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Yaffe Award Lecture

Ensuring Safe and Effective Medication Use in Pediatric Patients

Milap C. Nahata, MS, PharmD

College of Pharmacy and Departments of Pediatrics and Internal Medicine, College of Medicine, The Ohio State University, Columbus, Ohio

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INTRODUCTION

This is a tremendous honor to receive peer recognition carrying the name of late Dr Sumner Yaffe. I was fortunate to have worked with him over many years through professional organizations and as a part of the pediatric pharmacology research units (PPRUs). Dr Yaffe established pediatric pharmacology programs in Buffalo and Philadelphia and made important contributions to enhance pediatric care with his research, practice, and teaching. He led the development of PPRUs and the neonatal networks, and was a force behind the framing of what became the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA). He was indeed a visionary leader and mentor in the field of pediatric pharmacology.

The objectives of my presentation today are to briefly share my background, reflect on our work, and discuss potential opportunities to advance pediatric pharmacy, pharmacology, and therapeutics.

MY BACKGROUND

I grew up in a small town in the desert area of the state of Rajasthan in India. My father had completed sixth grade and mother never went to school. I saw financial constraints facing my family and learned little English during schooling. I had to leave my family at the age of 15 years to attend the University of Jodhpur where I completed a BS in physics, chemistry, and mathematics. This was followed by the University of Bombay (now Mumbai) for my pharmacy degree. Although the medium of instruction was English in Mumbai, I still lacked speaking ability and even writing ability in English beyond basic understanding and answering test questions in the college.

Coming to the United States to pursue graduate studies was a great opportunity. My family had to borrow money to send me so I knew the weight of this decision. I came to Duquesne University to complete a masters degree in pharmaceutics. During this time I was a teaching assistant and developed a passion for teaching. I also learned about the PharmD program and was immediately attracted to the possibilities of contributing to health care through clinical practice, teaching, and research. Thus, I pursued a PharmD degree (instead of PhD) after completing my masters degree and then a clinical pharmacy residency at Buffalo General Hospital, in affiliation with the University of Buffalo School of Pharmacy. These experiences clearly led me to seek a position in academic pharmacy.

The Ohio State University College of Pharmacy offered me a position where I gained experience in the development and implementation of first required didactic therapeutics and experiential courses for the BS (pharmacy) program. I also initiated the clinical pharmacy practice and research program, which then allowed us to build the postbaccalaureate PharmD and fellowship programs.

The professional journey, however, had some barriers but we persisted with optimism. After a few years in internal medicine, I moved to pediatrics, which opened the doors to so many opportunities in clinical practice (primarily pediatric infectious diseases), teaching, and research. Within a few years, we were able to develop a

Table 1. Time Required to Deliver 95% of Chloramphenicol Sodium Succinate Dose from Buretrol at Various Infusion Rates[2]

Infusion Rate	Time
5 mL/hr	7.6 hr
15 mL/hr	4.5 hr
30 mL/hr	2 hr

well-funded practice-based research program that allowed us to initiate the pediatric pharmacotherapy fellowship, which has been sustained through 3 decades.

I want to express my gratitude to nearly 200 pharmacy fellows, residents, students, and staff who chose to work with me; many of them are here to celebrate this occasion with me. I want to thank many colleagues and friends in pediatric pharmacy for their encouragement and support. Finally, I want to share this recognition with my collaborators for their contributions to our work over the years.

EXAMPLES OF OUR WORK

Soon after my arrival at the Nationwide Children's Hospital, we had an epidemic involving Reye syndrome. The mortality and morbidity for this condition were high. The efficacy and safety of glycerol to lower intracranial pressure in patients with Reye syndrome were unclear. Our study[1] demonstrated appropriate dosage regimen for these patients with favorable outcomes. Owing to lack of a vaccine against *Haemophilus influenzae* type b in the 1970s, chloramphenicol became the drug of choice for empiric therapy in infants and children with bacterial meningitis. Serum concentration was routinely monitored to prevent dose-related hematologic toxicities. However, we found marked variability in serum concentrations. In many cases, the peak was lower and the trough higher than expected. This led to investigation of the infusion delivery system. We found delayed delivery of the dose, especially when the dose was placed in the buretrol and infused at slow rates (Table 1).[2] This was confirmed in additional studies with other drugs (e.g., aminoglycosides).[3] These data became the basis for changing guidelines on intravenous infusion of drugs and increased use of microbore tubing and syringe pumps for drug delivery in infants. It was then possible to predict peak and trough serum concentrations of drugs more accurately.

Pharmacokinetics was a relatively new field in the 1970s for application to pediatrics. The conduct of these studies required development and validation of accurate, reproducible, and specific analytic methods using small blood samples (e.g., 50 µL), especially in newborn infants.[4–6] We performed pharmacokinetic studies with a number of drugs including antimicrobials (e.g., chloramphenicol, tobramycin, vancomycin, ceftriaxone, and azithromycin). Our chloramphenicol studies[7,8] were the first to show that after intravenous (IV) administration of chloramphenicol sodium succinate, the bioavailability of chloramphenicol was highest in the youngest infants owing to the lowest renal clearance of chloramphenicol sodium succinate. This contributed to excessive serum concentrations, in addition to previously known decreased metabolism of chloramphenicol in infants. Recommended doses of aminoglycosides and vancomycin did not account for prematurity of the newborns. Our studies[9–11] showed decreased clearances and thus lower daily dose requirements for premature infants, allowing reduced exposure to drugs in this population. We documented adequate cerebrospinal fluid concentrations of ceftriaxone, which replaced chloramphenicol for the treatment of bacterial meningitis.[12] Azithromycin was the first antibiotic that could be given once daily for only 5 days to treat certain infections in adults. We did pivotal studies to characterize its pharmacokinetics, documenting adequate concentrations in children with respiratory tract infections.[13] These studies, combined with our efficacy and safety studies, were submitted to the US Food and Drug Administration (FDA) for its approval in children.

We conducted efficacy and safety studies with antibiotics as well as amlodipine in children with hypertension and oral hypoglycemic agents in those with type 2 diabetes. Amlodipine studies[14] showed larger dose requirement per kilogram for patients younger than 13 years vs an older group (Table 2). The only oral hypoglycemic drug approved for children with type 2 diabetes was metformin. We documented substantial decreases in hemoglobin A1c with several other oral agents (Figure).[15]

A large group of our patients with chronic suppurative otitis media were unresponsive to Cortisporin (Draxis Pharma, Inc., Kirkland,

Table 2. Amlodipine Efficacy in Hypertension[14]

Dose	mg/kg/day
Starting	0.07 ± 0.04
Titrated (age <13 yr)	0.29 ± 0.11
Titrated (age >13 yr)	0.16 ± 0.11

** Quality of life (improved activity, functioning and overall health) enhanced with amlodipine therapy.*

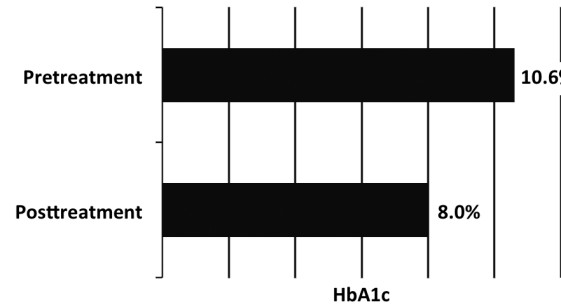

Figure. Effect of oral hypoglycemics on hemoglobin A1c in children with type 2 diabetes.[15]

Quebec) ear drops. We used ciprofloxacin eye drops (owing to lack of an otic formulation) for otic use and were able to successfully treat most patients unresponsive to Cortisporin.[16,17] Similarly, numerous patients with tinea capitis were unresponsive to standard therapy with griseofulvin. Our use of itraconazole led to effective treatment in approximately one-half of those unresponsive to griseofulvin.[18]

A cocktail of meperidine, promethazine, and chlorpromazine (Demerol, Phenergan, and Thorazine or DPT) was frequently used for procedural sedation (e.g., endoscopy) in the 1970s and 1980s. We observed prolonged sedation exceeding 7 hours in two-thirds of our patients and respiratory depression or arrest in some individuals.[19] This led to our studies with meperidine and midazolam, which replaced the use of DPT cocktail at our institution.[20,21]

We were curious to know which drugs were causing the most adverse drug reactions (ADRs) in pediatric patients. Antibiotics, opioids, anticonvulsants, and antineoplastic agents were the top 4 categories in our study. Nearly one-fourth of ADRs were preventable. Gaps in medication ordering, administration, and monitoring accounted for 95% of these preventable ADRs.[22]

Medication prescribing is increasingly being done electronically with systems such as EPIC (Verona, WI) with the aid of decision support systems.[23] We noted unnecessary dosing alerts for our patients. In fact, our recent study[24] found 86% of dosing alerts to be inappropriate. In addition, the incorporation of dosage ranges customized at our institution enhanced the sensitivity of rules for the detection of dosing errors.

Since many drugs are used off-label in infants and children, suitable dosage forms are often unavailable for use in this population. For example, intravenous drugs may be too concentrated for the accurate measurement of small doses (less than 0.1 mL). In such cases, the IV formulation intended for adults may require up to 10-fold dilution. This alteration will require documentation of stability and sterility of the modified IV dosage form to assure effective and safe use in patients. Similarly, certain oral dosage forms (e.g., tablets and capsules intended for adults) cannot be used appropriately in infants and young children who cannot swallow these and would require body weight–based dose rather than a fixed dose. Suitable oral dosage form in such cases would be a liquid but this alteration would require documentation of stability and suspendability for accurate use. We performed numerous studies with extemporaneously prepared dosage forms for use in pediatric patients (Table 3).[25]

POTENTIAL OPPORTUNITIES

Additional practice-based research is needed in all areas to advance knowledge. I recently served on a committee of the Institute of Medicine, which analyzed pediatric studies conducted under the BPCA and PREA. The report[26] identified numerous concerns with pediatric studies, including insufficient patient recruitment, weak study designs, lack of dose-ranging studies, limited information in labels, scarcity of long-term effectiveness and safety data, and lack of appropriate formulations for use in patients of various age groups.

As examples, prescribing has sharply increased for proton pump inhibitors and yet no label indicates their efficacy in infants younger than 12 months. It is unclear what is the drug of choice among biologics in children with juvenile idiopathic arthritis. Further, optimal duration of therapy and long-term safety, including effect on growth and development, are unknown in this

Table 3. Extemporaneously Prepared Dosage Forms of Drugs With Documented Stability Data[25]

Aminophylline	Granisetron	Phenobarbital
Amiodarone	Hydrocortisone	Pravastatin
Amitriptyline	Itraconazole	Propylthiouracil
Amlodipine	Labetalol	Pyrazinamide
Caffeine	Lamotrigine	Pyrimethamine
Captopril	Levodopa/Carbidopa	Ranitidine
Cimetidine	Levothyroxine	Rifampin
Ciprofloxacin	Lisinopril	Sildenafil
Clindamycin	Lorazepam	Sotalol
Dapsone	Mercaptopurine	Spironolactone
Dexamethasone	Methylprednisolone	Terbinafine
Doxycycline	Metolazone	Tiagabine
Enalapril	Mexiletine	Topiramate
Flucytosine	Midazolam	Trimethoprim
Fumagillin	Morphine	Ursodiol
Gabapentin	Nifedipine	Verapamil
Glycopyrrolate	Pentoxifylline	Zonisamide

population. Atopic dermatitis is among the most common skin conditions in children. However, no systemic therapies, including biologics, have been well studied and approved for use in this population. Premature infants are exposed to numerous drugs and yet longitudinal studies documenting long-term safety are rarely performed.[26]

Pharmacogenomic studies are being done with increasing frequency both in adults and children. As examples, the label for aripiprazole suggests dose modification in poor metabolizers with cytochrome P450 2D6 genotype, and methylphenidate metabolism is influenced by polymorphisms in the dopamine transporter gene. This would be an important area of focus for personalized drug therapy. The FDA Adverse Event Reporting System relies on voluntary reports and thus may sharply underestimate the actual short-term and long-term safety concerns with medications used in pediatric patients. Medication safety needs to be assessed in well-designed studies in various age groups over time.[26]

A report of the US Department of Health and Human Services found that only 12% of adults in the United States were proficient in health literacy. Over one-third had difficulty with common tasks (e.g., understanding drug label or adhering to childhood vaccines).[27] This report emphasizes the need for us as pediatric pharmacy practitioners to be engaged with the caregivers of our patients and assure appropriate use of medications at all literacy levels.

The gaps between research knowledge and its appropriate clinical application can be closed by effective practice models, where pharmacists work collaboratively with other providers including physicians and nurses. Desired pharmacy practice models should be identified to meet high-priority needs among patients. The Accountable Care Act focuses on value-based care with metrics requiring documentation of patient outcomes and satisfaction. We must continue our resolve to provide best possible care to our patients, which would require collaborative practice, conduct of practice-based research, and education and training of students, residents, and fellows. We need to develop and nurture effective and bold leadership among our peers, trainees, and students to advance pediatric health care. This is essential to meet our obligations described in the Oath of a Pharmacist: welfare of humanity and relief of suffering, assuring optimal patient outcomes, preparing next generation of pharmacists, holding highest principles, and offering lifetime of service.

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Abbreviations ADRs, adverse drug reactions; BPCA, Best Pharmaceuticals for Children Act; DPT, Demerol, Phenergan, and Thorazine; FDA, US Food and Drug Administration; IV, intravenous; PPRUs, Pediatric pharmacology research units; PREA, Pediatric Research Equity Act

Correspondence Milap C. Nahata, MS, PharmD, The Ohio State University, Pharmacy Practice and Administration, A206 Parks Hall, Columbus, OH 43210, email: nahata.1@osu.edu

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