Drug dosing for children:

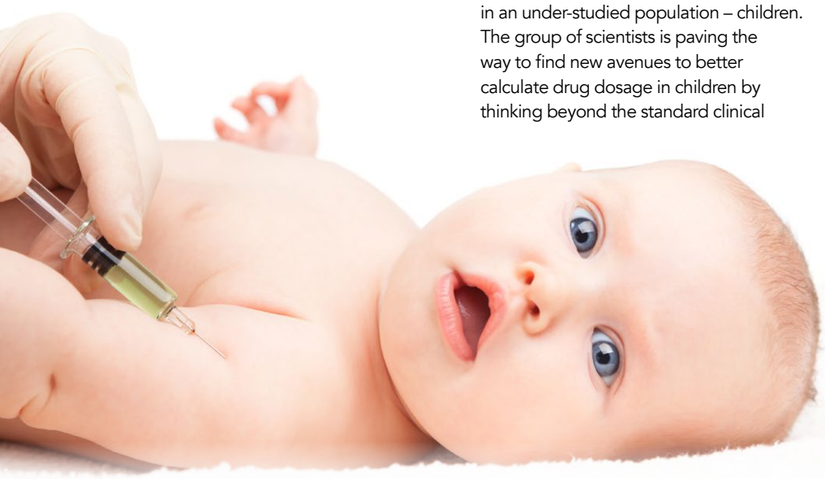
Bridging the gap in paediatric pharmacology

The safety and efficacy of medicines are dependent on accurate dosage parameters. However, the vast majority of clinical trials are carried out with adults and much remains unknown about how the immature physiology of children and babies impacts on drug disposition. Bhagwat Prasad, Assistant Professor at the School of Pharmacy at the University of Washington, is taking a state-of-the-art approach to better predicting safe paediatric dosage levels by refining pharmacological models that take children's development and physiology into account. This approach could revolutionise child health and herald a new era of safety in paediatric pharmacology.

Safe and effective medicines are a cornerstone of modern life and are crucial for ensuring public health by controlling disease, reducing pain and enabling safe surgeries. However, incorrect dosing can have catastrophic results for individuals. If the levels are too low, the drug will be ineffective. If too much of the medication is taken, toxicity levels can build, harming organs and can even lead to death. A key part of drug safety is getting this fine balance right and being able to calculate the appropriate doses for all patient groups. Whilst protecting patients is crucial and establishing safe dosage levels are a key part of drug discovery and clinical trial programmes, almost all trials are restricted to collecting data on adults.

Now pioneering efforts by a team of researchers led by Assistant Professor Bhagwat Prasad at the University of Washington are highlighting the need to better understand pharmacology in an under-studied population – children. The group of scientists is paving the way to find new avenues to better calculate drug dosage in children by thinking beyond the standard clinical trial and body-weight or body surface area normalized scaling. Their aim is to plug the existing data gap to characterise physiological idiosyncrasies that are unique to children and to refine predictive modelling to guide drug dosage guidelines. In order to do this, they will paint the clearest picture yet of how physiological processes that govern drug metabolism might change from neonates to adolescence and into adulthood. Their findings have the potential to make an enormous impact on child health and herald a new era in paediatric pharmacology.

Their findings have the potential to make an enormous impact on child health and herald a new era in paediatric pharmacology.



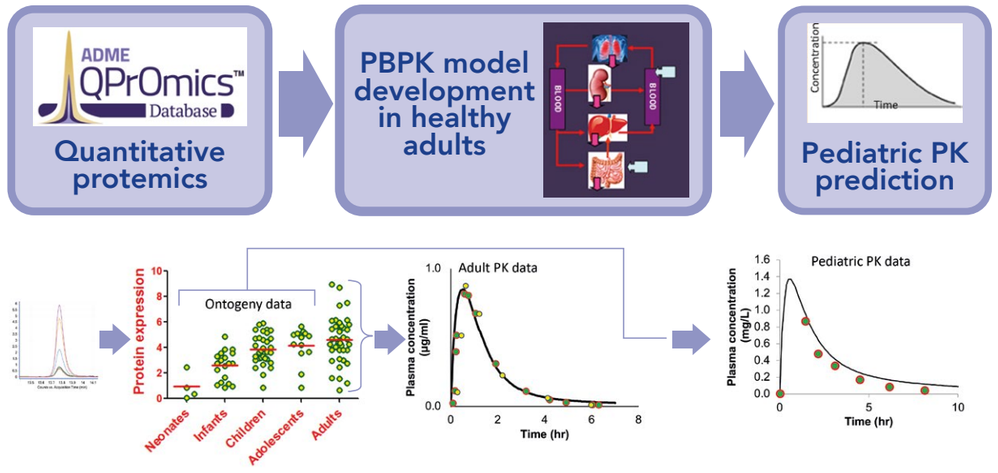
CURRENT APPROACHES

Prasad states in a recent paper that only 28 of 399 drugs prescribed to younger children between 1997 and 2010 had been studied for child safety and efficacy levels. As a result, many drugs given to children are simply prescribed off-label due to a lack of evidence about the precise dosages to use. Currently, some approaches to calculating medication dose for children are rudimentary with recommendations for adults used to estimate the child dose based on their body weight. What some current dosing approaches fail to take account of, however, is that children are not simply just small adults. Grey baby syndrome – a condition caused by antibiotic toxicity due to a lack of effective metabolising liver enzymes in neonates – is an example of what can happen when infant physiology is not taken into account in drug dosage regimes. In fact, as we understand more about paediatric pharmacology, it is becoming increasingly clear that children have distinct and immature physiological processes that differ to those seen in adults.

NOVEL APPROACHES

A key factor in drug development is understanding how the human body will process the substance. Drug disposition – which refers to the way that substances

QUANTITATIVE PROTEOMICS INFORMED PBPK MODELLING WORKFLOW



are metabolised, absorbed, dispersed and ultimately excreted from the body – can be affected by a number of factors, including genetics, sex, disease condition, circadian rhythmicity, pregnancy and even food consumption. Dr Prasad and his team are now exploring the effect of age on these processes at the level of proteome and metabolome. They believe that many complex factors – some of which have yet to be identified – will play a role in determining how drugs will be absorbed and metabolised in children and they argue that the current approach to calculate child and baby dosage rates for medicines is overly simplistic.

It is imperative that drug manufacturers and prescribing doctors have knowledge of the potential effects on paediatric patients, but carrying out clinical trials to establish dose regimens in children is legally, ethically and logistically challenging. To overcome this and develop our understanding of paediatric pharmacology, scientists have to look to novel approaches using quantitative proteomics and metabolomics informed modelling approach.

BUILDING MODELS FROM THE GROUND UP

Dr Prasad and colleagues are now working to build integrated models of paediatric pharmacology that will guide dosage levels and take into account key physiological factors in children and infants. The data are first derived using paediatric tissues and biofluids by quantifying drug disposition related proteome and metabolome using quantitative mass spectrometry and compared with adults to develop age-dependent physiological scaling factors. The approach then marries together this vital information about drug disposition in children with key drug factors, include *in vitro* rate of metabolism and transport. The bottom-up model is then validated by comparison with drug pharmacokinetics data, which refers to how drugs move around the body, that can ultimately affect pharmacodynamics, which refers to how substance mechanism of action. By combining child physiological factors with drug-dependent factors, the team aim to refine paediatric physiologically-based pharmacokinetic (pPBPK) modelling. In theory, their improved pPBPK modelling could be generalised for use for any drug given to children, revolutionising drug dosage approaches in paediatrics. The approach is particularly useful in the first-in-children dosing during initial clinical trials in this vulnerable population. The team hopes that the vast array of data that will inform the refinement of the model also means that it could predict the effects of drug-drug interactions.

In order to best improve existing models, which take into some factors including organ size, the team has to gather information about physiology. Much remains unknown about how proteins that are related to drug disposition – known as drug metabolising enzymes (DMEs)

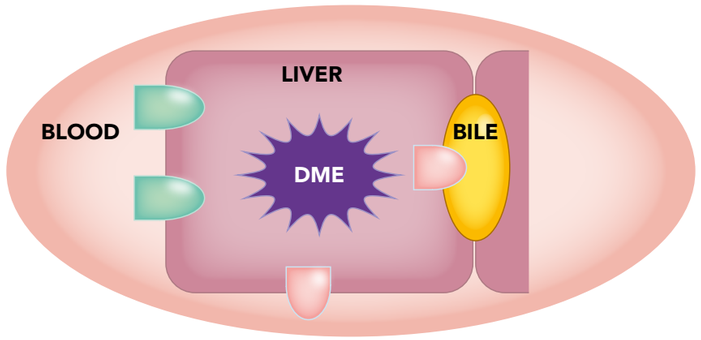
and drug transporters– function in small children. Liver enzymes or transporters, which are crucial to drug metabolism and transport, are known to differ in childhood and adulthood, but to the nature and magnitude of these differences is yet to be determined. Crucially, information about DMEs and drug transporters are not available for a majority of these proteins for consideration in existing PBPK models.

CHARACTERISING KEY ENZYMES AND TRANSPORTERS IN THE LIVER

Prasad and his colleagues have embarked upon a study characterising the function of DMEs and transporters in liver tissue from more than 200 children, aiming to compare these findings to liver DMEs and transporters in healthy adults. In a recently published manuscript, compounds known as uridine diphosphate-glucuronosyltransferases (UGTs), are much lower in children than in adults, and much lower in neonates than in older children. UGTs are involved in the clearance of 20 of the top 200 prescribed drugs in the United States and until now, very little data were available on their availability in children and babies. UGTs play a key role in metabolising drugs that are routinely given to children, including the anticonvulsants valproic acid and lamotrigine, as well as pain-relieving morphine.

In a further study, a gene coding for a key metabolising a UGT in the liver, known as *UGT2B17*, has been shown to be sparsely expressed in pre-pubertal children under nine years old. The UGT2B17 protein is found in abundance in children and adults over that age. The research also revealed an interaction between genotype and development of these enzymes, highlighting key individual differences that could be hugely important in determining the dosage of drugs for children. Similarly, Prasad and colleagues have found that levels of DMEs known as carboxylesterases and some of the major hepatic transporters are significantly lower in babies than in adults. Their findings will be absolutely crucial to accurately develop pPBPK models. The more enzyme and transporter data that can be used to refine modelling, the more accurate dosage predictions will be.

DRUG TRANSPORT AND METABOLISM IN LIVER



Transporters: OATPs,OCT1, NTCP, P-gp, MRP2, MRP3, BCRP, BSEP, **etc.**
DMEs: CYPs, UGTs, ALDH1A1, ADHs, GSTs, CESs, AOXs, **etc.**

What some current dosing approaches fail to take account of, however, is that children are not simply just small adults.

Dr Prasad and his team now focus on proteomics and use a technique known as data-independent acquisition (DIA) mass spectrometry, allowing them to quantify up to 10,000 proteins simultaneously. Approaching studies in this way allows them to look at a host of proteins at one time, meaning that they can make meaningful steps in understanding paediatric physiology that will govern drug metabolism rapidly.

A NEW AGE OF DRUG SAFETY

Parents and clinicians rely on being able to give children and babies effective doses of medicines at levels that have been proven safe, yet there is a dire need to better understand how children's bodies cope with drugs. Dr Prasad's pPBPK model, integrating information about drugs with key knowledge on child drug disposition, will go some way to help doctors and parents rest easier when they find themselves having to prescribe and administer medications to children. It is difficult to overstate the enormous impact that pPBPK modelling could have on public health for children all over the world. On the journey, Dr Prasad and his research team are revealing surprising insights into human ontogeny and genetics, uncovering evidence of unique features of child and infant physiology that are remarkably different from those seen in adults. Above all, their work sheds light on how much we have yet to learn about the physiological make-up of the youngest – and most vulnerable – members of our society and the importance of their safeguarding.

Behind the Research

Dr Bhagwat Prasad

E: bhagwat@uw.edu **T:** +1 (206) 221 2295 **W:** http://depts.washington.edu/qpromics/

Research Objectives

Dr Bhagwat Prasad's research is focused on the application of liquid chromatography-mass spectrometry (LC-MS) and quantitative proteomics and metabolomics to understand interindividual variability in drug disposition.

Detail

Assistant Professor Bhagwat Prasad
Department of Pharmaceutics,
Pharmaceutics Faculty,
University of Washington, Box 357610
H272U Health Sciences Building
Seattle WA 98195-7631
USA

Bio

Dr Prasad is a pharmacist by education with major research training in the field of pharmaceutical analysis, quantitative mass spectrometry and drug disposition. Dr Prasad has published >65 peer-reviewed articles and book chapters and he is a recipient of ISSX North American New Investigator Award. Dr Prasad obtained his MS in 2006 and PhD in 2010 in Pharmaceutical Sciences from NIPER, Mohali, India.

Funding

- National Institute of Child Health and Human Development (NICHD).
- National Institutes of Health (NIH) grant [R01 HD081299].

Collaborators

- Steven J Leeder, Andrea Gaedigk and Robin E. Pearce, Division of Pediatric Pharmacology and Medical Toxicology, Department of Pediatrics, Children's Mercy Hospitals and Clinics, Kansas City, MO, USA
- Jashvant D. Unadkat, Department of Pharmaceutics, UW, Seattle, WA, USA

UNIVERSITY of WASHINGTON

References

Bhatt DK, Mehrotra A, Gaedigk A, Chapa R, Basit A, Zhang H, Choudhari P, Boberg M, Pearce RE, Gaedigk R, Broeckel U, Leeder JS, Prasad B. (2018). 'Age- and Genotype-Dependent Variability in the Protein Abundance and Activity of Six Major Uridine Diphosphate-Glucuronosyltransferases in Human Liver'. *Clinical pharmacology and therapeutics.* [Epub ahead of print].

Bhatt DK, Basit A, Zhang H, Gaedigk A, Lee S, Claw KG, Mehrotra A, Chaudhry AS, Pearce RE, Gaedigk R, Broeckel U, Thornton TA, Nickerson D, Schuetz EG, Amory JK, Leeder JS, Prasad B. (2018). 'Hepatic abundance and activity of androgen and drug metabolizing enzyme, UGT2B17, are associated with genotype, age, and sex'. *Drug Metab Dispos.* [Epub ahead of print].

Boberg, M, Vrana, M, Mehrotra, A, Pearce, RE, Gaedigk, A, Kumar, D, Bhatt, JSL, Prasad, B. (2017). 'Age-Dependent Absolute Abundance of Hepatic Carboxylesterases (CES1 and CES2) by LC-MS/MS Proteomics: Application to PBPK Modeling of Oseltamivir In Vivo Pharmacokinetics in Infants'. *Drug Metabolism and Disposition.* [Epub ahead of print].

Prasad B, Gaedigk A, Vrana M, Gaedigk R, Leeder JS, Salphati L, Chu X, Xiao G, Hop C, Evers R, Gan L, Unadkat JD. (2016). 'Ontogeny of hepatic drug transporters as quantified by LC-MS/MS proteomics'.*Clin Pharmacol Ther.* 00(4):362-70.

Matthew M. Laughon, MD, MPH1; Debbie Avant, RPh2; Nidhi Tripathi, MD3; et al Christoph P. Hornik, MD3; Michael Cohen-Wolkowiez, MD, PhD3; Reese H. Clark, MD4; P. Brian Smith, MD, MPH, MHS3; William Rodriguez, MD, PhD2.(2014). 'Drug Labeling and Exposure in Neonates'. *JAMA Pediatr*;168(2):130-136. doi:10.1001/jamapediatrics.2013.4208.

Personal Response

If known, are age-related differences in drug disposition occur at the other end of the life spectrum, i.e. for elderly adults?

" Elderly adults are physiologically different from younger adults. However, with respect to DME or transporter abundance, they are less different from adults than children. Moreover, many factors such as diseases and drug use potentially affect the abundance or activity of DMEs and transporters in the elderly population. "