Published in final edited form as:

Clin Pharmacol Ther. 2015 September ; 98(3): 238–240. doi:10.1002/cpt.168.

Selecting the Proper Pediatric Dose: It is More than Size that Matters

Gregory L. Kearns, PharmD, PhD, FAAP

Arkansas Children's Hospital Research Institute and the Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR

Keywords

Pediatric; Dose; Size

Introduction

Appropriate pediatric dose selection remains one of the most vexing clinical problems faced by healthcare professionals who are charged to provide medical care to infants and children. While body size does reflect the ontogeny of processes that govern drug disposition, there are extremes of disease which perturb the expected relationships.

“The difficulty lies, not in the new ideas, but in escaping from the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds”

John Maynard Keynes. *The General Theory of Employment, Interest and Money*
(13 December 1935)

The Conundrum of Age-Appropriate Dose Selection

Over the past four decades, the apparent differences between pediatric and adult patients which impact pharmacotherapy have been primarily viewed through the lens of ontogeny where the patterns of maturation in the physiologic processes which collectively determine drug disposition have been “mapped”. [1] This information is used to guide pharmacometric approaches aimed at deriving age-specific drug dosing regimens for pediatric sub-populations (e.g., neonates, infants, children, adolescents) which produce a target level of systemic exposure that, based upon adult data, is associated with a beneficial drug response. This approach entails two significant assumptions. First, that drug action and response *in sick children* can be adequately predicted by population-derived data from adults and second, that the pediatric population is homogenous with respect to the association between body size and drug disposition. Indeed, the dearth of pharmacodynamic data in children and the continued reliance only upon pharmacokinetic data to accomplish the desired goal of

Address for correspondence: Gregory L. Kearns, PharmD, PhD, FAAP, President, Arkansas Children's Hospital Research Institute, 13 Children's Way, Little Rock, AR 72202, gregorykearns@mac.com, Telephone: (501) 364-7373.

Conflict of Interest Statement: Dr. Kearns has no conflicts of interest to disclose as relates to the information contained in this manuscript.

individualized (or precision) medicine in pediatrics has been declared as an untenable and unacceptable situation. [2]

Are Children Simply Small Adults? – It Depends.....

It has been said that children (2 years of age or older) are essentially similar to adults and differ only in size. [2] This tenant is true and is supported by the very early work of Kleiber who discovered that the unit of $\frac{3}{4}$ (0.75) power of body weight ($\text{kg}^{0.75}$) is a suitable unit of metabolic body size and that appeared to be constant across most all mammalian species. [4] The constancy of this relationship enables the use of allometric theory to accurately predict drug clearance in pediatric patients from adult data, especially when a maturation factor (e.g., fraction of adult metabolic capacity present in a child at a given stage of development) and a factor that adjusts for organ function (in the case of disease) are included. As illustrated by the Figure, the impact of ontogeny (using the surrogate of age) on drug clearance appears to disappear when allometric scaling of clearance is performed. This does not indicate that development has no impact on drug disposition but rather, illustrates the predictive relationship between body size (which includes body composition) and pharmacokinetics.

The rapid accretion of drug metabolizing enzyme activity during early life (e.g., 20-100 weeks postmenstrual age) [1] produces relationships where the allometric 0.75 power model may not accurately predict clearance [2] unless one knows the maturation and organ factor for a given child and the impact of disease severity on the function or organs responsible for drug clearance. [3] There are times, however, when the predictive accuracy of the best allometric model could be compromised. These instances are not related to normal human development but rather, to complex perturbations of “normal” physiology produced by conditions (e.g., diseases, concomitant treatments) where little may be known about a specific disease process and its impact upon drug disposition .

In Sickness and in Health – An Example of Relevant Extremes

In contrast to early phase clinical trials in adults, there is almost no such thing as a healthy pediatric volunteer in a pharmacokinetic or pharmacodynamic study. Out of ethical necessity and regulatory imperative, these studies in pediatrics are accomplished either by the inclusion of participants who have a medical condition but are clinically stable or in some instances, patients who are ill and may not be clinically stable. Thus, data produced from studies largely intended to examine the impact of development on drug disposition and/or action represent a montage of sickness and health which contributes “noise” to a given model that is frequently multifactorial in origin and may be unpredictable based on existing data. To illustrate situations where the use of body size alone to accurately predict drug disposition in a pediatric patient may be difficult, two conditions representing the extremes of body size can be considered. Namely, anorexia nervosa and obesity in children with acute lymphoblastic leukemia (ALL).

Anorexia Nervosa

Anorexia nervosa is an eating disorder commonly observed in which is associated with altered perception of body image. Patients with this disorder, usually young adolescent females, adopt dietary habits (e.g., severe caloric restriction, self-induction of vomiting) that in some circumstances, can lead to the point of self-starvation and malnutrition. In extreme cases, virtually every organ system in the body is affected. The profound changes in body composition produce alterations in energy metabolism [5], renal function [6] and electrolyte disturbances that can precipitate life-threatening cardiac arrhythmias. Whilst drug pharmacokinetics *per se* have not been investigated in such patients, changes have been reported in the disposition (apparent volume of distribution and plasma clearance) of exogenous luteinizing hormone releasing hormone. [7] In the extreme phenotypic expression of this disorder, the multi-system dysfunction coupled with altered body composition would be expected to alter both the distribution and clearance of drugs and xenobiotics. Thus, the use of body size alone to predict drug disposition could likely produce confounded or errant results. While anorexia nervosa is admittedly not a common disorder with respect to disease frequency, it is one that commonly involves therapeutic intervention where decisions regarding drug dosing must be made in the absence of experimental pharmacokinetic (or pharmacodynamic) evidence. A mechanistic approach which considers the multiple factors that could impact drug disposition must be used to augment the value of allometric approaches to guide therapy in patients with anorexia nervosa and potentially, other conditions which produce similar perturbations in physiology (e.g., profound protein-calorie malnutrition).

ALL in Patients with Obesity

While one might expect that allometric approaches should have predictive accuracy in patients with obesity, this condition in pediatric patients with acute lymphoblastic leukemia (ALL) could represent an exception to the rule.

We have recently reviewed the challenge of obesity in ALL as it relates to the optimization of anticancer treatment and in particular, the use of 6-mercaptopurine (6MP); an old drug that remains a mainstay in the treatment of this disease in children. [8] Historically, weight-based dosing of 6MP in pediatric ALL treatment protocols ignored differences in body composition in obese vs. non-obese children. As described in our recent review, there are published data which illustrate that the systemic exposure of 6MP in obese children is approximately 2-fold lower than in those who were not obese, and that obesity *per se* is associated with worse treatment outcomes and a greater risk of disease relapse in pediatric ALL. It is not known whether there is a cause and effect relationship between 6MP exposure and response that may be unique to obese children with ALL and what its mechanistic basis might be (e.g., variability in the activity of enzymes capable of metabolizing 6MP in the gut and liver such as xanthine oxidase)?

As illustrated by the aforementioned conditions, an intersection of disease, body size and metabolic differences associated with body size may be apparent. To improve the use of allometric-based approaches in specific pediatric sub-populations, it is essential that drug

pharmacokinetics and pharmacodynamics be appropriately characterized and that the disease and population-specific information be included into the approaches.

A Brief Word about Development and Pharmacogenomics

While a comprehensive treatise on developmental pharmacogenomics is outside the scope of this commentary, there are situations when polymorphic expression of a gene produces “populations within a population” when the clearance of a given drug is the predominant substrate for the enzyme coded by the polymorphically expressed gene. *CYP2D6*, a polymorphically expressed gene responsible for several drugs used in pediatrics (e.g., atomoxetine, many of the selective serotonin re-uptake inhibitors), provides an example. Prediction of the *CYP2D6* phenotype associated with a specific allelic variant is best accomplished through the assignment of a *CYP2D6* activity score from the genotype data in a given patient. [9] The utility of this approach for individualizing treatment with codeine is described by a recent Clinical Pharmacogenetics Implementation Consortium guideline. [10] Incorporation of pharmacogenomic data for polymorphically expressed genes regulating the expression of drug metabolizing enzymes and potentially, drug transporters, into an allometric approach to assess pharmacokinetics or drug regimen selection in pediatric patients would be expected to increase predictive accuracy of the models.

Conclusions

Historically, pharmacokinetic investigations conducted in pediatric patients have ignored the potential effects of the interaction between disease expression, nutritional status and the effects of concurrent therapy on drug disposition. The incorporation of allometric principles as they relate body size to the multiple factors which influence drug disposition can markedly enhance the ability to predict drug clearance and thus, individualize drug therapy in a given child. However, to do this successfully, the intersection of disease expression (acute or chronic), changes in body composition at the extremes of body size and pharmacogenetic constitution must be considered. Only then can the promise of “precision medicine” be realized in pediatrics.

Acknowledgement

The author gratefully acknowledges the contribution of Dr. Susan Abdel-Rahman whose thoughts on the prediction of body size and its relationship to drug disposition were illuminating.

This work is supported in part by funding received by the author through his participation in the Pediatric Trial Network (HHSN275201000003I) and a training grant (1T32HD069038-01) which is funded by the *Eunice Kennedy Shriver* National Institute of Child Health, National Institutes of Health, Bethesda, MD

Reference Citations

1. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology – drug disposition, action and therapy. *N Engl J Med*. 2003; 18:1157–1167. [PubMed: 13679531]
2. Holford N. Dosing in children. *Clin Pharmacol Ther*. 2010; 87:367–370. [PubMed: 20090674]
3. Anderson BJ, Holford NHG. Tips and traps analyzing pediatric PK data. *Pediatr Anesth*. 2011; 21:222–237.
4. Kleiber M. Body size and metabolic rate. *Physiol Rev*. 1947; 27:511–541. [PubMed: 20267758]

5. Russell J, Baur LA, Beumont PJV, Byrnes S, Gross G, Touyz S, Abraham S, Zipfel S. Altered energy metabolism in anorexia nervosa. *Psychoneuroendocrinology*. 2001; 26:51–63. [PubMed: 11070334]
6. Brion LP, Boeck MA, Gauthier B, Nussbaum MP, Schwartz GJ. Estimation of glomerular filtration rate in anorectic adolescents. *Pediatr Nephrol*. 1989; 3:16–21. [PubMed: 2702081]
7. Chikamori K, Suehiro F, Ogawa T, Sato K, Mori H, Oshima I, Saito S. Distribution volume, metabolic clearance and plasma half disappearance time of exogenous luteinizing hormone releasing hormone in normal women and women with obesity and anorexia nervosa. *Acta Endocrinol (Copenh)*. 1981; 96:1–6.
8. Tolbert J, Kearns GL. The challenge of obesity in paediatric leukaemia treatment: it is not just size that matters. *Arch Dis Child*. 2015; 100:101–105. [PubMed: 25336436]
9. Gaedigk A, Simon SD, Pearce RE, Bradford LD, Kennedy MJ, Leeder JS. The CYP2D6 activity score: translating genotype information in a qualitative measure of phenotype. *Clin Pharmacol Ther*. 2008; 83:234–242. [PubMed: 17971818]
10. Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther*. 2014; 95:376–382. [PubMed: 24458010]

Figure.

Illustration of the impact of allometric scaling on the apparent relationship between oral clearance of a drug and age when the latter is used as a developmental surrogate. Across the age range depicted in the illustration, metabolic competence of the pathway(s) responsible for drug clearance is assumed. Data were obtained and subsequently anonymized from an actual single-dose pharmacokinetic study performed in a pediatric cohort.