in the GHD patients, suggesting that these enzymes are adversely affected by reductions in circulating growth hormone. The results of this study confirm earlier pharmacokinetic studies showing a prolonged theophylline elimination half-life in GHD patients (7.2 hrs compared with 3 to 4 hrs in controls) and highlight the need for dose individualization in this population.

Ibuprofen Pharmacokinetics

Ibuprofen injection has recently entered the market in the U.S. as an alternative to indomethacin for closure of a patent ductus arteriosus in premature infants. Ibuprofen is a racemic mixture of the S- and R-enantiomers, with S-ibuprofen being the more pharmacologically active form. Gregoire and colleagues used data from three clinical trials to develop a population pharmacokinetic model for both ibuprofen enantiomers in premature neonates.[6] Samples were taken from 108 patients (< 34 weeks gestational age). The patients received IV ibuprofen (Pedea®, Orphan Europe), with an initial dose of 10 mg/kg followed by two doses of 5 mg/kg at 24-hour intervals. Timed samples were analyzed for the concentrations of both S- and R-ibuprofen. Pharmacokinetic parameters were calculated using NONMEM with first-order elimination. The mean estimated clearance of S-ibuprofen was 3.5 mL/hr/kg with a calculated half-life of 34.3 hrs. Clearance was considerably more rapid for R-ibuprofen, with a clearance of 25.5 mL/hr/kg and a calculated half-life of 8.3 hrs. When analyzed with relation to postnatal age, R-ibuprofen elimination increased during the first week of life, while S-ibuprofen kinetics remained relatively unchanged. Based on the differences found between the enantiomers, the authors recommend that future studies of ibuprofen evaluate these compounds separately.

Long-term Use of Mycophenolate

Mycophenolic acid (MPA) is the active drug produced from the prodrug mycophenolate mofetil. Short-term studies of MPA have been performed in the pediatric transplant population, but long-term data are scarce. A recent open-label longitudinal study evaluated MPA pharmacokinetics in 25 pediatric kidney transplant recipients (ages 1-16 years).[7] Patients received mycophenolate mofetil at a dose of 600 mg/m^2 (up to 1,000 mg) twice daily, along with cyclosporine and prednisone. Serum samples were collected after the first week of therapy and

at 3, 9, 24, and 36 months. For analysis, the patients were divided into 3 groups: < 6 years, 6-12 years, and 12-18 years of age. The authors found a 2.7-fold increase in MPA trough concentrations over the first 9 months of treatment, with the greatest increase occurring during the first 3 months ($p<0.05$). Concentrations stabilized after that time. Assuming a desired range for AUC of 30-60 mg·hr/L, 60% of the patients had a subtherapeutic concentration at the end of the first week, suggesting that a higher initial dose may be needed. Five of the patients switched from the suspension dosage formulation to capsules during the study, with no significant change in serum MPA concentrations. The dose-normalized MPA exposure was comparable in the three age groups, confirming the utility of body surface area as a means of calculating individual doses. The results of this study provide an interesting insight into the changes in MPA pharmacokinetics over time and suggest a need to further investigate initial mycophenolate dosing recommendations.

Neonatal Toxicity from Maternal Codeine

In 2006, a case report of neonatal opioid toxicity resulting from codeine transferred in breastmilk called attention to the risk for harm in susceptible infants.[8] The report described a fatal case of opioid toxicity in a breastfed infant whose mother was given codeine. The mother was a CYP2D6 ultrarapid metabolizer who produced significant amounts of morphine as a byproduct of codeine metabolism. In a January 2009 study, Madadi and colleagues compared metabolic function in the mothers of 17 infants with symptomatic central nervous system depression and 55 asymptomatic infants.[9] The mothers of the symptomatic infants had consumed a mean 59% higher codeine dose. Two mothers whose infants had severe toxicity were CYP2D6 ultrarapid metabolizers. These results support the dose-response relationship with opioid toxicity in infants and add further evidence of the risk for opioid toxicity in breastfed infants whose mothers produce higher levels of morphine as a codeine metabolite.

Pantoprazole in Children and Adolescents

While the use of proton pump inhibitors in the pediatric population has risen sharply within the past 5 years, there is still little known about their pharmacokinetic and pharmacodynamic profiles in children. Kearns and colleagues conducted two open-label, single-dose pharmacokinetic studies of pantoprazole in children between 2 and 16 years of age.[10] In the first study, 24 children were randomized to receive a single oral dose of either 20 mg or 40 mg pantoprazole after an 8 hr fast. In the second study, 19 patients were stratified by age (2-4 years, 5-10 years, and 11-16 years). All patients received a single IV dose of either 0.8 or 1.6 mg/kg pantoprazole (maximum dose 80 mg) infused over 15 minutes.

The mean maximum plasma concentration was 2.97 ± 1.51 mg/L after oral pantoprazole. The maximum plasma concentration with the 1.6 mg/kg IV dose was higher than the 0.8 mg/kg dose (10.3 ± 3.7 mg/L versus 5.7 ± 2.7 mg/L, $p<0.05$), demonstrating dose linearity similar to earlier adult studies. Clearance was similar in the oral and IV studies, with a mean rate of 0.26 ± 0.20 L/hr/kg in the oral study and 0.20 ± 0.23 L/hr/kg in the IV study. Mean elimination half-life was 1.27 ± 1.29 hrs after oral dosing and 1.22 ± 0.68 hrs after IV dosing. As anticipated, children known to be CYP2C19 extensive metabolizers had significantly lower plasma pantoprazole concentrations and a more rapid clearance than the children who were poor metabolizers. The results of this study suggest that the pharmacokinetic profile of pantoprazole in children is similar to that of adults and does not appear to vary with growth. The doses used in the study were well tolerated and suggest that additional clinical trials with pantoprazole in the treatment of children with gastroesophageal reflux are warranted.[10]

Sildenafil Pharmacokinetics in Neonates

In the January 2009 issue of *Clinical Pharmacology and Therapeutics*, Mukherjee and colleagues described the results of an open-label trial of intravenous sildenafil in 36 term neonates with persistent pulmonary hypertension of the newborn (PPHN).[11] The study utilized eight escalating-dose groups who received a loading dose followed by a maintenance infusion for up to 7 days. A mixed-effects model was used to describe the pharmacokinetic profile of sildenafil and its metabolite. The model utilized a two-compartment design and incorporated the effect of postnatal age on clearance. The authors found a three-fold increase in sildenafil clearance from the first day of life to the end of the first week. By that time, clearance in the infants was similar to values reported in adults. The volume of distribution was approximately four-fold adult values, with a terminal half-life of 48 to 56 hours (compared to 3 to 5 hours in adults). The authors proposed that this change reflected maturation of N-demethylation in the early postnatal period.

Voriconazole Use in ECMO

The authors of this case report describe the course of a 5-year-old boy with acute lymphoblastic leukemia who developed varicella zoster pneumonia.[12] On the third day of

hospitalization, his condition had deteriorated to the point where extracorporeal membrane oxygenation (ECMO) was initiated for ventilatory support. Hemofiltration was started on the fourth day of ECMO therapy. On day 5, voriconazole (6.7 mg/kg given IV twice daily) was started for pulmonary aspergillosis. A target trough serum concentration > 1 mg/L was selected based on literature recommendations. After an initial voriconazole serum concentration of 0.7 mg/L was obtained, the dose was increased to 14 mg/kg twice daily. Using additional serum samples, voriconazole pharmacokinetic parameters were determined as followed: peak concentration 8.2 mg/L, AUC 64 mg·hr/L, clearance 0.22 L/hr/kg, and half-life 4.7 hrs. Compared with previous studies of voriconazole pharmacokinetics in children, this patient had a larger peak serum concentration, greater AUC, and slower clearance. While the information that can be gained from an isolated case report is limited, this paper provides a starting point for further evaluations of voriconazole in patients requiring ECMO.[12]

Summary

A wide variety of pharmacokinetic studies have been published within the last year that further our knowledge of how medications are absorbed, distributed, metabolized, and eliminated in infants and children. These studies range from preliminary investigations and isolated case reports to clinical trials with the potential to alter drug dosing in children. As our understanding of pediatric pharmacology grows, so does our ability to safely and effectively utilize drug therapy to prevent and treat diseases affecting infants and children.

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Pharmacology Literature Review

Rate of Suicide in Patients on Montelukast

On March 28, 2008, the FDA announced that it was reviewing safety data for montelukast, a leukotriene receptor antagonist used in the management of asthma, after reports of a possible association with suicide or suicidal ideation. The FDA called for further investigation into the relationship between the drug and these effects. This brief report evaluated the rate of suicide in patients taking montelukast in the United Kingdom General Practice Research Database. A total of 252,593 montelukast prescriptions were written for 23,500 patients over a nine year period. There were no cases of suicide. Based on their survey, as well as the results of clinical trial data and other database reviews, the authors concluded that the risk of suicide attributable to montelukast was extremely low to nonexistent. Jick H, Hagberg KW, Egger P. Rate of suicide in patients taking montelukast. **Pharmacotherapy 2009;29:165-6.**

Formulary Update

The Pharmacy and Therapeutics Committee did not meet during February. Their next meeting will be on 3/27/09.

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