



Antibiotics and its altered pharmacokinetics in the pediatric population : An evidence-based review

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ABSTRACT

A better understanding of altered pharmacokinetic variables in the pediatric population is important to improve both the safety and efficacy of drug therapy. Even though pediatric patients are now considered as a special population for drug therapy, it should not give us the wrong idea of considering them like mini-adults. The difference in their pharmacokinetics may be attributed to the radical anatomical and physiological changes that happen with age. Antimicrobials are one of the most prescribed therapeutic agents, and they are used in the treatment of numerous infections. Children are always susceptible to various infections, which often results in their exposure to a wide variety of antibiotics at such an early age. Recent studies showed higher rates of antibiotic prescribing in the pediatric population. The pediatric population requires more attention when prescribing antibiotics due to the increased probability of serious adverse effects, the time required for the complete development of the organs, and augmented drug resistance.

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INTRODUCTION

Pharmacokinetics refers to the time course of drug movement in the body in terms of absorption, distribution, metabolism, and excretion (Charles, 2014). Any variation in any of these processes would have consequences on the pharmacokinetic profile of a drug, especially in the pediatric population, which is known to have unstable pharmacokinetics with age (Ndubuisi and Herbert, 2014). Another significant matter of concern is the increasing antibiotic

resistance among children due to the irrational use of antibiotics (Rogawski *et al.*, 2017; Downes *et al.*, 2014). The practice of scaling adult drug doses to infants and children based on body weight or body surface area also does not account for the developmental changes that affect drug pharmacokinetics or target tissue and organ sensitivity to the drug in children and its essential to understand the changes in the pharmacokinetic parameters (Germovsek *et al.*, 2019; Velde *et al.*, 2018). Only a few data reveal the rational use of antibiotics in pediatric. There is lack of enough data on pharmacokinetics and pharmacodynamics of many drugs in children owing to the limits in obtaining blood sample volumes and age-appropriate formulations for use in pediatric clinical studies (Batchelor and Marriott, 2015). Hence, this review focuses on the altered pharmacokinetics of various antibiotics used in the pediatric population.

MATERIALS AND METHODS

Altered Pharmacokinetics of Few Commonly Used Antibiotics in Pediatrics

Pharmacokinetics of Vancomycin

Vancomycin is widely used for many of the infections that occur in childhood. But its uncertainty still exists regarding the optimum dose and dosing interval of the drug in the pediatric population (Autmizguine *et al.*, 2018). This ambiguity could be explained by the age-related pharmacokinetics of vancomycin (Marqués-Miñana *et al.*, 2010). Vancomycin is a hydrophilic compound, and most of the drug (80-90%) is excreted unchanged in the urine. Hence, the elimination half-life of vancomycin is largely determined by individual renal function (Hoang *et al.*, 2014). The age-related differences in the clearance of vancomycin could be attributed to rapid changes in renal maturation and function in this population. In neonates and infants, the reduced vancomycin clearance is explained by the larger volume of distribution, as a result of their increased body water content and extracellular fluid (Marqués-Miñana *et al.*, 2010). The child's current body weight could also have an impact on vancomycin clearance (Stockmann *et al.*, 2013). A correlation between vancomycin clearance in infants and co-administered drugs such as amoxicillin-clavulanic acid and spironolactone was also found in a study (Marqués-Miñana *et al.*, 2010). Thus, the child's illness state and the co-administered drugs can also alter the pharmacokinetics of vancomycin apart from the known age-related factors. Vancomycin is a time-dependent antibiotic where its concentration must be maintained above minimum inhibitory concentration to ensure its therapeutic efficacy between the two consecutive doses (Levison and Levison, 2009). The targeted trough level for vancomycin is usually 10-20 mg/L. However, many studies conducted show that the current recommended dose of 40-60mg/kg/day as empiric therapy is not sufficient to maintain this therapeutic range of 10-20 mg/L in most of the pediatric population. In patients 1 to 5 months of age and 13 to 18 years of age, a starting dose of 60 mg/kg daily at 6 hour dosing intervals is suggested whereas a higher starting dose of 70 mg/kg daily for patients 6 months to 12 years of age due to the prolonged half-life and resulted in higher clearance of vancomycin seen in this age group (Hoang *et al.*, 2014).

The child to adult ratio of vancomycin clearance and volume of distribution (at steady state) was found to be 0.66 (3.79 /5.66 L/hr) and 1.44 (39.4/27.3 L/kg) respectively. A difference of at least 2- to 3-fold in the clearance of vancomycin within the neonatal age range, is also reported in the literature (Holford *et al.*, 2013). Thus, the altered pharmacokinetics of vancomycin is evident in the pediatric popu-

lation owing to the rapid anatomical and physiological changes that occur in this age, and hence, dosing requires more attention to avoid sub-therapeutic and toxic doses in them.

Pharmacokinetics of Trimethoprim-Sulfamethoxazole

The trimethoprim-sulfamethoxazole combination is widely used in children, though very limited data exist regarding its pharmacokinetics and optimal dosing in children. The trimethoprim requires only smaller doses in infants compared to adults, whereas children require larger doses than adults as a result of its age-related pharmacokinetics. This could be a result of rapid changes in both metabolism and elimination in the newborn child (Hoppu, 1989). The elimination of both trimethoprim and sulfamethoxazole is primarily through renal (Bactrim, 2013), while the remaining portion is metabolized by liver enzymes. The plasma half-life and volume of distribution of TMP-SMX were found to be least in the age group 0-3 years, where they exhibited an increased plasma clearance compared to other age groups. However, these altered values would be nearer to adult values once they reach puberty (Hoppu, 1989). The volume of distribution (V/F) of TMP and SMX in adults is 1.4 -1.8 L/kg and 0.43 L/kg, respectively. However, a great variation was found in V/F of TMP and SMX in pediatrics ranging from 1.4-2.5L/kg (median 2.1 L/kg) and 0.34L/kg each. The value of SMX and TMP clearance (CL/F) would attain 50% of the mature adult value at about 0.12 years (approx.6 weeks PNA) and 0.24 years (approx.13 weeks PNA) respectively (The Pediatric Trials Network Steering Committee, 2017).

The exposure achieved in children after oral administration of TMP-SMX at 8/40,12/60 and 15/75 mg/kg/day at a dosing interval of every 12 h will be parallel with the exposure achieved in adults after administration of TMP-SMX at 20/1,600 mg/day (8/40) and 640/3200mg/day (15/75and 12/60) every 12 hr, respectively. The dose of 8/40mg/kg/day every 12 hours could achieve the PD target for bacteria with an MIC (Minimum Inhibitory Concentration) of 0.5 mg/L in most of the pediatric patients whereas oral administration of TMP-SMX at 12/60 and 15/75 mg/kg/day divided into administration every 12 hours in subjects 6 to _21 years and 0 to 6 years of age respectively, was found to be optimal for bacteria with an MIC of up to 1 mg/L (The Pediatric Trials Network Steering Committee, 2017).

Pharmacokinetics of Gentamicin

Gentamicin's bactericidal activity depends upon its

concentration at the site of action and is considered as a concentration-dependent antibiotic (Lacy *et al.*, 1998). The therapeutic efficacy and adverse effects of gentamicin are correlated to the peak serum concentration and the trough concentrations, respectively (Goda *et al.*, 2016). The risk of nephrotoxicity can be related to the renal cortical aminoglycoside concentration, and ototoxicity is most likely associated with repeated exposures and prolonged courses than to transiently elevated peak concentrations of aminoglycosides >12 mg/L (Garcia *et al.*, 2006).

A wide inter and intra-individual difference exists among neonates that depend on both growth and maturation represented by body weight and GA (gestational age) and PNA (post-natal age), respectively. Extracellular fluid constitutes about 65% of BW at 35 weeks of GA that reduces to 40% at term; this decline in body water continues even after birth, and extracellular fluid becomes closely related to body weight and influences the volume of distribution (Fuchs *et al.*, 2014). They have a larger weight normalized volume of distribution (Bijleveld *et al.*, 2017) and reduced clearance due to the increased intracellular volume and body water content. The gentamicin clearance and volume of distribution was estimated to be 0.0014 l/hr/kg and 0.646 l/kg each, in a population pharmacokinetic study in pediatric population (Goda *et al.*, 2016) whereas the child to adult ratio of volume of distribution and clearance of gentamicin was found to be 0.66 and 1.30, respectively (Holford *et al.*, 2013).

The very preterm newborn requires larger doses and extended dosing intervals compared to the term neonates. The proposed dosing regimens in preterm neonates are 5 mg/kg/48 h and 4 mg/kg/24 or 36h for neonates <32 weeks and >32 weeks of GA, respectively (Goda *et al.*, 2016). A once-daily regimen of gentamicin is preferred compared to the multiple-dose daily dosage regimen due to its comparative efficacy and less potential to cause nephrotoxicity in children (Lacy *et al.*, 1998).

The patient's creatinine clearance, age, current body weight, and disease state has significant correlation with gentamicin kinetics whereas gender did not have any influence on the same (Lacy *et al.*, 1998; Fuchs *et al.*, 2014; Bijleveld *et al.*, 2017). Gentamicin clearance is found to increase with age. Gentamicin pharmacokinetics exhibits clinically significant inter-individual variability among different age groups within the pediatric population. Therefore, therapeutic drug monitoring services and population pharmacokinetic studies could help in optimizing gentamicin therapy in pediatric patients (NCC-

WCH, 2012).

Pharmacokinetics of Amikacin

Amikacin is one of the most commonly used drug either alone or in combination with β -lactams for gram-negative bacterial infections in the pediatric population. However, owing to its narrow therapeutic range and wide inter-individual variability, amikacin dosing in children requires more attention. Amikacin is predominantly eliminated by renal excretion through glomerulus due to its hydrophilic nature as gentamicin (Pacifci and Marchini, 2017a). It should be used with extra caution in preterm infants because of the prolonged serum half-life that could be explained by the renal immaturity in these patients (Siddiqi *et al.*, 2009). In neonates, the half-life of amikacin ranges from 5.9 to 7.6 hours, whereas in adults, it is about 1.3 hours. The pharmacokinetics of amikacin has shown variable drug levels in neonates. Furthermore, the half-life is 7-14 hours in neonates with a postmenstrual age of less than 30 weeks and 4-7 hours at a postmenstrual age of 40 weeks, which indicates the influence of postmenstrual age on prolonged half-life and clearance of amikacin in preterm neonates. It is expected that children who are born premature and/or have intrauterine growth retardation are associated with a slower glomerular filtration rate and a low nephron endowment (Pacifci and Marchini, 2017b). The volume of distribution in children and adults is estimated as 31.7 L/70 kg and 18.9 L/70 kg with a child to adult ratio of 1.5, which indicates a significantly larger V/F in children (Holford *et al.*, 2013).

However, the usual amikacin therapeutic serum concentrations are not ototoxic and nephrotoxic in term neonates. The usual peak levels of amikacin are 20-30 μ g/ml, and trough levels are expected to be <5 μ g/ml, respectively. In neonates, the suggested dose of amikacin is 15 mg/kg. A loading dose of 10 mg/kg followed by a maintenance regimen of 7.5 mg/kg has been proposed during the first 7 days of life while the corresponding doses are 17 mg/kg (loading dose) and 15 mg/kg (maintenance dose) after the first week of life. In neonate's, amikacin clearance was found to have a significant correlation with gestational age, postnatal age, and size (Siddiqi *et al.*, 2009).

A once-daily dosage of amikacin (15 mg/kg per day), with a loading dose of 20mg/kg/day, is preferred over frequent administration and is well tolerated in pediatric patients (1-12 years) due its relative efficacy and reduced potency for renal toxicity (Alqah-tani *et al.*, 2018; Belfayol *et al.*, 1996). The volume of distribution of amikacin is greater in children

than in adults and it is inversely related with age. This interindividual variability in volume of distribution has a direct effect on the targeted therapeutic peak levels and clearance of amikacin (Belfayol *et al.*, 1996). Therefore, an individualized dosage regimen, along with therapeutic drug monitoring, is proposed for amikacin due to its narrow therapeutic index and wide variability in pediatric patients.

Pharmacokinetics of Cefotaxime

Cefotaxime is the drug of choice in the management of numerous infections in neonates, especially meningitis and septicemia caused by gram-negative bacteria.

In neonates, the half-life of cefotaxime is 2 to 6 hours (Pacifci and Marchini, 2017a), whereas in adults, it is about 1.1 hours (Patel *et al.*, 1995). In preterm infants, the half-life is even more prolonged than term infants (Pacifci and Marchini, 2017b). The cefotaxime clearance and volume of distribution in preterm neonates are estimated to be approximately 1.37 ml/min/kg and 0.61 L/kg, whereas in term neonates, the values are 4.45 ml/min/kg and 0.69 L/kg, respectively (Pacifci, 2010).

Cefotaxime is generally well-tolerated in neonates. The pharmacokinetics of cefotaxime is continually changing during the first month of life owing to the maturation of both hepatic and renal function. Thus, the cefotaxime clearance is influenced by post-natal age, gestational age, and renal maturation (Pacifci and Marchini, 2017a). Nevertheless, creatinine cannot be considered as the best marker of cefotaxime clearance in neonates due to the influence of residual maternally derived creatinine. However, the renal pathway is matured by one year of age only, even though the biotransformation pathway is almost matured by 27-28 weeks in term infants (Leroux *et al.*, 2016).

In neonates, the recommended dose of cefotaxime is 25 mg/kg every 6 hours by intravenous or intramuscular administration due to its shorter half-life (Pacifci and Marchini, 2017b). However, dosing regimens of 50 mg/kg BID (twice daily) for newborns with a PNA of <7 days, 50 mg/kg TID for newborns with a PNA of ≥ 7 days and a GA of <32 weeks, and 50 mg/kg QID for newborns with a PNA of ≥ 7 days and GA of ≥ 32 weeks is also found to be effective in neonates with less frequent administration required compared to a 6 hour interval (Leroux *et al.*, 2016).

The disposition of both cefotaxime and diacetyl cefotaxime was found to be altered in children with renal dysfunction, and a dosage adjustment was proposed. A change in dosage interval than in dose

is suggested since the renal disease was found to have no significant impact on the volume of distribution of cefotaxime. A 25 to 50% reduction of dosage in children with moderate renal impairment (CLCR 30 -80 ml/min/1.73 m²) and a 50 to 75% reduction in dosage in children with severe renal impairment (CLCR <30 ml/min/1.73 m²) is suggested to maintain effective therapeutic concentrations of cefotaxime in plasma. However, dosage adjustment must be considered on an individual basis based on each patient's clinical status and renal function (Paap *et al.*, 1991).

RESULTS AND DISCUSSION

Pharmacokinetics of Penicillin G

Penicillin G is widely used in neonatal sepsis due to its high clinical efficacy and safety. But there had been very few data regarding the pharmacokinetics of penicillin G in neonates and infants. Penicillin is hydrophilic compounds that are mainly eliminated by renal excretion. Both renal glomerular filtration and tubular secretion are reduced in a newborn infant, which in turn reduces the disposition of penicillin's and their clearance (Cl) in newborn as compared to children. The clearance is even lower in preterm neonates and is estimated to be 1.7 ml/min/kg (Pacifci, 2010). On the contrary, the volume of distribution (V_d) of penicillin's will be greater in the neonate (0.5 L/kg) than in the adult (0.3 L/kg) (Pacifci, 2010) because of the larger water body content in the newborn infant as observed with cefotaxime and gentamicin (Pacifci *et al.*, 2009; Muller *et al.*, 2007). The half-life ($t_{1/2}$) of penicillin G reduces from 3.2 hours in the first week of life to 1.4 hours in the third week and is influenced by postnatal age and gestational age (Muller *et al.*, 2007). The maturation of renal clearance begins even before the birth and thus explains the influence of gestation age on penicillin clearance. The current body weight also exhibits a positive correlation with drug clearance (Muller *et al.*, 2007). The penicillin half-life is prolonged in very low birth weight infants (4.6 hours) than term neonates and adults (0.5 hours) (Metsvaht *et al.*, 1995).

A dose of 45 to 60 mg/kg and 15 to 30 mg/kg is suggested for the treatment of meningitis and bacteremia, respectively. When the postmenstrual age ranges from ≤ 29 to ≤ 44 weeks, the suggested dosing interval is 8 or 12 hour, and when the postmenstrual age is ≥ 45 weeks, benzylpenicillin may be administered every 6 hours (Pacifci, 2010).

Pharmacokinetics of Azithromycin

Azithromycin exerts a bacteriostatic effect against

many Gram-positive and Gram-negative bacteria (Mcmullan and Mostaghim, 2015). However, oral and intravenous formulations of azithromycin are not recommended for children less than 6 months and 16 years, respectively, due to the lack of adequate clinical studies in this population (Smith et al., 2015).

Azithromycin is administered once daily due to its long half-life. The mean clearance of azithromycin was estimated to be 1.288L/h/kg in a population pharmacokinetic study conducted in children of 2-12 years of age. Another study estimated the clearance and elimination half-life as approximately 0.18L/hr and 58 hours in a preterm neonate of 1 kg compared to 0.95L/kg and 26-83 hours in older children (0.5-16 years) (Hassan et al., 2011). Very few studies have been conducted in this age group; hence, there is a lack of standardized dosing regimen and data on the safety of azithromycin in neonates (Smith et al., 2015).

A loading dose of 15 mg/kg followed by maintenance doses of 10 mg/kg for azithromycin with appropriate dosage adjustment in patients with hepatic dysfunction is proposed by a population pharmacokinetic model (Smith et al., 2015).

Pharmacokinetics of Ciprofloxacin

Ciprofloxacin is used to treat many infections such as complicated urinary tract infections, brucellosis, prostatitis, traveler's diarrhea, respiratory tract infections, etc. However, there are very few data regarding the ciprofloxacin pharmacokinetics in children.

The clearance of ciprofloxacin is significantly lower in new-borns than the other children; however, a wide interindividual variability exists within each age group (Meesters et al., 2018). The postnatal age, current body weight, renal function indicated by serum creatinine concentrations has a significant effect on the clearance of ciprofloxacin in children. The association of renal function and ciprofloxacin clearance is explained by the difference in renal physiological and anatomical maturation since ciprofloxacin is primarily excreted by the kidneys. Ciprofloxacin clearance is increased allometrically with current weight in neonates and young infants and illustrates the independent impact of both gestational and postnatal ages on antenatal and postnatal renal maturation. Fat-free mass and glomerular filtration rate standardized for body surface area may also act as considerable covariates for ciprofloxacin clearance in children (Meesters et al., 2018; Payen et al., 2003; Zhao et al., 2014).

The clearance of ciprofloxacin in children and adults was found to be 29.9 L/hr and 31.9 L/hr with a child to adult ratio of 0.94 whereas V_d was found to be 260 and 154L/kg (child: adult-1.69), respectively (Holford et al., 2013). However, more pharmacokinetics studies are required to design an optimum dosage regimen for ciprofloxacin in the pediatric population.

CONCLUSIONS

Even though it is generally accepted that pharmacokinetics of the drug in children vary from adults, there is no adequate data to provide clear information on the extent of variability and its impact on clinical management of diseases in the pediatric population. Therefore, further pharmacokinetic studies are required to be conducted to design a safe and optimum dosing regimen of antibiotics in children.

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