Pediatric Pharmacotherapy

A Monthly Newsletter for Health Care Professionals
Children's Medical Center at the University of Virginia

Volume 3 Number 11 November 1997

Pharmacology Literature Review

Marcia L. Buck, Pharm.D.

Recent issues of *Pediatric Pharmacotherapy* have contained longer feature articles, resulting in less room for abstracts of current publications. This month the entire issue is devoted to abstracts, in order to "catch up" on some very interesting articles published in the August, September, and October issues of several pharmacy and pharmacology journals. Most of these journals are available through the University of Virginia Claude Moore Health Sciences Library. Others are available through the UVA Drug Information Center.

Aminoglycosides in Children Following Bone Marrow Transplantation

The pharmacokinetic profiles of gentamicin and tobramycin were studied in 33 children after bone marrow transplantation. Mean parameters for the group were: volume of distribution 0.32±0.07 L/kg, half-life 2.32±0.65 hrs, and clearance 1.71±0.53 ml/min/kg. These values are similar to those reported for children with cancer who have not been transplanted. Typically in these children, drug elimination is more rapid than in children without cancer. The authors found no relationship between pharmacokinetics and disease state, type of marrow graft, gender, or use of cyclosporine. A weak relationship was observed between serum creatinine and clearance. Based on their results, the authors suggest the following daily doses: children > 6 yrs: 8 mg/kg/day; children 7-12 yrs: 7 mg/kg/day; and children 13-15 yrs: 6 mg/kg/day. Jacobson PA, West NJ, Price J, et al. Gentamicin and tobramycin pharmacokinetics in pediatric bone marrow transplant patients. **Ann Pharmacother 1997;31:1127-31.**

Antimicrobial Desensitization Protocols

This article provides a useful review of the literature published on methods for desensitization. Preparation methods (dilution standards), dosing, and administration schedules are included for penicillin, trimethoprim-sulfamethoxazole, vancomycin, and pentamidine. The need for an accurate history and allergen testing prior to desensitization are emphasized. The authors also caution readers that a successful completion of the desensitization protocol does not imply future safety from reactions or true resolution of the drug allergy. Tidwell BH, Cleary JD, Lorenz KR. Antimicrobial desensitization: A review of published protocols. **Hospital Pharmacy 1997;32:1362-9.**

Azithromycin Pharmacokinetics

The safety and pharmacokinetics of high-dose azithromycin were evaluated in 28 hospitalized children. Twelve of the children were admitted for febrile neutropenia following chemotherapy. Oral doses of 12 mg/kg were given once daily for 5 days. Azithromycin was tolerated by all but one child, who developed abdominal cramps. Pharmacokinetic parameters were evaluated in 23 children. Combining data from all evaluable patients (after one or more doses), the average maximum serum concentration was 318.2±174.5 mcg/L. The average time to achieve maximum serum concentration was 2.4±1.1 hours and the mean elimination half life was 54.5±36.4 hours. Pharmacokinetic parameters were no different in children with cancer than in other children. Stevens RC, Reed MD, Shenep JL, et al. Pharmacokinetics of azithromycin after single and multiple doses in children. **Pharmacotherapy 1997;17:874-80.**

Betamethasone-induced Leukemoid Reaction

The case of a 25 week gestational baby who developed a leukemoid reaction shortly

following birth is described. The patient's mother received two 12 mg betamethasone injections within the week prior to delivery. The infant's white cell count reached a maximum of 159,000 cells/mm^3 on day 3 of life with no signs of infection or other laboratory abnormalities. The authors discuss the case as well as previous reports of leukemoid reactions associated with corticosteroid administration. Hoff DS, Mammel MC. Suspected betamethasone-induced leukemoid reaction in a premature infant. **Pharmacotherapy 1997;17:1031-4.**

Ceftibutin Review

This in-depth review will be a useful resource for clinicians in primary care. Ceftibutin (Cedax®) is an extended spectrum oral cephalosporin with indications for treating both upper and lower tract respiratory infections as well as otitis media. It offers the advantage of once daily dosing with an adverse effect profile similar to other oral cephalosporins. In addition to an extensive review of the antimicrobial spectrum of ceftibutin, the article includes a discussion of published clinical trials, pharmacokinetic data, and a cost comparison to other oral antibiotics. Guay DRP. Ceftibutin: A new expanded-spectrum oral cephalosporin. **Ann Pharmacother 1997;31:1022-33.**

Drug-induced Arrhythmias

The author of this review discusses both the pro-arrhythmic potential of some antiarrhythmic agents and the arrhythmogenic effects of other non-cardiac medications. The mechanisms of these effects are discussed in detail. Brief sections on prevention and treatment are also included. Doig JC. Drug-induced cardiac arrhythmias: Incidence, prevention and management. **Drug Safety 1997;17:265-75.**

Effect of Halving Ritalin-SR®

When faced with the need for a variable dosage regimen (20 mg and 10 mg), families are often required to keep two separate supplies of methylphenidate tablets. In an effort to eliminate the confusion and reduce possible dosing errors, the option of halving the 20 mg Ritalin-SR® has been suggested. This study documents that halving the sustained release product does not alter the rate or extent of dissolution. While these results support the halving option, further work is needed to identify any differences in pharmacokinetic parameters or clinical response. Erramouspe J, Jarvi EJ. Effect on dissolution from halving methylphenidate extended-release tablets. **Ann Pharmacother 1997;31:1123-6.**

EMLA for Bone Marrow Aspiration or LP

EMLA, a mixture of lidocaine and prilocaine used for topical analgesia, was evaluated in children with cancer undergoing lumbar punctures (LP) or bone marrow aspirations. Comparisons were made to procedures done without EMLA. Only children 5 years of age or older were evaluated, in order to use a pain scale. Pain ratings (by both the patient and observer) decreased after EMLA use for LP, but not bone marrow aspiration. The efficacy of EMLA was significantly reduced for repeated LP, causing the authors to conclude that EMLA should not be relied on as a sole analgesic. Interestingly, observer pain scores correlated well with patient scores initially, but became less representative after repeat procedures. Holdsworth MT, Raisch DW, Winter SS, et al. Differences among raters evaluating the success of EMLA cream in alleviating procedure-related pain in children with cancer. **Pharmacotherapy 1997;17:1017-22.**

Herbal Medicines

A system used for monitoring herbal medicine safety is presented in this article. The author first addresses the need for monitoring natural remedies, including the lack of safety information and quality assurance of product content. He then uses the program developed in Hong Kong as an example of a system designed to capture safety data and provide on-going surveillance of potential adverse effects. Chan TYK. Monitoring the safety of herbal medicines. **Drug Safety 1997;17:209-15.**

Indinavir-associated Nephrotoxicity

The authors present a case of a 16 year old boy who developed nephrotoxicity while receiving indinavir, a protease inhibitor used in HIV infection. The patient's symptoms: hyperbilirubinemia, nephrolithiasis, and subsequently, interstitial nephritis and decreased renal function were temporally related to the addition of indinavir. Symptoms slowly resolved after the discontinuation of therapy. Ritonavir therapy was substituted for indinavir without further renal complications. Ascher DP, Lucy MD. Indinavir sulfate renal toxicity in a pediatric hemophiliac with HIV infection. **Ann Pharmacother 1997;31:1146-9.**

Isoniazid Acetylation

The metabolism of isoniazid was studied in 61 children being treated for tuberculosis. Isoniazid acetylation metabolic ratio (an indicator of N-acetyltransferase activity) was found to have a bimodal distribution in these children, consistent

with previous studies grouping adults into either fast or slow acetylator categories. During continued treatment, 12 of the children initially described as slow acetylators became fast acetylators. None of the initially fast acetylators changed their rate of isoniazid metabolism. The rate of acetylation was correlated with age, showing maturation of enzymatic function over the first four years of life. Beyond the information gained about isoniazid, this study provides significant insight into the nonlinear development of metabolic pathways during childhood. Pariente-Khayat A, Rey E, Gendrel D, et al. Isoniazid acetylation metabolic ratio during maturation in children. **Clin Pharmacol Ther 1997;62:377-83.**

Medication Taste and Compliance

Does prescribing medications that taste good result in improved compliance? Many clinicians assume so, but this study casts doubt on this belief. Forty-five children and their parents evaluated the taste of three liquid antibiotics. Parents rated their own taste preference and evaluated their children's response. The results from the 39 children completing the study and their parents were consistent regardless of age: cefixime was rated as good-tasting, cefpodoxime as poor-tasting, and amoxicillin was considered intermediate. Despite the preference for the taste of cefixime, compliance was no different among the groups. While taste should still be considered when choosing medications for children, compliance may be more strongly associated with education regarding the importance of medical therapy. Higa SK, Chan DS, Bass JW, et al. Oral antibiotic suspensions: Do adult taste tests predict compliance in infants and young children? **J Pediatr Pharm Pract 1997;2:265-70.**

Metabolic Function During Pregnancy

This study of pregnant women was performed to evaluate the function of the CYP2D6 enzyme during gestation. Genotyping was performed in 141 women. Of those, 17 were selected for phenotyping with dextromethorphan both during pregnancy and following delivery. In the women who were extensive metabolizers, metabolite production was consistently elevated during pregnancy. As a result, the authors concluded that CYP2D6 activity is increased during pregnancy, which may result in more rapid metabolism of many medications. Wadelius M, Darj E, Frenne G, et al. Induction of CYP2D6 in pregnancy. **Clin Pharmacol Ther 1997;62:400-7.**

Minocycline-induced Lupus

Minocycline has become an accepted treatment for acne in adolescents. This case report describes a 14 year old girl who developed symptoms consistent with drug-induced lupus after approximately 5 months of minocycline use. She experienced myalgias, arthralgias, polyarthritis, and facial flushing over a period of 2 months. All symptoms greatly improved within a week of stopping minocycline. Following the case description, a review of the literature for this adverse drug reaction is provided. Farver DK. Minocycline-induced lupus. **Ann Pharmacother 1997;31:1160-3.**

Tobramycin Pharmacokinetics in Neonates

Population pharmacokinetic parameters were determined from the retrospective data of 140 neonates receiving tobramycin. Based on the results, the authors recommend the following dosing schedules: gestational age < 32 weeks: 4 mg/kg every 48 hours; gestational age 32-37 weeks: 4 mg/kg every 36 hours; gestational age > 37 weeks: 4 mg/kg every 24 hours. After implementing this regimen, a prospective validationwas performed in 23 neonates. Only one patient had a peak concentration less than the target of 5 mcg/ml. Three patients had trough levels greater than 2 mcg/ml. This study, while demonstrating the utility of population pharmacokinetic analysis, also shows the efficacy of longer empiric dosing intervals than those currently used. de Hoog M, Schoemaker RC, Mouton JW, et al. Tobramycin population pharmacokinetics in neonates. **Clin Pharmacol Ther 1997;62:392-9.**

Treatment of Childhood Obesity

This review provides a brief introduction to the pathophysiology of childhood obesity and its treatment. The author provides a detailed table listing the studies of drug treatment in children published to date, along with case studies. Treatment of both obesity and Prader Willi syndrome are included. In addition, several investigational therapies are described. Diamond FB. Childhood obesity, pharmacological and hormonal basis for treatment. **J Pediatr Pharm Pract 1997;2:271-84.**

Ursodeoxycholic Acid in Infants with CF

The authors present two interesting cases of infants with cystic fibrosis who were treated with ursodeoxycholic acid within the first 6 weeks of life. Ursodeoxycholic acid acts as a choleretic and has been used successfully to treat children and adults with hepatic disease associated with cystic fibrosis (CF). In these two infants, the

diagnosis of CF was made after presentation with meconium ileus. Ursodeoxycholic acid was added for subsequent symptoms of hepatobiliary disease. Doses of 20-40 mg/kg/day resulted in reduction of liver enzymes and hepatosplenomegaly. Scher H, Bishop WP, McCray PB. Ursodeoxycholic acid improves cholestasis in infants with cystic fibrosis. **Ann Pharmacother 1997;31:1003-5.**

Vancomycin Pharmacokinetics in Neonates

This article features a sparse sampling technique, designed to provide population pharmacokinetic data (averages) from a small number of serum samples. The principle behind this system is to obtain all the standard pharmacokinetic information (volume of distribution, elimination half-life, and clearance) from the least amount of serum vancomycin samples possible without introducing significant error. While the methodology section of this paper will likely be enjoyed only by true pharmacokinetic enthusiasts, the results are well worth reading by all clinicians treating babies. The authors conclude that the standard technique of obtaining only two vancomycin samples is adequate for two-compartment modeling, when one is obtained 30 minutes following a dose and another immediately prior to a dose. Using a one-compartment model requires prolonging the timing of the first vancomycin sample until 3-4 hours post-dose. Burstein AH, Gal P, Forrest A. Evaluation of a sparse sampling strategy for determining vancomycin pharmacokinetics in preterm neonates: Application of optimal sampling theory. **Ann Pharmacother 1997;31:980-3.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/24/97:

1.Sodium sulfacetamide 10%/sulfur 5% lotion (Novacet® by GenDerm) was added to the formulary for the treatment of acne vulgaris, acne rosacea, and seborrheic dermatitis. This lotion may be applied 1-3 times daily.

2. All-*trans*-retinoic acid, or tretinoin (Vesanoid® by Roche), was added to the formulary for the treatment of acute promyelocytic leukemia.

3. Nifedipine in the standard (immediate-release) form was restricted to use in pediatric and obstetric patients.

4. Thiothixene injection (Navane® by Pfizer) was removed from the formulary.

5. The quarterly summation of the Adverse Drug Reaction Reporting Program was presented. For more information about this report, please refer to the November issue of *P & T Forum* or contact Dr. Michelle McCarthy at the Drug Information Center by calling 924-8034.

PMET is Here!

There is a new resource available for health care providers who counsel the parents of young children on medications. The Pediatric Medication Education Text (PMET) has recently been published by two members of the *Pediatric Pharmacotherapy* staff, in conjunction with the American College of Clinical Pharmacy. The book features instructions for administering 200 commonly prescribed medications.

The single page instructions are meant to be photocopied and given to parents by physicians, nurses, or pharmacists. The text is written at approximately the 6th grade reading level and uses a standard question and answer format. Both English and Spanish versions are provided for each drug. PMET meets all regulations currently proposed for written medication information.

PMET is available for $40. For more information or to place an order, contact the American College of Clinical Pharmacy by phone at (816) 531-2177, by fax at (816) 531-4990, by mail to ACCP, 3101 Broadway, Suite 380, Kansas City, MO 64111, or through their website at http://www.accp.com.

If you have any comments or would like to be on our mailing list, please contact Marcia Buck by mail at Box 274-11, University of Virginia Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.