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Overview of Clinical Pharmacokinetics in Pediatrics: Possible Implications in Therapy

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ABSTRACT

Rapid age-related changes in anatomic and physiologic parameters which may profoundly affect pharmacokinetic variables are characteristics of the first post-natal year and continue thereafter in childhood but to a lesser extent. Allometric methods mostly employed in dosage computation in pediatric age group which regrettably consider children as small adults; should be discarded in favour of the physiologically based pharmacokinetic approach considered far more ideal. Delayed gastric emptying resulting from prolongation in time required to achieve maximal plasma concentration (Tmax) occurs commonly in neonates and infants. Developmental changes that occur in body composition and protein binding are very crucial determinants of drug distribution in the pediatric age group. The pharmacokinetics, clinical efficacy and safety profile of administered drugs in children can be profoundly influenced by the developmental expression profile for the enzymes that support phases 1 and 2 metabolism. The lower rate of drug clearance due to impaired renal blood flow in preterm newborns as compared to normal ones necessitates the need for less frequent dosing interval and lower doses for drugs administered during the neonatal period. In conclusion, the outcome of this review emphasizes the need for understanding changes in developmental pharmacology amongst clinicians, particularly age-related variations in pharmacokinetic processes with obvious implications in enhancing clinical response and minimizing adverse effects.

Key words: Clinical pharmacokinetics, Developmental changes, Pediatrics, Physiologically based pharmacokinetic (PBPK) model.

INTRODUCTION

The pediatric age group notably neonates, infants and children are known to exhibit unstable pharmacokinetics. The first postnatal year is characterized by rapid age-related changes in physiologic parameters which may profoundly affect the absorption, distribution, metabolism and excretion of drugs. The knowledge of these age-related changes in pharmacokinetic variables is invaluable in enhancing optimal drug efficacy and reducing occurrence of adverse effects. Pediatric clinical pharmacology studies have now become an integral part of regulatory requirements by FDA (United States Food and Drug Administration) for all drugs used in children. Specialist knowledge is required in the case of infants and neonates as they differ significantly from adults in their physiology, pharmacodynamics and pharmacokinetics particularly in the first year of life[1]. Body weight correlates in neonates are not necessarily ontogenic (developmental) maturation processes related to drug disposition. Integrated pharmacokinetic/pharmacodynamic modeling has been advocated for use in optimal design of

clinical trials for vulnerable pediatric population[2]. Pharmacokinetic and pharmacodynamic behaviour differ greatly at extremes of age compared to normal adult population[3]and generally clearance may vary significantly during single course of therapy and may be reduced at both extremes of age[4,5]. Allometric methods which take into account variations in age, body weight and/or body surface area are commonly employed in the computation of dose for pediatric age group. Regrettably, these calculation methods consider children as small adults, which is certainly not the case and unacceptable. Hence, the physiologically based pharmacokinetic modeling is advocated as more realistic approach for determination of appropriate dosage regimen and dose adjustment in children[6].

A study highlighted the relevance of physiologically based pharmacokinetic model based on knowledge of appropriate developmental physiology and anatomy to describe a top down "from model to clinical observation" concept[7]. However, other studies have described a bottom-up "from clinical observation to model"concept predicated on compound specific observations to mechanism based model[8,9]. The comparison of both approaches and understanding the discrepancies between them may serve as a guide to clinical pharmacologists and neonatologists to facilitate basic and clinical research in developmental pharmacology. This paper critically examines the pharmacokinetic variables which govern the rational dosing of drugs in neonates, infants and children aimed at optimizing clinical response and decreasing incidence of adverse effects.

MATERIALS AND METHODS

A detailed advanced literature search using PubMed, Goggle Scholar and Medline was done, aimed at accessing peer reviewed full journal articles, abstracts, reviews, comments, letters to editors, project reports, dissertations, theses and books relevant to the subject area. The keywords employed include the following: clinical pharmacokinetics, developmental changes, drug absorption, drug distribution, drug elimination, drug interaction, drug metabolism, pediatrics and physiologically based pharmacokinetic (PBPK) model.

Drug Absorption

There is a wide range of routes of drug absorption in children. Common routes of absorption include oral, rectal, inhalational, subcutaneous, intramuscular and topical. The less common routes include intranasal, intrathecal, sublingual, intraosseous and intra-articular. A number of factors including route of administration, concomitant administration of food or other drugs, age of recipient, drug formulation and disease state affect drug absorption[10]. The bioavailability of intravenously administered drug is 100% since no absorption process is involved. The rate of absorption of orally administered drugs is slower in neonates and young infants due to delayed gastric emptying resulting to prolongation in time required to achieve maximal plasma concentration (Tmax)[11]. The approach to adult values occur after 6 months in neonates during which gastric emptying time may be considerably prolonged[12]. The major physiologic factors affecting bioavailability of oral drugs include hepatic first-pass metabolism, enterohepatic circulation, intestinal blood circulation, biliary excretion, gastric/duodenal pH, drug efflux in gut wall (P-glycoprotein) and cytochrome P450 microsomal enzyme (CYP3A4). However, inhibition of the activities of cytochrome (CYP3A4) microsomal enzyme in intestinal phase 1 metabolism and P-glycoprotein involved in drug efflux and implicated as possible mechanism in multiple drug resistance, may profoundly affect oral bioavailability of specific drugs[13,14]. Diazepam, midazolam and atropine by circumventing the portal blood supply are more effectively absorbed following rectal rather than oral or intramuscular injection[11].

Drug Distribution and Protein Binding

Drugs are distributed into various compartments on entering the bloodstream irrespective of the route of administration. The changes in body composition that occur in the course of development are the major determinants of drug distribution in neonates and children. Pre-term neonates possess 85% of total body weight as total body water compartment compared to 70–75% in term neonates and 50–60% in adults. However, the extracellular water compartment is 20% of body weight in the adult compared to 40% in neonates. Similarly, total body fat in term neonates is 15% of total body weight compared to 1% in pre-term neonates. The clinical significance of above is that

neonates and infants have relatively higher volume of distribution relative to adults given water soluble drugs such as aminoglycosides which are distributed throughout the extracellular water compartment.

Protein binding is a very important determinant of drug distribution. Neonates, particularly pre-terms are at increased risk following change in drug protein interaction. Newborns exhibit decrease in drug protein binding due to decline in plasma concentrations of total protein and albumin. Albumin binds mostly to acidic drugs while alpha$_1$-acid glycoprotein binds mostly to basic drugs. Inflammation, infection, malignant disease and surgery increase the plasma concentration of alpha$_1$-acid glycoprotein[15]. Several drugs bind poorly to neonatal serum since the level of alpha$_1$-acid glycoprotein in neonates is low. A study showed that the binding of both lidocaine and propranolol was significantly elevated in serum obtained from healthy adult controls compared with binding in cord serum[16]. The request for free drug concentration measurements in the pediatric population may be necessary mostly for drugs such as phenytoin which are strongly protein bound. This is in view of the effects of protein binding on the pharmacologically active free unbound fraction, which is of notable clinical significance particularly in highly bound drugs[17-19]. Certain disease conditions such as nephrotic syndrome, malnutrition or severe liver disease results to decreased plasma protein levels, thereby increasing free drug concentration of highly bound drugs leading to increased incidence of adverse effects.

Similarly, the unbound fraction of the drug may increase following competition for plasma protein binding sites, whereas displacement of bilirubin from albumin binding sites may lead to severe neonatal jaundice.

Drug Elimination

Most drug elimination processes follow the first-order elimination kinetics, in which the drug is completely removed from systemic circulation while maintaining the half-life constant. Hepatic metabolism and or/renal excretion are the major processes involved in drug elimination. Metabolism entails the conversion of a parent drug to another compound known as metabolite by chemical reactions while excretion is the removal of materials (drugs) from the body to the external environment.

Hepatic Metabolism

A number of clinically important drugs are metabolized by the microsomal enzyme system, which is subject to influence of many factors including, genetic control[20]. The liver is the major organ for drug metabolism, notwithstanding that other organs such as lungs, gastrointestinal tract, kidney and skin also contain drug metabolizing enzymes. The pharmacokinetics, clinical efficacy and safety profile of a drug in children can be profoundly influenced by the developmental expression profile for the enzymes that support phase I and phase 2 metabolism. The expression profiles of drug metabolizing enzymes from fetal life into adulthood have been well documented[21]. A study predicated on mechanistic-based analysis, revealed that drugs which are solely metabolized by specific cytochrome P450 isoenzymes CYP3A4, CYP1A2 and CYP2C9 in children need weight-corrected doses that are substantially greater than adult doses[22]. It was also noted in the same study that weight–corrected doses for drugs eliminated by renal excretion or metabolism involving CYP2C19, CYP2D6, N-acetyl transferase 2 or uridine 5-diphosphoglucuronosyl transferase (UGT) did not differ significantly in both children and adults[22]. The maturation of drug metabolizing enzymes such as CYP1A2 and CYP3A4; partly involved, for instance, in the metabolism of caffeine and dextromethorphan is diminished in breast-fed rather than formula-fed infants[23].

Water solubility is enhanced by conjugation of a drug with phase 2 metabolizing enzymes such as uridine 5-diphosphoglucuronosyl transferase, sulfotransferase (SULT) and N-acetyl transferase functional groups which are constituted by multiple isoforms, each demonstrating a unique developemental expression profile. Attainment of adult levels within 3 to 6 months following increment immediately after birth has been reported in (UGT1A1)[24]. This contrasts with the 1.5 to 2-fold increase at birth in the levels of glutathione S-transferase (GST) A1 and A2, without any significant changes in adulthood. The various pathways for which a particular drug is a substrate, its therapeutic index and nature are determinants of the impact of developmental drug metabolizing

enzyme expression on drug disposition.

Renal Excretion

The kidney is one of the most important organ systems involved in drug excretion. However, hepatic excretion via bile which is dependent on active transport processes occur, whereas, the kidneys utilize both passive and active transport processes. The multi-drug resistance protein 1 (MDR1), the multi-drug resistance-associated protein 2 (MRP2), the salt export pump and the breast cancer-related protein (BRCP) are the active transporters that mediate efflux into the biliary canaliculus. The situation differs in the kidneys in which MDR and MRP family member transporters mediate efflux into the lumen of the proximal convoluted tubules, whereas the organic anion and cation transporters facilitate influx into the proximal tubular cells. There is age-dependent change in functional capacity of the kidney. The clinical relevance of these changes is more pronounced in such drugs as digoxin, penicillins and aminoglycosides. The value of GFR is 30 to 40% higher in adulthood than in neonates, increasing to 50% by end of the first week of life, 60% by the end of third week and reaches adult value by twelve months. Kidney maturation continues throughout childhood, although nephrogenesis is complete by 36 weeks of gestation. There is lower rate of drug clearance due to impaired renal blood flow in preterm newborns compared to otherwise normal ones. The clinical implication of above emphasizes the need for less frequent dosing interval and lower doses for drugs administered during the neonatal period and need for close monitoring, particularly for drugs with narrow therapeutic index. Certain drugs such as caffeine and theophylline that rely on renal pathways for clearance pending maturity of primary hepatic pathway are typical examples of drugs that demonstrate very slow rates of elimination in pre-mature newborns[25].

Drug Interactions

The concurrent administration of other drugs can significantly modify pharmacological response. The underlying mechanisms of drug interaction can be categorized as pharmacokinetic, pharmacodynamic or both. The oral bioavailability of drugs can be reduced by drug interactions in the gastrointestinal tract. Tetracycline chelates cations such as calcium, iron and magnesium, thereby, effectively reducing its bioavailability. Gastrointestinal motility is influenced by concurrent use of other drugs that have large surface area to which drugs can be adsorbed and may affect transport proteins such as P-glycoprotein. The inhibtion of ABC transporter P-glycoprotein involved in active tubular secretion of certain drugs results to decreased renal excretion leading to concomitant increase in serum drug concentration. The metabolism of other drugs in the pediatric age group may be potentiated or inhibited by certain drugs such as cimetidine, ciprofloxacin, erythromycin and omeprazole known to have inhibitory effects on hepatic drug metabolism. The concomitant use of these agents with a drug that has low therapeutic index such as theophylline, may lead to incidence of adverse effects due to elevation in serum drug concentration of theophylline. Theophylline has been known to be converted to caffeine in human fetuses[26]. Post-conceptional age is quite important in describing theophylline metabolism in neonates. It has been shown that 55 weeks after post-conceptional age, theophylline clearance attained adult values[27].

The steady state concentration of drugs that undergo extensive first pass such as morphine, tricyclic antidepressants, calcium channel blockers and beta blockers may be raised following co-administration of a drug such as cimetidine that reduce hepatic blood flow. The deleterious effect of drug interaction in children can be seen in the excessive rise in plasma concentration of metformin when co-administered with cimetidine, which is known to inhibit the secretion of metformin into the urine[28]. The increased clearance of immunosuppressant drugs, prednisone and cyclosporine, resulting from co-administration with rifampin may be attributed as potential cause of graft rejection in organ transplantation. The plasma concentrations of a number of drugs including metronidazole, chloramphenicol, doxycycline, acetaminophen, warfarin and propranolol co-administered with phenobarbital are reduced, necessitating increment in dose of the index drug. There is, therefore, need for a high index of suspicion amongst practitioners on potential risks of drug interactions in the pediatric age group, particularly in the use of drugs with steep dose-response curve and low therapeutic index.

CONCLUSION

In conclusion, the outcome of this review emphasizes the need for better understanding of changes in developmental pharmacology amongst clinicians, particularly age-related variations in pharmacokinetic processes of absorption, distribution and elimination (metabolism/excretion). This no doubt will breech the gap in knowledge of clinical pharmacokinetics in the pediatric age group, with obvious implications of minimizing adverse drug effects and enhancing clinical response. The need for a physiologically based pharmacokinetic model in designing dosage regimen rather than the traditional "one dose fits all" approach in pediatric practice can never be over-emphasized.

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