Supplement Article

Developmental Changes in Pharmacokinetics and Pharmacodynamics

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Abstract

Effective drug therapy to optimally influence disease requires an understanding of a drug's pharmacokinetic, pharmacodynamic, and pharmacogenomic interrelationships. In pediatrics, age is a continuum that can and does add variability in drug disposition and effect. This article addresses the many important factors that influence drug disposition and effect relative to age. What is known about the influence of maturation on the processes of drug absorption, distribution, metabolism, excretion, and drug receptor dynamics are outlined. Our state of understanding of many of these factors remains in flux, however, and only with additional study will we be able to better anticipate and model drug-response relationships across the age continuum. Being able to continuously improve our care of the ill pediatric patient while simultaneously being able to accurately determine the utility of new drugs and chemical entities in this population requires our enhanced understanding of these disposition characteristics.

Keywords

developmental pharmacology, pediatric pharmacology, pharmacokinetics, pharmacodynamics, drug-metabolizing enzymes, drug transporters

The accurate determination of a safe and effective dose of a drug being prescribed to a neonate, infant, child, or adolescent is dependent on understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of that particular drug, as well as the clinical characteristics of the unique neonatal or pediatric patient being treated with this drug. The discipline of developmental pharmacology aims at understanding the impact of maturation on drug disposition and action in the neonatal and pediatric population. It encompasses (1) developmental PK, representing the mathematical description of the drug concentration-time profile and showing what the human body does with the drug; (2) developmental PD, describing the relationship between a given concentration and the extent of a specific response and showing what the drug does with the human body (eg, pain relief, sedation, fever reduction); and (3) the ways by which human growth and development will change the PK/PD relationship of a drug in each unique patient.

Fifteen years have passed since the publication of the seminal paper of Kearns et al on developmental pharmacology that focused primarily on developmental changes in drug disposition and action in infants and children.[1] Since 2003 our understanding of the impact of growth and development on the absorption, distribution, metabolism, and excretion of drugs in neonates, infants, children, and adolescents has increased significantly.[2–5] Moreover, there also have been advances in our knowledge on the impact of developmental changes on PD.[6,7] This article will provide an overview of the current status of our knowledge on developmental changes in PK and PD in the neonatal and pediatric population.

Developmental Changes in PK

The 2 most important parameters of the PK of drugs are the volume of distribution (V_d) and clearance (CL). The V_d is defined as a proportionality constant that links the amount of drug administered, dose, to the measured plasma concentration. CL is a measure of drug elimination and represents the volume of blood or plasma from which a given drug is completely removed per unit of time (hours or minutes). CL occurs through

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metabolism and/or excretion. The combination of V_d and CL is reflected in the still frequently used PK parameter estimate, the elimination half-life. This means that a prolonged half-life can be explained by either a reduced CL or an increased V_d or both.

With the exception of a drug formulation as a prodrug, drugs administered by the intravenous route are completely available to the systemic circulation. In contrast, the PK parameter estimate of absorption (rate and extent) is relevant when other routes of drug administration (eg, enteral, subcutaneous, intramuscular, inhalational) are used. All these PK processes (absorption, distribution, metabolism, elimination [ADME]) display maturation.[1–5] The rate of maturation of these ADME processes is most pronounced in the first 2 years of life.

Absorption of Drugs

There are many ways to deliver drugs to neonates, infants, children, and adolescents. The most frequently used are the extravascular routes such as the gastrointestinal tract, skin, or lungs. Most drugs prescribed to neonatal and pediatric patients are administered orally. Gastrointestinal absorption is influenced by specific drug characteristics such as a drug's physicochemical properties but also by physiological parameters (eg, gastric pH, intestinal transit time, drug-metabolizing enzymes, and drug transporters) and environmental factors (eg, food including milk, drug formulation). All these factors may vary considerably with growth and development and result in maturational changes in the drug absorptive capacity of the individual pediatric patient.[8–10]

Maturational Changes in Gastrointestinal Physiology

Gastric pH is important for drug stability, dissolution, and ionization, all of which have an impact on absorption. At birth, gastric pH is neutral, probably because there is amniotic fluid in the stomach.[11] However, what happens after birth is still not clear. Available literature presents information that varies from a neutral gastric pH 1-3 days after birth followed by a progressive decrease over several weeks to years to reach adult values[12] and an acidic gastric pH soon after birth that persists even in the most preterm neonates.[13] Thus, there remains no clear consensus about the ontogeny of gastric acid production (rate and amount) and secretion or on its impact on drug absorption in the preterm/full-term infant and during infancy. Perhaps the fact that preterm infants receive virtually continuous oral feeds containing acid-buffering milk might result in higher pH values than those seen in more mature infants. That might explain the reduced absorption of weak acids such as phenytoin because of increased ionization[14] as well as reduced absorption of weak bases such as ketoconazole because of decreased solubility.[15]

Gastric emptying and intestinal motility are the primary determinants of the rate and extent of intestinal drug absorption, and until very recently it was assumed that gastric emptying was much slower below the age of 6-8 months because of the immaturity of the neuroregulation of gastric motility.[16] This prolonged gastric emptying should result in a decreased absorption rate and a delay of absorption of drugs that are dependent on the rate and extent of gastric emptying. Until recently this finding was substantiated by the findings of several clinical investigations involving different drugs such as acetaminophen and cisapride.[17,18] However, in a recent meta-analysis of 49 published studies including data on almost 1500 individuals with ages between 29 weeks of gestation and adults, differences in age did not explain variation in gastric emptying, which seemed to be more driven by the type of food (water, milk, solid food).[19]

As a consequence, it seems that at this moment, as for the aforementioned developmental changes in gastric pH, there is very limited understanding of the effect of age on the rate and extent of gastric emptying in the neonate and during early infancy. Although also poorly defined, it appears that gastrointestinal functions achieve adult values and activity by the age of 2 years. In contrast, it appears that age has minimal influence on the transit time for the small intestine and colon.[20]

Maturational Changes in Intestinal Transporters and Enzymes

The intestine contains a range of influx and efflux drug transporters as well as a diversity of drug-metabolizing enzymes (DMEs). These transporters and enzymes contribute substantially to the absorption and, thus, the overall bioavailability of a large number of orally administered drugs. However, the effects of developmental changes in specific intestinal transporters on drug absorption are still unclear.

The overall task of the efflux transporters is to move compounds or drugs that have penetrated the intestinal epithelium back into the intestinal lumen. Many transporters belonging to the ATP-binding (P-glycoprotein [P-gp], breast cancer resistance protein, multidrug resistance-associated protein [MRP]) or solute carrier (PEPT1, OATPs) superfamilies are present in the intestine and are important determinants of the PK of orally ingested medicines.[8] The most frequently studied transporter is P-gp. Others include MRP2 and breast cancer resistance protein. Whereas intestinal transporters modulate drug absorption, intestinal DMEs are responsible for the metabolism of a variety of drugs. The most important family of these enzymes

is that of cytochrome P450 (CYP) with CYP3A4 as the most abundantly expressed family member.[8]

In the search for maturational changes in drug transporters and DMEs, several investigators have detected MDR1 mRNA expression in the intestines of fetuses, neonates, and children but have not been able to demonstrate any relationship between MDR1 (P-gp) expression and age.[21,22] However, Mooij et al found such a relation for MRP2.[23] The same holds true for CYP3A4 mRNA expression where a significantly higher mRNA expression has been found in young adults but also a much higher expression in the first year of life as compared to 1- to 6- and 6- to 17-year-olds. Recent data show the level of liver CYP3A4 mRNA to be positively correlated with age, whereas duodenal CYP3A4 mRNA showed a more complex and almost opposite pattern.[24]

Thus, there remain very limited data from these mRNA expression investigations to support a developmental, maturational pattern of P-gp and/or CYP3A4 activity in the intestine of infants and children. Very few clinical investigations have provided additional insight into the possible impact of CYP3A4 maturation on the CL of any of its substrates. Very recently[25] a physiological population PK model was developed that was able to distinguish between intestinal and hepatic intrinsic CL of midazolam in preterm infants. This model indicated a very low first-pass effect by intestinal and hepatic metabolism by CYP3A in preterm infants as compared to adults, resulting in a very high intestinal and hepatic bioavailability of CYP3A substrates. As illustrated with the above examples, the impact of intestinal CYP3A and P-gp ontogeny on drug disposition is not yet fully understood and requires further investigations, which should also explore potential confounding factors such as pediatric formulations and feeding regimens as well as different disease states.

It is important to emphasize that drug metabolism in the intestinal wall is not restricted to CYPs but involves other enzymes that are even less studied with respect to ontogenic changes.[10,26] Glutathione-S-transferase (GST) and carboxylesterase-2 (CES2) are just 2 of these enzymes. GST is responsible for the metabolism of busulfan, a drug used to treat hematological malignancies. It was shown that intestinal GST participates in the first-pass extraction of this drug, showing an upregulated activity in children younger than 5 years of age.[26] Chen and colleagues[24] measured CES2 mRNA and protein in duodenal samples from human donors of various ages and showed an increase with advancing age, reaching adult values at 0.5-1 year of age. However, despite this developmental pattern of intestinal CES2, the prodrugs candesartan cilexetil and olmesartan medoxomil showed the same PK profile after oral dosing in children as in adults.[27,28]

Uridine 5′-diphosphoglucuronosyltransferases (UGTs) are also highly expressed in the intestinal wall and are linked to the low oral bioavailability of drugs such as raloxifene.[29] Unfortunately there is very little information about the ontogeny of intestinal UGTs. The mRNA of UGT2B7, the enzyme involved in the metabolism of morphine, zidovudine, and chloramphenicol was found to be highly expressed in adult but not in fetal liver.[30] This finding might help us in improving our understanding of a condition described in 1959,[31] the "gray-baby" syndrome, a life-threatening syndrome seen after chloramphenicol exposure in neonates. High exposure to chloramphenicol, based on immature hepatic UGT2B7, has been seen as the cause, but surely intestinal UGT2B7 could also have contributed.[32] Other enzymes such as epoxide hydrolase, glutathione peroxidase, and alcohol dehydrogenase show only little change with age.[33,34] The developmental patterns of other DMEs are yet unknown.

It is important to note that developmental changes in DMEs based on mRNA expression are not the same as changes occurring at the protein or activity level because of the diverse regulatory mechanisms that occur after the production of mRNAs.[33] The same holds true for mRNA levels for intestinal transporters because these may also not correlate with the corresponding proteins or functional activities.[35,36] Thus, the interpretation and extrapolation of these findings to the ontogenic impact on drug disposition must be applied cautiously and, most importantly, confirmed in vivo. A very recent review concluded that data for individual transporters are currently still scarce and that there is a striking information gap regarding the role of human membrane transporters in drug therapy in children.[37] As a consequence, a clear transporter-specific maturation pattern cannot be deduced at this time.

Distribution of Drugs

A drug will distribute in different tissues or organs after reaching the systemic circulation. The distribution pattern will partly depend on physical (eg, lipophilic or water soluble, degree of ionization) and physiological (eg, protein binding, tissue uptake) processes. As a consequence, distribution is dependent on the extent of protein binding, pH, systemic and regional blood flow, permeability of natural "barriers" (eg, blood-brain, placenta), and body composition. Clearly, these covariates will display both inter- as well as intrapatient variability, partly explained by maturational changes or disease-related differences.[12]

Impact of Body Composition

Age-dependent maturational changes in body composition change the physiological spaces into which a drug will distribute. Neonates and young infants have a proportionally higher amount of body water per kilogram of body weight when compared to children and adults, and preterm neonates have an even higher value when compared to term neonates.[1,4,5] For the total body water content, this is about 80% to 90% in preterm and 70% in term neonates, with a progressive decrease to about 60% at the end of first 1-2 years and subsequent stabilization throughout childhood.[38] This pattern is similar for the extracellular water content, starting at 40% and decreasing to about 25% to 30% at the end of infancy. For the lipid compartment, the trends are somewhat more complex, with an initial increase from 10% to 15% at birth to 20% to 25% at the end of infancy, and a subsequent decrease back to 10% to 15% until adolescence.[4,5,38]

Larger extracellular and total body water spaces in neonates and infants result in lower plasma concentrations for drugs that distribute into these respective compartments when administered in a weight-based fashion.[2] The reverse is true for lipophilic compounds. To illustrate this, the volume of distribution of aminoglycosides (water soluble) displays a progressive decrease within neonates (extreme preterm, 0.7 L/kg, to term neonates, 0.5 L/kg) and throughout childhood (0.5 L/kg in neonates to 0.3 L/kg in young adults).[39] A similar pattern has been described for paracetamol (acetaminophen).[40,41] In contrast, diazepam, a lipophilic compound, exhibits a proportionally lower distribution volume in the newborn (1.6 L/kg) when compared to children or adults (2.4 L/kg).[42] A similar pattern has been estimated for propofol, another lipophilic compound, (2.8-5.6 L/kg in the newborn up to 5.6-8.6 L/kg in toddlers) throughout early childhood.[43]

Protein Binding

Protein binding also influences drug distribution. Compared to adults, infants and children have lower concentrations of the most relevant plasma binding proteins such as albumin, α-1 acid glycoprotein, or plasma globulins. Because protein concentrations reach adult values in infancy, this effect is likely to be most pronounced in newborns and young infants. In addition to the absolute values or concentrations, competitive binding with endogenous compounds (eg, bilirubin, free fatty acids) may further affect the binding capacity.

In the newborn there is a simultaneous lower concentration of different plasma proteins in combination with increased bilirubin concentrations and/or increased levels of free fatty acids.[44] Moreover, the amount and type of circulating plasma proteins will not only influence drug disposition but also drug action because only unbound or free drug can be distributed throughout the body and exert a pharmacological effect.[2] Clinical implications of alterations in the extent of protein binding of a drug are most relevant for those drugs that are highly protein bound and also have a narrow therapeutic index.[45] A recent published example to illustrate this is the protein binding of cefazolin to albumin: the free fraction is related to the total concentration of cefazolin as well as to the serum albumin amount, but even after incorporation of these covariates, the free fraction remained higher in the newborn.[46] Similar patterns have been described for other antibiotics (eg, ampicillin, flucloxacillin, vancomycin),[47,48] antiepileptics (eg, phenytoin) or chemotherapeutics (eg, etoposide).[49,50]

Reduced protein binding increases the free concentration and the free fraction of drugs, thereby enhancing the capacity of the active drug to diffuse more easily to other compartments. This will result in more interaction with receptors, but it also will increase the CL rate of the drug. Moreover, when higher free fractions of a given compound are circulating in the plasma compartment, these fractions are able to penetrate to deeper tissue compartments, resulting in a higher distribution volume.[45] These principles must be factored in when prescribing a drug for these patients. For drugs with defined therapeutic serum concentration relationships (eg, theophylline), the target concentrations will be lower, accounting for less protein binding/greater free drug concentration in the neonate (eg, apnea of prematurity) than target concentrations in older infants, children, and adults (eg, asthma).

In summary, the influence of protein binding on free plasma-drug concentrations is limited to drugs that have a moderate to high degree of protein binding and a narrow therapeutic index (eg, phenytoin, etoposide).[49,50] This is because even a minor difference in protein binding will result in a significant difference in the free concentration of the administered drug.

Membrane Permeability

Drug distribution to deep compartments such as the central nervous system is delayed and limited due to endothelial tight junctions in combination with efflux transporters. This is why intrathecal injections are performed to bypass this barrier for children with, for example, acute leukemia or brain tumors. Although the number of observations is still limited, it seems that there are also maturational changes in this barrier, with a progressive increase in both efflux transporter (P-gp) expression and function as well as tight junction (higher passive diffusion in early infancy) capacity.[51,52]

Disease-Related Differences in Distribution

The phenotypic distribution volume estimates throughout childhood are to a large extent driven by maturational changes. However, these estimates may be further affected by disease-related changes in body composition, protein-binding capacity, or membrane permeability.

Both obesity and malnutrition are of importance in children. At present, a single size descriptor to estimate the distribution volumes of all drugs in both lean and obese children does not exist, but it is reasonable to anticipate that a higher fat mass mainly alters the distribution of lipophilic drugs and has a more limited impact on water-soluble compounds.[53,54] Based on the currently available evidence, protein malnutrition does not extensively affect distribution volume for most compounds but does affect absorption and CL to a larger extent.

Similarly, the presence of a patent ductus arteriosus or sepsis has been associated with a further increase of the distribution volume in (pre)term neonates, most pronounced for water-soluble compounds.[55] Also, the use of extracorporeal membrane oxygenation will affect drug disposition because of the additional external volume (membrane and tubing) as well as the lower plasma protein and associated fluid retention commonly observed.[56]

Protein binding is obviously affected in the setting of hypoalbuminemia (eg, nephrotic syndrome), but environmental aspects (pH, free fatty acids, competitive binding) may also affect protein-binding characteristics.[46] Competitive binding is a major issue in neonates with hyperbilirubinemia because displacement of initially bound bilirubin may result in kernicterus.[45] This is why ceftriaxone should not be given to neonates with elevated bilirubin concentrations. Binding characteristics may also relate to disease states because α-1 acid glycoprotein will increase after surgery, resulting in a somewhat higher binding capacity for local anesthetics. Finally, in addition to maturational changes, membrane permeability may also be affected by disease state. In the setting of meningitis, the associated inflammation will result in less effective tight junctions, and a similar pattern can be anticipated in the setting of (severe) traumatic brain injury.[57]

Drug Metabolism

It is generally assumed that the major site of drug metabolism is within the liver, although the first-pass effect of orally administered drugs is also driven by intestinal drug metabolism, and other organs such as kidneys, lungs, blood cells (eg, esterase function), placenta, or brain may also display relevant drug metabolism capacity. The major pathways involved in drug metabolism are commonly divided into either phase I or phase II reactions. Phase I mainly encompasses "destructive" processes and results in structural changes of the compound, whereas phase II reactions are synthetic in their pattern. Phase I reactions involve the processes of oxidation, reduction, and hydroxylation, whereas phase II reactions involve conjugation with molecules increasing water solubility.

As noted above, the most relevant group of DMEs are the CYP enzymes, with a major contribution of CYP3A4/5 involved in the metabolism of about 50% to 60% of all therapeutic drugs currently on the market. Other relevant DMEs include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.[1–3,58] Phase II reactions involve glucuronidation, sulfation, methylation, acetylation, or glutathione conjugation. The most relevant groups of DMEs involved in phase II metabolism are the UGTs.[1–3,58] Drug-drug interactions mainly relate to phase I metabolism because of substrate specificity, whereas phase II metabolism is important for detoxification of reactive molecules initially produced by phase I metabolism.

The phenotypic drug-metabolizing capacity observed or estimated in an individual patient is affected by multiple covariates. Throughout childhood, the most obvious covariates relate to growth and maturation and are reflected or quantified by weight, length, age, body surface area, or lean body mass. These maturational differences often result in different disposition patterns throughout childhood when compared to those of adults and are of clinical relevance to determine doses or may explain differences in (side) effects.[59]

The gray baby syndrome following chloramphenicol exposure relates to "normal" dosing in the presence of impaired glucuronidation[60]; valproate hepatotoxicity in infants and children likely relates to differences in the capacity of specific DMEs (CYP2A6 and different UGTs)[61]; and ifosfamide renal tubular toxicity also can be explained by differences in the ontogeny of specific DMEs (CYP3A4 vs CYP2B6) in the kidney.[62] The maturational, ontogeny-related variability is further affected by interfering disease characteristics (eg, hepatic and/or renal impairment/failure, hemodynamic changes, sepsis),[63,64] treatment modalities (eg, comedication, extracorporeal membrane oxygenation, whole-body cooling)[65,66] or other specific covariates (eg, pharmacogenetics, environmental factors).[67,68] All these covariates will affect inter- as well as intrapatient variability in drug metabolism. When the degree of their influence can be estimated or even quantitated, specific dose modifications can be used to allow the safe and effective use of these medications in these patients.

Maturational Changes Throughout Childhood

Metabolic CL relates to regional blood flow, extraction rate, and intrinsic DME specific capacity, and all of these aspects may display age-related differences. The extraction rate depends on the free concentration or fraction. The ratio of liver weight to body weight is greater in infants and toddlers and subsequently decreases with age. Related to this, the regional liver blood flow is also higher during infancy and in young children. Finally, the intrinsic CL capacity relates to the overall microsomal as well as to DME-specific activity.

Liver microsomal protein content (20-25 mg/g liver proteins) is low in neonates and subsequently increases with age to reach a maximum level of microsomal protein content (40 mg/g) at about 30 years of age. However, a picture showing that drug metabolism is low in neonates, rising throughout infancy, and in early childhood, and then in prepuberty to reach adult levels in puberty is too simplistic.[69] Hines et al[70] suggested 3 different developmental patterns for DMEs: high in fetal life to low or absent postnatally (class 1), stable throughout development (class 2), or low in fetal life to high postnatally (class 3). Moreover, for a specific DME, significant interindividual variation is observed in the timing of these perinatal changes, creating DME-specific windows of variability. These results , in regard to age-related differences and changes in fractional elimination pathways for specific drugs, may affect the magnitude and extent of drug-drug interactions or age-related (side) effects.

Genetics, comorbidity, or environmental issues interact significantly with these developmental changes: ontogeny is only 1 of the relevant covariates. Finally, it seems that the age-dependent DME-specific activity may also be organ specific: CYP3A7 decreases after birth and almost disappears after infancy but remains relevant in the bronchial tree. These developmental changes in DMEs have a clear impact on drug disposition in neonates, infants, and young children.[71]

Maturational Changes in Phase I Enzymes

Phase I covers both non–CYP- and CYP-mediated reactions. Non–CYP-mediated DMEs relate to flavin-containing monooxygenase (FMOs), alcohol and aldehyde dehydrogenases (ADHs) or esterases.[70] It seems that the FMO-1 activity is high at birth and has a subsequent decrease over the first 2 years of life (class 1), whereas FMO-3 ontogeny is the opposite, being low at birth and showing an age-dependent increase (class 3). Overall alcohol dehydrogenase capacity in the newborn liver is about 10% of adult capacity, but there are different patterns of ontogeny for different DMEs with a high fetal activity and a subsequent decreasing activity for ADH1 (class 1), and the reverse for ADH2 and ADH3 (class 3).[70] Based on in vivo observations (eg, N^1-methylnicotinamide to pyridine conversion), it has been suggested that aldehyde oxidase is lower throughout infancy. Esterase function already matures from at least 28 weeks of gestational age onward, as reflected in effective remifentanil or propacetamol degradation in neonatal blood samples (class 2).[72,73]

CYP1A2 hepatic protein concentrations and in vitro activity are very low with a slow developmental pattern after birth, starting with 5% at birth, 25% at the end of infancy, up to only 50% at the age of 6 years. This is in line with the available in vivo observations on caffeine and theophylline metabolism and clearance.[74,75] CYP2B6 expression and activity increase significantly (2-fold) in the first month of life, with subsequent conflicting information, suggesting either that there are no additional changes between 1 month and 18 years or a 7-fold increase between 1 year and adulthood. In vivo observations relate to ifosfamide, efavirenz, or methadone disposition.[76]

The CYP2C subfamily covers CYP2C8, 2C9, 2C18, and 2C19. CYP2C9 ontogeny is faster and earlier (from birth onward) when compared to CYP2C19 ontogeny (only slowly rising in the first 6 month of life).[77] Related in vivo observations are on ibuprofen or warfarin (2C9) or pantoprazole (2C19),[78] respectively.

CYP2D6 is already present in fetal liver tissue, with a subsequent increase in neonatal life and early infancy, with more uncertainty on how the maturational pattern subsequently evolves. Similar patterns have been described for in vitro observations on dextromethorphan or tramadol disposition.[79,80]

The CYP3A subfamily covers CYP3A4, CYP3A5, and CYP3A7 with completely different age-related activity patterns. CYP3A7 has a high activity during fetal life and early infancy, with a subsequent decrease for hepatic but not for bronchial mucosal tissue. In contrast, CYP3A4/5 matures slowly and only reaches an adult level of activity at the end of infancy.[81] The most extensively evaluated in vitro CYP3A model compound is midazolam.[82]

Maturational Changes in Phase II Enzymes

Phase II enzymes catalyze different conjugation reactions, including sulfation (GST), acetylation (N-acetyl transferases), and most importantly, glucuronidation (UGT).[83] Compared to glucuronidation, sulfation activity is already higher in early infancy but still limited because of an overall lower capacity. Sulfation is the second major phase 2 metabolic pathway (catechol or phenol sulfotransferases). Compared to the CYP patterns, drugs are quite commonly metabolized by different UGT isoforms and/or sulfotransferases.

Consequently, the DME-specific ontogenic pattern is more difficult to describe based on in vivo observations. Moreover, the ratio of glucuronidation to

sulfation may also differ throughout development, as illustrated for paracetamol metabolism.[84] Glutathione conjugation is already at a relevant level of activity at birth (65% to 70% of the adult level) and is of clinical relevance for paracetamol detoxification.[85] Based on isoniazid in vivo observations, relevant phenotypic acetylation activity and the impact of the different polymorphisms (slow, intermediate, and rapid acetylators) have been described in infants.[86]

The UGTs are responsible for the glucuronidation of hundreds of hydrophobic endogenous compounds and drugs, including morphine or chloramphenicol (both UGT2B7), propofol (UGT1A9), and acetaminophen (UGT1A6/1A9). In vitro ontogeny data are limited[87,88]: in fetal liver samples, activities were low (1% to 10% of adult levels) for UGT1A1, UGT1A3, UGT2B6, UGT2B15, and UGT2B17,[30] whereas after birth, UGT1A9 and UGT2B4 activities remained significantly lower in infants (0.5-2 years) than in older children and adults.[30]

The above-mentioned information on maturation of drug metabolism can be used to predict compound-specific or DME-specific patterns. For compound-specific patterns, DMEs are important determinants of drug disposition. The fact that their activities are not stable throughout childhood commonly results in different PKs and different disposition of drugs metabolized by these enzymes, specifically the variability observed with age. The consequences of this DME-specific ontogeny are not just maturational-related lower total clearances but are also reflected in the age-related different contributions of different pathways involved in a drug's disposition, as has been illustrated for dextromethorphan metabolism.[79] The urinary ratio of the different metabolites evolves through infancy because of the initially faster CYP2D6 activity, subsequently taken over by the increasing CYP3A4 capacity.[79] This is also of relevance to predict or anticipate drug-drug interactions.

DME-specific patterns can also be used to estimate or to predict drug disposition. The impact of developmental changes in drug metabolism on drug efficacy and safety throughout pediatric life has been studied increasingly, and more and more compound-specific observations have been reported. Translation of existing knowledge to dosing guidelines and clinical trial design is needed urgently.[89] It should be noted that extrapolation can avoid some PK studies by reducing the need to study a compound in each subpopulation if the drug's PK can be predicted reliably.[89] Such extrapolations can be cautiously performed between populations or between drugs that undergo elimination through the same route,[89] but predictions must also be confirmed in age-defined human studies.

In summary, the phenotypic drug-metabolizing capacity observed or estimated is affected by multiple covariates. Throughout childhood, the most obvious covariates relate to growth and maturation. However, thinking of drug metabolism as being low in neonates and rising throughout infancy, early childhood, and prepuberty to reach adult levels in puberty is too simplistic. Genetics, comorbidity, and environmental issues further interact with these developmental changes: ontogeny is only 1 of the relevant covariates.[90–92] Translation of the existing knowledge on ontogeny into age-adjusted dosing guidelines and clinical trial design is a powerful tool to improve pharmacotherapy and clinical study design and to predict effects/side effects throughout childhood.[89]

Renal Elimination of Drugs

Elimination of drugs by the kidneys is dependent on 3 processes: glomerular filtration, tubular excretion, and tubular reabsorption. The first step in this staggered process of drug elimination is that the free drug in the plasma is filtered across the glomerular membrane into the renal tubule. The tubule transporter systems in the renal tubular membrane may then increase drug excretion by promoting the passage of drugs from the plasma into the tubule. Moreover, in the distal part of the renal tubule, lipophilic drugs may be reabsorbed by passive diffusion from the tubule back into the blood. Overall, the renal clearance of drugs is the sum of these 3 processes. From a maturation standpoint, each of these processes exhibits an independent rate and pattern of development.

Glomerular filtration is responsible for the elimination of a large number of water-soluble drugs and drug metabolites, and the glomerular filtration rate (GFR) is often used to quantitate or assess renal function. In the full-term newborn, GFR approximates 10 to 20 mL/(min·m^2) at birth. This increases rapidly to 20 to 30 mL/(min·m^2) during the first weeks of life and typically reaches adult values (~70 mL/[min·m^2]) by 3-5 months.[93] Furthermore, the increase in GFR is highly dependent on postnatal age, the chronological age since birth. Hayton et al described the maturation of GFR with postnatal age using a nonlinear function.[93] A more practical equation was proposed by Schwartz and co-workers.[94] For drugs that are mainly excreted by glomerular filtration (eg, aminoglycosides), initial dose adjustments can be made by either increasing the dosing interval or decreasing the dose. However, partly due to the expression of GFR per body surface area, the application of these functions in the analysis of renally excreted drugs in different age categories is complicated, which underlies the need for novel functions quantifying GFR across the pediatric lifespan.

GFR can be determined on the basis of the concentrations of endogenous (creatinine, cystatin C) or exogenous compounds (inulin, radioisotopes).[95,96] Nevertheless, several limitations are linked with each of these methods in the pediatric range.[95] Therefore, the most pragmatic method to assess maturation in GFR is the determination of the CL of a (model) drug that is almost entirely eliminated through GFR (ie, not tubularly reabsorbed or excreted) and that is widely used in clinical practice across the pediatric age range.[97] The advantage of the use of clearance of renally excreted drugs as a measure to determine GFR is that this information can be gathered in daily clinical practice.[97] This has resulted in the development of a semiphysiological modeling function to describe GFR maturation on the basis of simultaneous population PK modeling of gentamicin, tobramycin, and vancomycin, drugs that are almost entirely eliminated through GFR.[98] A very recent review has elegantly summarized the currently available pharmacometric approaches to personalize the use of primarily renally excreted antibiotics in preterm and term neonates.[99]

In contrast to glomerular filtration, tubular secretory and reabsorptive capacity appear to mature at much slower rates. Tubular secretion is reduced at birth to approximately 20% to 30% of adult capacity but matures by 15 months of age. Tubular reabsorption is the last renal function to mature and does not reach adult levels until 2 years of age. This delay in development of tubular functions may have variable effects on the CL of some drugs for which tubular secretion or reabsorption is important in adults. For example, digoxin, which undergoes some active secretion, has a reported average renal CL of 1.92, 3.94, and 5.20 L/(h·1.73 m^2) in full-term infants less than 1 week of age, 3-month-old infants, and children 1.5 years of age, respectively.[100]

Unfortunately, at this time, there is little information in the literature about the ontogeny of renal drug transport systems in the human being and their impact on renal elimination in infants and children. In summary, developmental changes in GFR have been well described, but measuring GFR in clinical practice in neonates and young infants is challenging with the currently available GFR markers such as serum creatinine. Therefore, recent developments in using population PK modeling of different, frequently used, antibacterial agents in these young infants have resulted in an elegant description of the maturation of GFR during pediatric development.

Developmental Changes in PD

Much has been learned about the impact of maturation on developmental changes in PK. In contrast, there is little information about how human growth and development and their intersection with disease impact PD. In the context of pediatric therapeutics, it is commonly assumed that attainment of a systemic drug exposure in an infant or child comparable to that observed in adults, which is associated with a desired or adverse drug action, will produce an identical action in the pediatric patient. In some cases this can be an errant assumption. Thus, developmental changes in PD must be considered to have their own dimension.

In contrast to adults, pediatric patients continue to be "pharmacodynamic orphans." It is widely appreciated that normal human growth and development can influence both PK and PD.[1] A 2010 commentary by Holford[101] emphasized the PD knowledge gap in pediatrics and that the impact of development on drug effect could only be known when PD and PK were studied in tandem. Although this approach is certainly ideal, the challenge is formidable given the current lack of knowledge and technology.

Developmental changes in PD can be defined as the age-related maturation of the structure and activity of biologic systems and how they impact the response to pharmacotherapy across the continuum of pediatrics. Clinically, there are well-described examples of age-dependent differences in PD such as the higher incidence of valproic acid–associated hepatotoxicity in young infants, the greater frequency of paradoxical central nervous system reactions to diphenhydramine in infants, a higher incidence of weight gain associated with the use of atypical antipsychotic agents in adolescents, and altered concentration-versus-effect profiles for warfarin in children with congenital heart disease.[102] The topic of developmental PD has been previously reviewed by Mulla.[6] In this review, he highlights not only the paucity of studies examining developmental PD but also the lack of suitable juvenile animal models that are developmentally and physiologically comparable to human models. Examples include species differences in the maturation of important neurotransmitters (eg, norepinephrine, serotonin) and receptors (eg, ontogeny of GABA receptors and association with paradoxical seizures in infants treated with benzodiazepines, increased sensitivity of neonates to morphine associated with increased postnatal expression of the μ opioid receptor). In addition, there appears to be enhanced sensitivity to drug response that is associated with development and that is not produced solely by age-associated changes in drug disposition (eg, altered concentration-vs-effect profile for cyclosporine in young infants and higher sensitivity toward QTc prolongation in neonates as compared to older children).

In human infants and children, developmental PD must be considered in the context of the exposure-versus-response relationship. As illustrated in Figure 1,

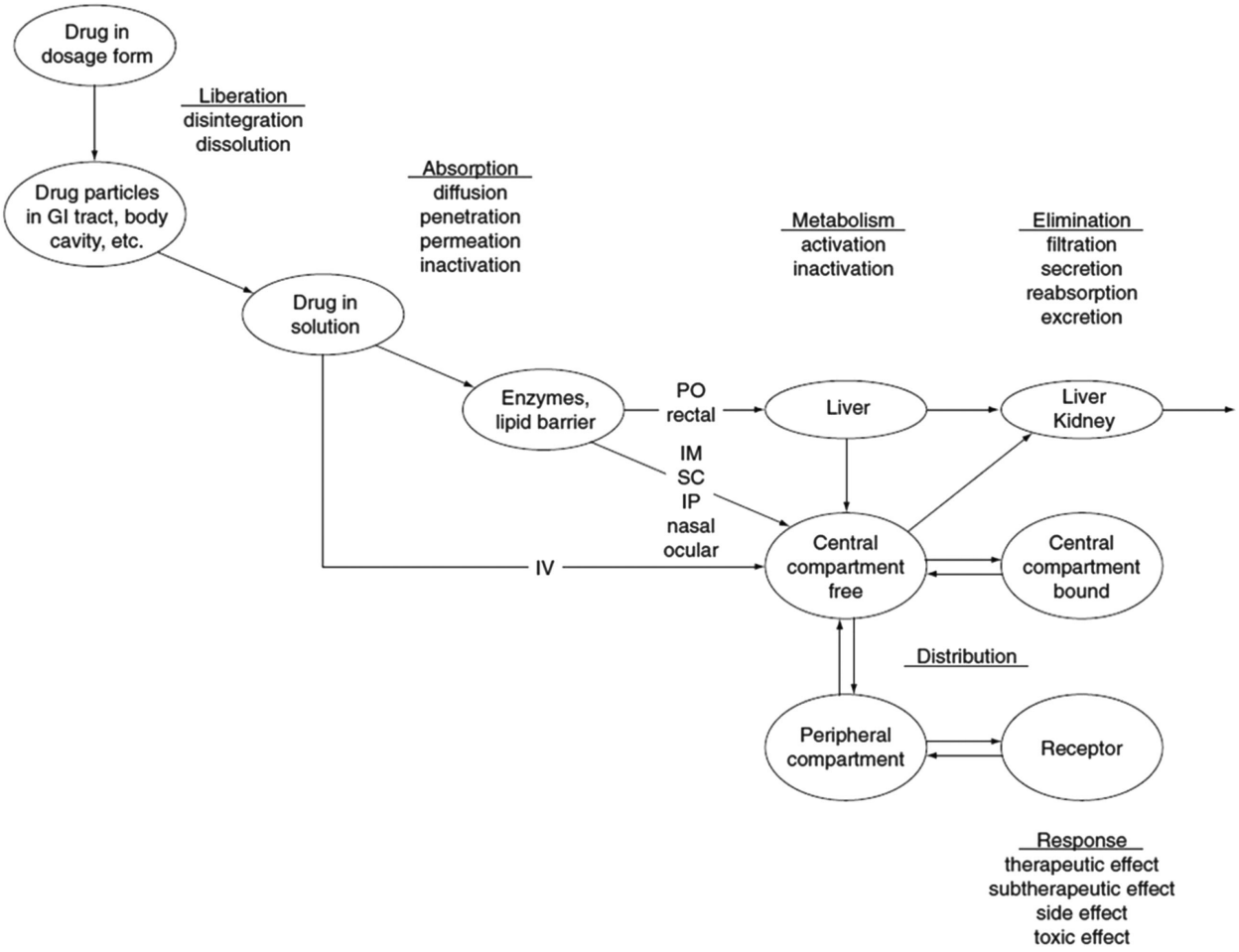

Figure 1. A hypothetical compartment model linking drug administration to effect. The effector compartment is represented by the receptor that exists in the biophase. GI indicates gastrointestinal; IM, intramuscular; IP, intraperitoneal; PO, oral; SC, subcutaneous. From Kearns and Artman[7] (reprinted with permission).

the receptor compartment (the site of action for most drugs) is located outside of the circulatory system and is within the biophase (ie, the tissue compartment). However, the amount of drug available to the receptor compartment is determined by the PK processes (eg, ADME) that collectively comprise drug disposition. Although the impact of development on PKs is discussed above, 2 specific drug examples highlight the intersection among ontogeny, PK, and pharmacogenetics as a determinant of drug action in the developing child.

Famotidine, a histamine-2 (H_2-receptor) antagonist acid-modifying agent, is a compound with predominant (>90%) renal clearance whose PK is similar in adults and children older than 1 year of age. A previous study of the PK of famotidine in infants from birth through 12 months of age demonstrated that the renal CL of the drug in the first 3 months of life was concordant with expected developmental differences in renal function.[103] Consequently, knowledge of the ontogeny of renal function[1] and the desired "target" systemic exposure of famotidine to produce its desired pharmacologic effects could be used to reliably predict drug dose for term infants whose renal function is developing normally. A similar but contrasting example is apparent with atomoxetine, a second-line nonstimulant medication used to control the symptoms of attention deficit hyperactivity disorder that is extensively metabolized by the polymorphically expressed drug-metabolizing enzyme, CYP2D6. Brown et al[104] demonstrated that despite significant intersubject variability, CYP2D6 activity scores, a biomarker derived from the *CYP2D6* genotype that provides a semiquantitative assessment of relative enzyme activity, were associated with marked differences in the plasma concentration-versus-time profile for the drug in children 6 to 17 years of age (Figure 2). They concluded that for individuals who had an extensive metabolizer CYP2D6 phenotype, simulated steady-state plasma concentration-versus-time profiles resulting from currently recommended (ie, in the approved product labeling) daily atomoxetine doses would likely not attain adequate therapeutic

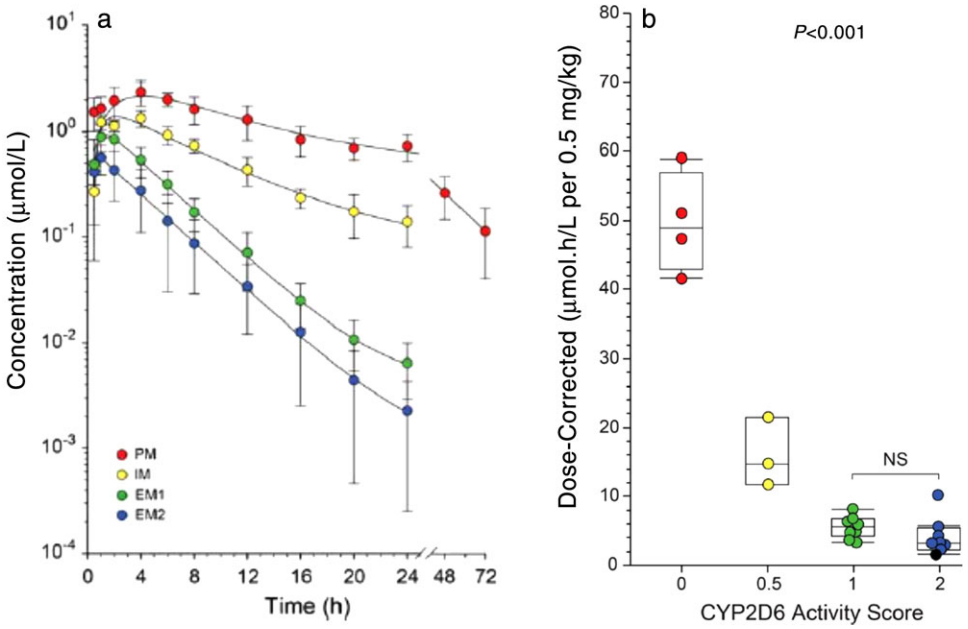

Figure 2. Plasma concentrations of atomoxetine following oral administration of a standard 0.5 mg/kg (maximum dose 40 mg) to children 6 to 17 years of age (a). The right panel (b) is the dose-corrected area under the plasma concentration-vs-time curve (AUC) for atomoxetine in the study cohort grouped based on CYP2D6 phenotype as reflected by the genotype-derived CYP2D6 activity score. Illustration from Brown et al[104] (reprinted with permission). EM, extensive metabolizer; IM, intramuscular; NS, nonsignificant; PM, poor metabolizer.

exposure. In the case of atomoxetine, dose prediction simply from *CYP2D6* genotype may be complicated not only by the significant variability in CYP2D6 activity but also in understanding the contribution of competing metabolic pathways, especially in those individuals who have lower CYP2D6 activity.[105] These data reflect that in the case of atomoxetine, assessment of *CYP2D6* genotype (as a surrogate for enzyme activity and predictor of drug clearance) alone may not afford a PK biomarker that is entirely predictive.

Indirect Assessment of Developmental Changes in PD: Role of Functional Biomarkers

Perhaps the greatest challenge and obstacle in characterizing the impact of growth and development on drug action and resultant PD reside with directly measuring drug effect. As denoted previously, the receptors for most drugs do not lie within the vascular space but, rather, are located in tissue spaces. In infants and children this tissue "compartment" cannot be easily accessed repeatedly due to technical and/or ethical constraints. Accordingly, PD assessment must often rely on indirect measurements of drug action. To mitigate these challenges, investigators have begun to explore the use of functional biomarkers as tools to assess developmental PD.

The US National Institutes of Health has defined a "biomarker" as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (https://www.ncbi.nlm.nih.gov/books/NBK326791). We have recently reviewed the use of functional biomarkers to bridge PK and PD in pediatric clinical trials.[7] In clinical practice the main utility of biomarkers is to guide drug dosing to a desired effect or the continued use of a drug or other intervention. During drug development, biomarkers may be used to establish proof of concept that a given agent produces a desired pharmacologic response and in some instances (eg, use of plasma drug concentration and microbial sensitivity data) can be used to guide dose-response studies.

As illustrated in Table 1, pediatric biomarkers can generally be placed in 3 categories: (1) those used to describe disease progression or response; (2) those used to predict systemic drug exposure or effect; and (3) those used to describe PD. In some instances PD biomarkers can be directly assessed to reflect physiological function in response to a therapeutic intervention (eg, functional MRI, blood pressure, esophageal or gastric pH monitoring). When biomarkers are used as PD surrogate end points to clinically assess drug effects in infants and children, they must have specific properties, which are summarized in Table 2. A test with these properties can enable robust, dynamic assessment of exposure-response relationships when combined with PK evaluation. We have recently reviewed specific examples of PD biomarkers that have been developed and evaluated in pediatric patients. A complete description of these

Table 1. Categorization and Examples of Biomarkers Used in Pediatrics

Disease Progression or Response	Systemic Drug Exposure or Effect	Pharmacodynamic Biomarkers
Hemoglobin A_{1c} (diabetes mellitus)	CYP2D6 (codeine response)	Plasma drug concentrations
C-reactive protein (inflammation)	TPMT (azathioprine or 6-mercaptopurine effect)	PET imaging and functional MRI
Alanine aminotransferase (hepatitis C)	VKORC1 (warfarin response)	Blood pressure
Exhaled nitric oxide (asthma)	CYP2C9 (warfarin metabolism)	Epicutaneous histamine response
MYCN (neuroblastoma)	Methotrexate polyglutamates (JIA response)	Esophageal pH monitoring (gastroesophageal reflux)
C-reactive protein (inflammation)	CYP2C19 (proton pump inhibitors)	AUC/MIC ratio (antimicrobial effect)

From Kearns and Artman[7] (reprinted with permission).
AUC, area under the plasma concentration vs. time curve; CYP2C19, Cytochrome P450 2C19; CYP2C9, Cytochrome P450 2C9; CYP2D6, Cytochrome P450 2D6; JIA, juvenile idiopathic arthritis; MIC, minimal inhibitory concentration; PET, positron emission tomography; TPMT, Thiopurine methyltransferase; VKORC1, Vitamin K epOxide Reductase Complex (VKORC) subunit 1.

Table 2. Desired Characteristics of Pharmacodynamic Biomarkers for Pediatric Use

1. Predictive association with normal growth and development
2. Sufficient sensitivity to discriminate time-dependent changes in disease progression from drug effect(s)
3. A reasonable, direct association with a drug's mechanism of action (ie, specificity)
4. Accuracy and precision with regard to repeated measurement
5. Not subject to epigenetic changes that could alter genotype-phenotype association
6. Suitable for repeated assessment in infants and children (ie, child-friendly)
7. Ease of performance by individuals skilled in the assessment and treatment of children

Adapted from Kearns and Artman[7] (reprinted with permission).

biomarkers and the relevant citations appertaining to them can be found elsewhere.[7] In the sections that follow, we summarize some examples and their relevance to developmental changes in PD.

Pupillometry

The use of hand-held infrared pupillometry to assess the PD of opiate analgesics has been well described. The assessment with this technology involves repeated (serial) evaluation of both static (eg, pupillary diameter) and dynamic (eg, pupillary constriction velocity) measurements of pupillary response. Boev et al,[106] in a study of 90 healthy pediatric volunteers, demonstrated the suitability of pupillometry for use in children by characterizing pupil constriction and dilation velocity. Connelly et al[107] described the initial use of pupillometry as a PD biomarker to assess pain and opiate response in children 8 to 17 years old with postoperative pain. These investigators found statistically significant, predictive associations between mean pupillary constriction velocity and opiate dose associated with pain control.

Stable Isotope Breath Tests

Stable isotope–labeled xenobiotics can be used to provide noninvasive measurements of drug-metabolizing enzyme activity (ie, phenotype). ^{13}C-Dextromethorphan and ^{13}C-pantoprazole have been previously used to assess the activity of CYP2D6 and CYP2C19, respectively.[108] Leeder et al[109] demonstrated that the ^{13}C-dextromethorphan breath test had a sensitivity of 100%, a specificity of 95%, and an accuracy of 95% in predicting CYP2D6 phenotype. The potential application of these breath tests as PD biomarkers resides with their ability to serve as surrogates for the activity of a given drug-metabolizing enzyme, which in turn can be used to predict dose-versus-exposure relationships for drugs that are substrates for a polymorphically expressed enzyme.

Another application of stable isotope breath tests resides with the use of the ^{13}C-acetate test to assess gastric emptying in infants[110] and children.[111] In a more recent study, Jones et al[112] found a predictive association between scintigraphy-determined (with 99m-technetium) gastric emptying time and that estimated using exhaled $^{13}CO_2$ from the ^{13}C-acetate breath test. These findings would support the potential use of this breath test as a noninvasive, safe functional surrogate biomarker to assess the PD of drugs that have an impact on gastric motility (eg, prokinetic agents).

Drug Hypersensitivity and Adverse Drug Reactions

In most cases adverse drug reactions have a PD component. A challenge in pediatric therapeutics is the prediction of delayed drug hypersensitivity reactions or idiosyncratic drug reactions. Recent data generated in pediatric patients support a potential role for selected PD biomarkers as possible predictors of specific adverse drug reactions. For example, Jones et al[113] have demonstrated the ability to use transcutaneously delivered histamine followed by assessment of cutaneous microvascular blood flow velocity to quantitatively describe histamine PD. These same investigators also used this technology to assess histamine response in a cohort of pediatric patients with allergic rhinitis and discovered 3 distinct histamine PD response phenotypes.[114] This technology holds promise for assessing the developmental changes in PD of antihistamines in infants and children because it meets the desired criteria for a PD biomarker (Table 2).

In studies examining the association between methotrexate disposition and its actions (both desirable and adverse) in pediatric patients with juvenile idiopathic arthritis, Becker et al have examined both the intracellular concentrations of methotrexate polyglutamates[115] and the impact of genotype on methotrexate polyglutamate variability.[116] More recently, they have demonstrated that, in pediatric patients with juvenile idiopathic arthritis, plasma cytokine levels (tumor necrosis factor-α and interleukin-6) appeared to have a predictive association as a PD biomarker of etanercept activity.[117]

With the resurgence of methicillin-resistant *Staphylococcus aureus* in the community, the antimicrobial combination product, trimethoprim-sulfamethoxazole (TMP-SMX) has become more widely used in pediatric practice. This medication has been linked to hypersensitivity reactions including 2 that are potentially life-threatening: Stevens Johnson syndrome and toxic epidermal necrolysis. As reported by Goldman et al,[118] the increased use of TMP-SMX in pediatrics from 2005 to 2009 was associated with nearly doubling of the adverse effects associated with the medication. A focus on the pathogenesis of TMP-SMX hypersensitivity reactions has centered on the biotransformation of both components. These investigators more recently demonstrated that a reactive, potentially cytotoxic iminoquinone methide metabolite resulted from TMP biotransformation and that N-acetyl-L-cysteine adducts produced by these metabolites could be reliably detected in the urine of patients receiving TMP-SMX.[119] These N-acetyl-L-cysteine–TMP adducts have promise as potential biomarkers to assess risk of hypersensitivity reactions to TMP.

Psychoactive Drug Response

As mentioned previously, challenges in optimizing the dose of the norepinephrine reuptake inhibitor atomoxetine require consideration of the impact of normal growth and development (ontogeny) and pharmacogenomics on the disposition of the drug. Kielbasa and Lobo[120] used atomoxetine as a probe to examine inhibition of the norepinephrine transporter. Specifically, plasma and cerebrospinal fluid concentration of 3,4-dihydroxyphenylglycol, the metabolic product of norepinephrine deamination by monoamine oxidase, were examined as a potential biomarker of drug effect in both the central (ie, blood) and peripheral (ie, brain) compartments. Based on this initial work, it is possible that plasma and CSF concentrations of 3,4-dihydroxyphenylglycol could be further evaluated in pediatric patients requiring treatment with atomoxetine and potentially could be used with pharmacogenomic information to reduce the variability in dose-versus-concentration-versus-effect relationships for the drug and thereby improve its pediatric use.

In summary, selective and specific use of physiological and pharmacologic biomarkers provides an avenue to truly explore the association between ontogeny and PD. Incorporation of these biomarkers will be essential to inform and streamline the process of pediatric drug development. When possible, linked PK-PD approaches should be considered when the effects of growth/development and disease are explored as modulators of drug disposition and action in infants, children, and adolescents.

Conclusions and Future Directions

An understanding of drug disposition across the pediatric age continuum is necessary for the design and implementation of an optimal drug regimen to treat disease. Many factors influence these processes. The ontogeny of major organ function, body composition, endogenous functions that process drug transfer and disposition, combined with genomics and disease influence drug disposition and effect. Despite the many advances in technology, study design, and pharmacometric analysis, our understanding of the exact influences of age and disease on drug disposition and effect remains challenged. More specific and accurate data are needed for each aspect of the ADME for therapeutic agents used in the pediatric population. Enhancing our knowledge of these processes and influences will support our increasing sophistication in drug disposition-effect modeling that will compliment clinical trials and experience while it fosters more rapid and comprehensive effective evaluation of new pharmacologic agents for treating the pediatric patient.

Moreover, in addition to knowledge synthesis, knowledge creation remains critical to further improve pediatric pharmacotherapy. Recent advances in pediatric rheumatic diseases, cystic fibrosis, and spinal muscular atrophy all were driven by improved insights in the underlying pathophysiology and mechanisms of these diseases. These examples also illustrate that advances can relate to specific genetic defects or be restricted to specific pediatric subpopulations and do not always cover the full spectrum of a given disease entity. Depending on the currently available knowledge of the pathophysiology of a specific indication, systems pharmacology can provide a useful platform to evaluate unexplored scenarios for future clinical trials.

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