JPPT

## Yaffe Award Lecture

# The Pursuit of Pediatric Clinical Pharmacology: Perspectives from a Current Journey

*Gregory L. Kearns, PharmD, PhD*

*Division of Pediatric Pharmacology and Medical Toxicology and the Departments of Pediatrics, Pharmacology and Medical Research, Children's Mercy Hospital and the University of Missouri – Kansas City Schools of Medicine and Pharmacy, Kansas City, Missouri*

J Pediatr Pharmacol Ther 2009;14:10–16



*"Dr. Yaffe's vision of improved therapy for sick children is becoming a reality. He has inspired an entire generation of pediatric clinical pharmacologists to grow the field into a mature and evolving scientific discipline."*

*–Stephen P. Spielberg*

It is my distinct honor to have been selected by the Pediatric Pharmacy Advocacy Group (PPAG) to be the 2008 recipient of the Sumner J. Yaffe Lifetime Achievement Award and to join the august group of Pediatricians and Pharmacists who have also received this great honor. As reflected by the aforementioned quote excerpted from a biographical sketch of Dr. Yaffe published by PPAG in 2004,[1] Sumner remains as one of the true forefathers of Pediatric Clinical Pharmacology in the world. At this juncture, he has truly been responsible for inspiring three generations of professionals in the discipline of Pediatric Clinical Pharmacology. With a true sense of humility, it remains my sincere pleasure to be among their ranks.

Without having had the pleasure of ever receiving a grade from Dr. Yaffe (to my knowledge, at least), he unwittingly became one of my first instructors in this field. As an undergraduate student at the St. Louis College of Pharmacy in 1976, I had the good fortune to be selected by one of my professors to be one of 10 students who would be "permitted" to participate in a newly designed, eight week clinical rotation. In this evolution, Pharmacy students were to be inserted into a medical practice setting for the purpose of observing the decision making process as it related to the selection and prescription of drugs. Consequent to a genuine twist of fate, I was instructed to report to the Pediatric Allergy Clinic located in the St. Louis Children's Hospital. Knowing really nothing of either pediatric allergy or pediatric therapeutics, I was convinced that some time in the library was in order. A cursory review of the contemporary literature revealed an article co-authored by Dr. Yaffe which was entitled "Inadequacies in the Pharmacologic Management of Ambulatory Children,"[2] a paper that was quite critical of dispensing errors (e.g., incorrect volume of liquid antibiotics, incorrect labeling) and also, indicated complete compliance with antibiotic treatment for otitis media occurring only 7.3% of the time. In considering this information, two revelations became immediately apparent to me: 1) that children were different and 2) that professional intervention by a Pharmacist might just make the difference between effective and failed therapy. Having successfully completed this "experimental" rotation, I had the good fortune in my 5th year of Pharmacy school to arrange an elective clinical research experience in the labor and delivery unit at Barnes Hospital. A significant portion of this

Address correspondence to: Gregory L. Kearns, PharmD, PhD, Marion Merrell Dow / Missouri Endowed Chair in Pediatric Medical Research, Professor of Pediatrics and Pharmacology, University of Missouri–Kansas City, Chairman, Department of Medical Research, Associate Chairman, Department of Pediatrics, Director, Pediatric Pharmacology Research Unit, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108, email: gkearns@cmh.edu

experience was focused on collecting information on the effects of anesthetic and analgesic drugs administered in the immediate peripartum period and thereby, provided me with a first taste of clinical investigation. In asking for relevant background reading, I remember being given a review article authored by Dr. Yaffe entitled "Drugs and Pregnancy."[3] By this time, I was totally convinced that pediatric pharmacology was a most noble and necessary pursuit. For this early directional influence and the knowledge gained from Dr. Yaffe's exemplary works and faithful example, I will remain eternally grateful.

## THE JOURNEY THUS FAR

*"I would like, in my arbitrary way, to bring one nearer to the actual human being."*

*–Sir Francis Bacon*

Much like my esteemed colleague and 2004 recipient of the Yaffe Award, Dr. William Evans,[4] my academic career over the past 25 years has had a consistent "pharmaco-" theme. Despite a decidedly pharmacokinetic predominance, I have endeavored to use and/or implement many of the "tools" of pharmacology (e.g., pharmacokinetics, pharmacodynamics, pharmacogenetics) in trying to understand the some of the mysteries of developmental pharmacology. Specifically, how children are different from adults with respect to drug disposition, action and adverse events.

A driving principle behind much of my previous research and pediatric pharmacology in general has been to engage a fundamental understanding of the predictable "patterns" of normal physiology during the continuum of human development and how they influence the processes which serve collectively as the determinants of age-associated differences in drug absorption, distribution, metabolism, excretion and action (Figure).[5] While much of this work was, out of necessity, done from a macroscopic, physiologic perspective (i.e., clinical) as opposed to being molecular or mechanistic in nature, it has served to:

1. generate new information about a host of drugs (e.g., antimicrobials, antivirals, antifungals, anti-asthmatics, prokinetic agents) shown to be generalizable, of therapeutic importance in the definition of age-appropriate therapeutic regimens and in selected instances (e.g., midazolam, linezolid, ranitidine, famotidine, nizatidine, pantoprazole, omeprazole, montelukast), enabled expanded product labeling to include pediatric information.
2. demonstrate the feasibility (scientific, technical and ethical) of conducting rigorous, non-therapeutic clinical trials in populations of neonates, infants, children and adolescents who are either healthy, have a stable medical condition or are acutely ill.
3. demonstrate the utility of treating development as a continuum when exploring age-associated changes in drug disposition and action and also how pharmacogenetic information (e.g., genotype and phenotype association) can be used to refine the assessment of variability in drug disposition related to development.
4. provide proof-of-concept for the use of data-rich designs in the investigation of drug disposition in neonates, infants and children.

Without question, this past record of academic accomplishment focuses squarely on both demonstrating that children are different (from adults) and also how they are different. The new frontier for our research as it evolves will be to explore <u>why</u> they are different. Specifically, how normal and abnormal developmental biology produces signals and/or alterations in cellular function which culminate in processes that collectively alter drug disposition and effect. Fortunately, the ever expanding toolbox of science and the evolving coalescence of gifted individuals from many disciplines into the field of pediatric clinical pharmacology will enable this "journey" to continue in a purposeful and meaningful way which makes it possible for even an old dog to learn new tricks!

## LIFE LESSONS FROM THE JOURNEY

In contemplating the preparation of this "acceptance speech" manuscript, I was fortunate to have received useful suggestions and directional guidance from Dr. Stephanie Phelps, the Editor-in-Chief of The Journal of Pediatric Pharmacology and Therapeutics and Mr. Matthew Helms, Executive Director of PPAG. Perhaps the most insightful guidance was given to me by my long-time

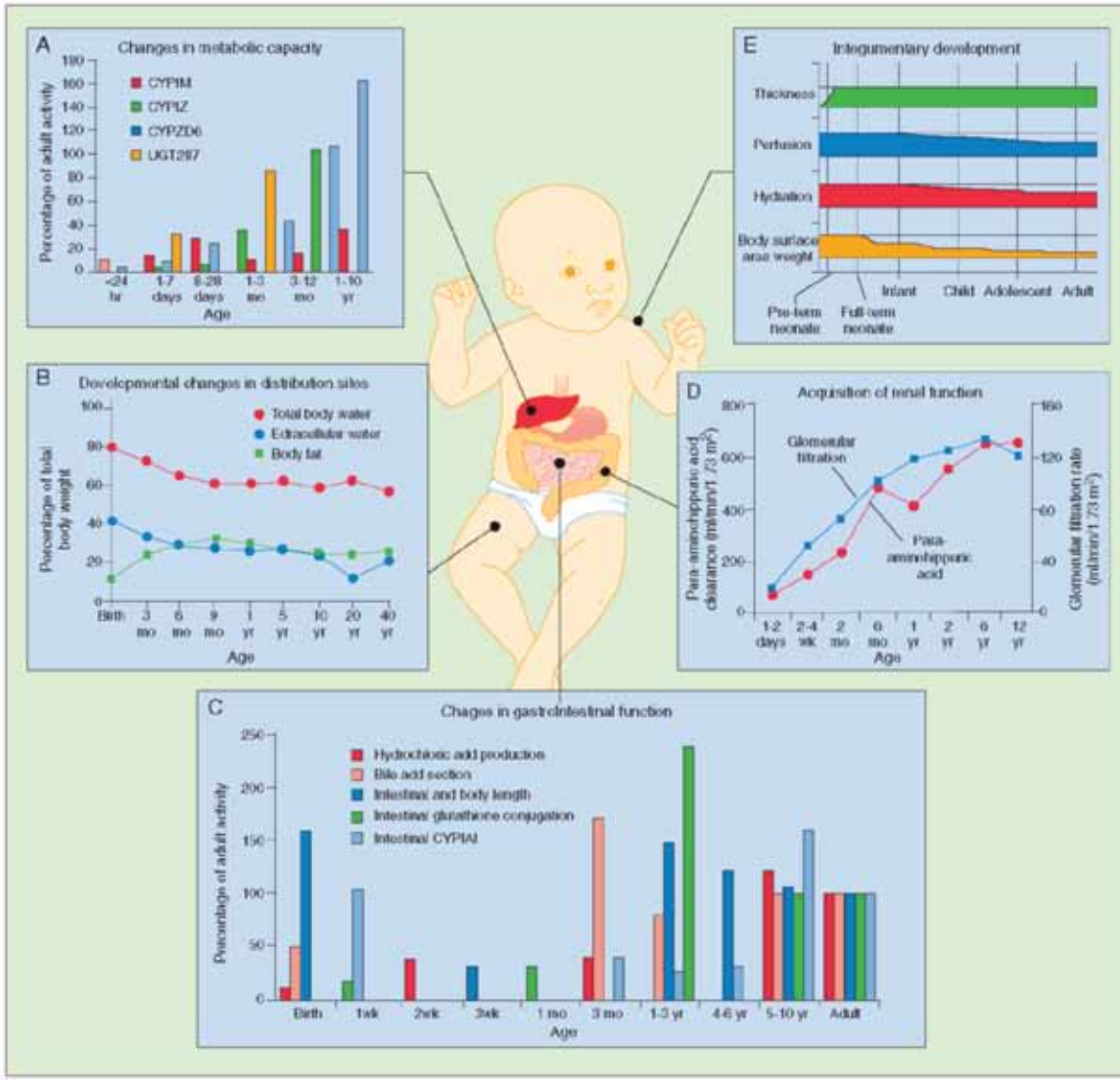


**Figure.** Developmental changes in physiologic factors that influence drug disposition in infants, children, and adolescents. Physiologic changes in multiple organs and organ systems during development are responsible for age-related difference in drug disposition.

A) The activity of many cytochrome P-450 (CYP) isoforms and a single glucuronosyltransferase (UGT) isoform is markedly diminished during the first 2 months of life. In addition, the acquisition of adult activity over time is enzyme- and isoform-specific.

B) Age-dependent changes in body composition, which influence the apparent volume of distribution for drugs. Infants in the first 6 months of life have markedly expanded total body water and extracellular water, expressed as a percentage of total body weight, as compared with older infants and adults.

C) Age-dependent changes in both the structure and the function of the gastrointestinal tract. As with hepatic drug-metabolizing enzymes (A), the activity of CYP1A1 in the intestine is low during early life.

D) The effect of postnatal development on the adult activity by 6 to 12 months of age.

E) Age dependence in the thickness, extent of perfusion, and extent of hydration of the skin and the relative size of the skin-surface area (reflected by the ratio of body surface area to body weight). Although skin thickness is similar in infants and adults, the extent of perfusion and hydration diminishes from infancy to adulthood.

Reprinted with permission from Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology—drug disposition, action, and therapy in infants and children N Engl J Med 2003;349:1157-1167.

friend and colleague, Dr. Steve Leeder, in whom I confided that I was having difficulty with trying to chronicle and/or otherwise recapitulate my academic achievements. In his wonderful very direct way, Steve suggested that I might use the manuscript to communicate some of the things that I am most passionate about. Specifically, to use it as a vehicle to provide "insightful, inspirational instruction" to people who may be starting their professional journies. With that bit of wise guidance, I put my fingers to the keyboard. While I cannot promise that the following insights will be inspirational to anyone, I offer them for the purpose of reflection and consideration.

### *1. Focus on Serving the Patient*

*"Only a life lived for others is a life worthwhile."*
*–Albert Einstein*

In my career, I have been fortunate to have witnessed and been part of a profound evolution for the profession of Pharmacy. Namely, the transformation from a customer/product oriented mission to a patient-centered service mission. Fortunately, I did not have to wait until I entered Pharmacy school to embrace this new revelation brought to me by a wise, avant-garde professor. Rather, I had observed it first hand working as a high school student in a small town (New Athens, IL), family-run pharmacy where the pharmacist fitted trusses, adjusted hearing aids, recommended over-the-counter treatments (for both humans and animals), took blood pressures and occasionally rendered on-demand first aid. Thus, from my first introduction, I had no sense that Pharmacy was anything other than a profession where direct, caring and compassionate service to others WAS the mission and thereby, the most noble of pursuits that a Pharmacist was obligated to engage in.

In many instances, those who elect to pursue an academic career elect to sacrifice a practice at the bedside and, instead, pursue the creation of knowledge with a belief that it will be generalizable and of immediate clinical utility. In some instances, I have sadly watched this situation become polarizing and degenerate into a perspective of stature and station where the efforts of pharmacists who practice clinically are perceived to be of lower value than their peers who produce their contributions through laboratory research. Without question, publications and research grants are universally valued pieces of academic currency. If their pursuit is undertaken with an intention that is not driven by a primary desire to benefit the patient but rather, the producer, their value may serve as nothing more than phalacteries of academia. Simply, always keep the patient first.

### *2. Find, Keep and Develop Mentors*

*"My success is due in large measure to my mentor's unflagging attention to my career."*
*–Samuel Lux*

*"A teacher affects eternity; he can never tell where his influence stops."*
*–Henry Brooks Adams*

Great mentors have been described as individuals who serve as an advocate, coach, teacher, guide, role model, valued friend, door-opener, benevolent authority, available resource, cheerful critic and career enthusiast. Throughout my career, I have been extremely fortunate to have had many incredible mentors, all of whom performed in one or more roles described above. One of my favorite office decorations through the years has been my gallery of mentors, a collection of photographs of individuals who functioned in major ways to guide, shape and propagate my career. Individuals in this gallery include Ronald E. Karber, R.Ph., the Pharmacist who gambled on a young high school student and demonstrated to me what the profession was really all about; Wolfgang Ritschel, M.D., Ph.D., a professor and now, dear friend, colleague and fellow artist who deftly and patiently taught me how to apply the tool of pharmacokinetics in the context of research and patient service; John T. Wilson, M.D., my fellowship director turned friend and confidant who taught me much about pediatric clinical pharmacology, more about life and the most about what it means to unselfishly serve others and the late Donald R. Hill, M.D., a colleague and friend who, in the arenas of research and life, taught me how to confidently embrace and enter avenues that in the eyes of some, would be considered unconventional. As I assess my past and current career, mentoring has made the difference every step along the way. Simply stated, to be a mentor is to have been mentored by one. Everyone needs and should have the experience.

Through the years, I have had the pleasure of mentoring many excellent and truly outstanding individuals as students, postdoctoral fellows and junior faculty members; each of them challenging (in good ways), different and dedicated to excellence and the overall mission of improving the lives of children and their families. I have found that there is really no playbook which articulates a specific approach that guarantees success. Rather, effective mentoring requires the application of a risk and reward paradigm which is dynamic, professional and personal in nature. While the process often starts on a conditional basis, a successful experience produces a relationship that decidedly has unconditional dimensions. Finally, mentoring has always resulted in my becoming more knowledgeable (often out of necessity to keep up), flexible, compassionate, tolerant and appreciative. One of my greatest joys continues to be the ability to witness the achievements of those I have been privileged to mentor and to witness the impact that their efforts have on others.

### *3. Be True to Your Beginnings*

*"Dance with the one who brung you."*
*–Darrell Royal*

The aforementioned is attributed as a favorite expression of Darrell Royal, a University of Texas football coach. In sports, it is said to mean that you go with the players and plays that result in wins. I would opine that this dictum is equally applicable to an academic career as it is to a football strategy.

As a college student, our faculty implored us to commit to the necessary practice of life-long learning. No single bit of anticipatory guidance could ring more true. Upon my graduation from Pharmacy school, I remember my elders describing the tremendous technologic advancements they witnessed during their lifetime. All the while, it was easy to take my current state of affairs for granted and to feel secure that the knowledge that I had acquired made me the consummate educated person and put me at a great advantage as compared to the generations represented by my parents and grandparents. What a delusion! My first introduction to a computer was pushing through over 500 punch-cards to do a simple Student t-test. Three decades later, the "norm" is using sophisticated computer-based algorithms to perform *in silico* simulation of disease progression and the results from a pediatric clinical trial yet to be conducted. What a tremendous privilege it is to be living in a time where things regarded as nothing more than Orwellian fantasy have become not only a reality but rather, a necessity as we apply the tools of technology to solving complex problems in pediatric pharmacology.

As I survey the careers of some contemporaries who started and stayed in academia, I see many whose current endeavors and abilities appear quite different than was apparent from their work in the early 1980s. With information in science and technology more than doubling every decade, it is essential that we constantly learn new things and confirm our knowledge through application. In this process, innate talent drives the acquisition of new and different skills. In this process of professional evolution, I have witnessed a number of individuals who verbalized a perceived need to re-make themselves as opposed to re-tool or re-engineer their career. While such an approach can be considered as not all bad if it culminates in expanded knowledge and useful application, it has the potential to produce everything from disgruntlement and disaster when, in the process, an individual sacrifices their "first love." The answer to prevent this is, simply, don't make this sacrifice. To stay grounded in the principles that formed the foundation of an individual's entry into the profession of Pharmacy will go a long way to ensuring that the career which is built is solid, substantial and survivable. In the process, you will make admirers who respect and in some cases, revere your accomplishments, valued colleagues who value and depend upon your opinions and most importantly, dear friends with whom you will want to weather both accomplishments and failures.

### *4. Think and Act Out of the Box*

*"The significant problems we face in life cannot be solved at the same level of thinking we were at when we created them."*
*–Albert Einstein*

Whether in the context of providing clinical care or doing research, there are two phrases that always give me profound dyspepsia: 1) "we can't do this" and 2) "we have always done it this way." For creativity to occur and flourish, it is

impossible for an individual to be imprisoned by intellectual myopia or inflexibility. Most regrettably, I have observed such stunted approaches to thinking in both the research and clinical arenas. When it occurs in the course of patient care, therapeutics can quickly become de-personalized as practitioners strive to protocolize treatment in a quest to reduce variability and, thereby, improve quality through actions predicated on an evidence-based approach that is often fixed in time. The result can be adoption of a paradigm where treatment that is "good enough" is not truly as good as it can be. What can make this worse is when the practitioner considers himself/herself to be completely sufficient based on a static base of knowledge and perceives no need for it to evolve and expand.

An effective antidote for this lethal condition is to engage a multifaceted approach which oddly enough, works for both prevention and treatment. First, firmly commit to engage the mind, exercise its abilities and infiltrate one's thinking with creativity across the dimension of problems which ranges from seemingly mundane to highly complex. Second, adopt the perspective that "good enough never is." Finally, no matter what the challenge, never, never, never give up. There is much knowledge in the world and it resides in many places and with all manner of people. To use it wisely and to improve upon it requires that one seek it diligently.

### *5. Make the Biggest Difference for as Many People as You Can*

*"I just get up and greet every day as another opportunity to do good"*

*–Phillip L. Berry*

In 1977 during my residency at the Cincinnati Children's Hospital Medical Center, I had the good fortune of meeting, collaborating and commiserating (as an office mate) with Dr. Phillip Berry (currently the Chief of Pediatric Nephrology at the Dell Children's Hospital in Austin, Texas), a fellow in Pediatric Nephrology. Our friendship and sojourn through professional and personal life together started with a patient encounter. Specifically, the first use of charcoal hemoperfusion in our hospital to treat a comatose child who had ingested a very lipophilic drug that hemodialysis simply could not touch. There was no literature, no experience and in the opinion of our superiors, no other option. Thus, we were left in the intensive care unit to get it done and to periodically report on the progress of the patient. We made a plan, executed it through the night and 12 hours after we started, had the little girl (who was intubated) writing a note ("I'm okay") to her mother. The following morning, Phillip and I looked at each other and the aforementioned quote was borne. Since that time, it has served as both my moral barometer and raison de'etre.

Daily, I continue to seek and find many avenues where tremendous good can be done. When our careers begin, these "avenues" can often appear as only a small path. As our careers develop, the opportunities can represent boulevards. Irrespective of their size, length or tortuosity, choosing the path leading to good in the world always accomplishes the goal. In 2007 and 2008, I had the exceptional opportunity to serve the World Health Organization as the only U.S. member of the Paediatric Subcommittee of the Essential Medicine's Committee. This group of pharmacists and physicians from continents across the world was charged with developing the first Essential Medicines List for Children. While it was a distinct honor to have received this appointment, the experience created in me an immediate and simultaneous sense of humility, inadequacy and opportunity. For the first time in 30 years of a career, I was given an opportunity to focus my efforts and abilities, with new colleagues that I had never met, to make an effort to improve pediatric therapeutics in countries where conditions don't exist for the reconstitution of an antibiotic powder with clean water or the electricity to power the refrigerator needed to ensure stability of the formulation necessary to adequately treat a young child. The reward in this experience was both profound and simple. Namely, to be able to truly understand that the "greater good" could only be influenced when engaged with a sense of diligence, purpose and respect.

### *6. Don't Take Yourself Too Seriously*

*"Maturity consists of no longer being taken in by oneself."*

*–Kajetan van Schlaggenberg*

Accomplishment in a career, be it in academia,

industry or in providing clinical services, has a way of removing the cloak of anonymity. The paradox is that when many of us begin on our career journeys, we don't always relish or fully appreciate the joy of anonymity and the sense of alacrity that it affords one in a quest to be creative and innovative. Instead, we work diligently and as success is achieved, have a tendency to operate from a personal pronoun perspective (e.g., focus on I, me, my and mine). Only when we are convinced that we have found our rightful place in the world does the "m" of me become routinely inverted to the "w" of we. This perspective is offered not to castigate or condemn individuals for a character flaw but rather, to be blatantly honest about the importance of how any of us see ourselves in the context of what we do and how it may, or may not, appear to define us. As suggested by the aforementioned quotation, it is maturity that brings us to the point of reflection and relief. There is a tremendous difference in taking pride in one's accomplishments and being enamored by them. Through our work done on behalf of others does our value to them grow. Greatness is not required.

### *7. Know When to Say When*

*"He who knows that enough is enough will always have enough."*

*–Lao-Tsu*

It is now time to bring these momentary reflections to a close. In offering this admittedly personal address, I hope that the insights and perspectives I have shared are useful to those who will read them, whatever their station or career position. As stated at the outset, I do not guarantee that any of this will be inspirational or counted as anything more than the musings of a middle-aged pharmacist who has been given a chance to work and to serve. Continuing on my professional journey, I will endeavor to keep taking my own medicine, ever hoping to make a difference. Again, I want to thank my colleagues and PPAG for honoring me with this award, my students and mentors for taking a chance and the children and their families that I remain privileged to serve.

**ACKNOWLEDGMENTS** Supported in part by the Marion Merrell Dow Foundation, Kansas City, MO and grant # 2 U01 HD31313-16, Pediatric Pharmacology Research Unit Network, The Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD I want to express my sincere gratitude to my partner, Dr. Kathleen Neville and my sons, Justin and Graham, who have enabled my career through bringing me great joy and unconditional love and admiration. I also want to thank my many colleagues who continue to add richness to my journey and in particular, to my dear friends Dr. Susan Abdel-Rahman and James Herden who provided great inspiration and guidance during the preparation of this manuscript.

## REFERENCES

1. Spielberg SP. Sumner J. Yaffe Lifetime Achievement Award, Pediatric Pharmacy Advocacy Group, 2004. Available at http://www.ppag.org/en/articles/printview.asp?5. Accessed 05 January 2009.
2. Mattar ME, Markello J, Yaffe SJ. Inadequacies in the pharmacologic management of ambulatory children. J Pediatr 1975;87:137-141.
3. Yaffe SJ. Drugs and pregnancy. Clin Toxicol 1978;13:523-533.
4. Evans WE. A journey from pediatric pharmacokinetics to pharmacogenomics. J Pediatr Pharmacol Ther 2005;10:8-13.
5. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology – Drug disposition, action and therapy in infants and children. N Engl J Med 2003;349:1156-1167.