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Review

Nephrotoxic effects of aminoglycosides on the developing kidney

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Abstract

Aminoglycosides are the most commonly used antibiotics in infants hospitalized in neonatal intensive care units. Despite their outstanding efficacy profile, aminoglycosides remain relatively toxic with a narrow therapeutic index and a potential to cause nephrotoxicity and/or ototoxicity. Although aminoglycoside-induced nephrotoxicity has been the subject of multiple studies, the short- and long-term effect of aminoglycosides administration on the developing kidney of the fetus or premature newborn has not yet been determined. In this review the currently available evidence about the effects of aminoglycosides on the developing kidney and the mechanisms involved in aminoglycoside-induced nephrotoxicity are presented.

Keywords

Aminoglycosides, nephrotoxicity, kidney, infants, fetuses, nephrogenesis.

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Introduction

Aminoglycosides (AGs) belong to one of the oldest classes of antibacterial agents and have been in use since the mid-1940's [1]. Nine different AGs are approved by the US Food and Drug Administration (FDA) for use in adults and four have extensive usage in neonates [2]. AGs remain the drug of choice in many clinical scenarios including neonatal bacterial sepsis and serious gram-negative infections, and they are one of the most commonly reported antibiotics used in the neonatal intensive care unit (NICU) [3-5]. The successful and continuing use of AGs can be attributed to various factors including a rapid concentration-dependent bactericidal effect, synergism with β-lactam antibiotics, a low rate of true resistance and a low cost [6, 7].

The incidence of culture proven neonatal sepsis, in the United States, is approximately 2 to 4 per 1,000 live births [8]. Due to the high case-fatality of sepsis in newborns and also the challenge of its accurate and timely diagnosis, a much larger number of infants are exposed to antibiotics for the diagnosis of presumed sepsis [9]. This has resulted in a high rate of exposure to AGs among the vulnerable population of the NICU [3]. Despite the outstanding efficacy profile of AGs, they remain relatively toxic with a narrow therapeutic index and a potential to cause nephrotoxicity and/or ototoxicity [1, 6].

The AG associated nephrotoxicity has been one of the major drawbacks in the clinical use of these drugs. The reported incidence of functional renal impairment related to AG therapy ranges between 8 to 30% in older age groups [10, 11]. Although the rate of toxicity is not very clear among neonates, tubular damage has been reported in up to 50% of neonates being exposed to AGs [12]. Beside the fear of known glomerular and tubular nephrotoxicity, there has been an increasing worry around the potential short and long-term effect of AGs on the developing kidney if administered during pregnancy or in the early stages of fetal and neonatal development. Up to 12% of newborns are delivered before 34-35 weeks gestation, at a time when glomerulogenesis is still going on [13-15]. The effect of exposure to AG therapy on the morphology, structure and functional characteristics of the developing kidney, during these early stages of life, is not well established.

This review presents the currently available evidence about the effects of AGs on the developing kidney and the mechanisms involved in AG-induced nephrotoxicity.

Pharmacodynamics (PD) and Pharmacokinetics (PK)

Pharmacodynamics

All AGs have a similar structural pattern, composed of amino sugars and saturated carbon rings [1]. The antimicrobial activity of AGs happens through binding of AGs to the 30S ribosomal subunit of the bacteria and consequently interfering with bacterial protein synthesis [1, 16]. AGs are among the concentration-dependent killing antimicrobials with a maximum serum (Cmax) to the minimum inhibitory concentration (MIC) ratio (Cmax/MIC) playing an important role in their antibacterial effect [4, 17]. *In vitro* and *in vivo* studies have shown that after a brief exposure, there is a period of delayed bacterial regrowth for up to 4 hours. Furthermore, after each exposure, there is an interval of resistance to killing that may last for several hours [4, 18, 19].

Although the described PD characteristics of AGs are similar in neonates, older children and adults, the PK characteristics are substantially different.

Pharmacokinetics

Fetus. The data on placental transfer of AGs are derived from a few studies on amikacin, gentamicin, kanamycin and streptomycin [20-23]. All of these drugs follow an incomplete pattern of transfer with initial appearance in the placenta and fetal serum within 30 minutes of maternal administration. The fetal plasma concentrations reach approximately 30 to 50% of the maternal ones in preterm and term fetuses, respectively. Peak serum concentrations are detected 2 hours after administration but in general there is no clear relation between the maternal and fetal serum concentrations [20-22]. Currently available evidence reports a fetal serum half-life of approximately 5 hours. In contrast, a significant increase in the fetal kidney concentration of AGs, to a bactericidal range, for up to 34 hours post single maternal IV administration has been reported. This increase is despite undetectable maternal and fetal serum levels and has not been reflected by either

the fetal serum or fetal urine concentration [20, 24, 25]. The half-life of AGs in the human fetal kidney has not been examined but it's known to reach over 100 hours in animal models [26]. The tissue concentration of AGs at which the initial damage to the developing kidney might occur remains unknown.

Neonate. PK of AGs in neonates is marked by large inter-individual variability necessitating an individualized therapeutic approach [6]. After parenteral administration (30-minute infusion) the peak serum concentration will be reached at the end of that infusion at 0.5 hours (Tmax) [27]. The average volume of distribution of AGs is approximately 0.5 L/kg in term newborns [6]. Extremely premature infants have a significantly higher total body water content with a larger extracellular volume compartment, which results in a larger volume of distribution as compared to their term counterparts [6, 28]. AGs are mainly excreted through the kidney. The elimination half-life of gentamicin is approximately 8 to 10 hours in infants with a gestational age (GA) of 26-34 weeks and around 6 hours in infants with a GA of 35-37 weeks [6]. When corrected for birth weight, GA did not play a significant role in the clearance of gentamicin in preterm or term infants. This finding was further reaffirmed in a study of the PK of amikacin in neonates, which showed that birth weight and postnatal age were the two main determinants of amikacin clearance representing prenatal and postnatal kidney maturation [7, 29, 30]. The presence of a patent ductus arteriosus, the use of Extracorporeal Membrane Oxygenation (ECMO) or coadministration of medications have also been found to change the PK of AGs with both an effect on the volume of distribution as well as the renal clearance [7]. In a study of over 800 newborns of 24-43 weeks gestation, ibuprofen was found to be a major covariate for the prediction of amikacin clearance [30].

Nephrotoxicity

Among all the adverse events related to the use of AGs, nephrotoxicity and ototoxicity present the major limitations for the widespread use of these drugs [6, 7, 31]. The relatively large blood flow to the kidney besides its capacity to extract and concentrate toxic substances make this organ a common target for adverse events of drug therapy [32]. Nephrotoxicity of AGs is known to affect both glomerular and tubular structure and function via immune and non-immune processes [33]. Tubular toxicity can occur in up to 50% of neonates, with variable incidence among population presumably because of immunological differences of individuals [34].

Following glomerular filtration, a small portion of AGs accumulate in the epithelial cells of mainly the proximal, but also distal and collecting tubules for a extended period and results in intracellular alterations, causing damage that can range from loss of the brush border to complete tubular necrosis [33, 35]. Furthermore, AGs cause significant functional damage to the mechanisms involved in water and solute transport, causing tubular luminal obstruction [36].

Besides tubular injury, persistent contraction of the glomerular mesangial cells, cellular apoptosis, proliferation and necrosis have all been described in the histopathological evidence of AGs nephrotoxicity [36-38]. Other contributing factors to the nephrotoxicity of AGs are the generation of free radicals and the decrease of renal blood flow through local enhancement of the vasoconstrictors, blocking the vasodilators and promoting leukocyte margination [39, 40].

In the clinical picture, all the above adverse events, manifest as a non-oliguric renal failure with a slow rise in the serum creatinine, disturbed serum electrolytes and a hypo-osmolar urinary output. The slow repair process of the damaged kidney secondary to the change in the renal growth factors further complicates the adverse events in the rapidly growing newborn [41, 42].

Effects on the developing kidney

Years ago, the kidneys of fetuses and infants were considered less vulnerable to AG toxicity and administration of AGs to pregnant mothers was considered safe [41, 43]. AGs were found to have incomplete pattern of transfer through the placenta and reach only the fully differentiated nephrons, so the kidney of the fetus or the premature newborns, which is still in its phase of nephrogenesis and in need for further maturation, was assumed to be protected [20, 44]. In 1978 for the first time, kidney injury in the fetuses of pregnant mothers who were exposed to AGs during pregnancy was described in the German literature. This report was quickly followed by further evidence, making an argument against the old belief, that although fully differentiated nephrons have the highest susceptibility to the tubular toxicity of AGs, the

damage to the glomeruli can occur regardless of the age of differentiation of the exposed nephrons [45].

It is known that fetal kidney concentrates maternally administered AG for up to 34 hours [24]. High concentrations of gentamicin in the medulla and cortical region of the developing kidney in the animal models in which the pregnant mother received AGs, have been reported for up to 2 weeks after the cessation of the therapy [26]. The fetal kidney concentration of AGs has been found to be far more than any other organs and independent of the maternal or fetal serum or urine concentration [21, 24]. This finding enlightens the fact that obtaining plasma or urine AG concentration is not an accurate indicative of its concentration in the kidney and may not be reflective of the potential kidney injury.

AGs concentrate in different structures of the developing kidney based on their degree of maturity [45, 46]. As the kidney goes through the process of organogenesis, the pattern of distribution of AGs in the developing kidney changes. At the stage when nephrons of deep cortical zone, which develop to juxtamedullary structures, contain mature glomeruli and tubules with considerable concentrating ability, the mid-cortical and sub-capsular zones of the kidney are commonly occupied by nephrons with immature glomeruli and proximal tubules. The evolving maturity of different structures of the developing kidney can result in a variable concentration ability and degree of damage [45].

Besides maturity, the pattern of blood distribution in the developing kidney plays an essential role in the degree of exposure to drug toxicity. Medullary structures of the kidney are the main recipients of blood during early stages of development. As the kidney goes through further development, more blood will be received by the outer cortical structures [45].

The knowledge of the change in concentrating ability and drug exposure of variable parts of the kidney during organogenesis is essential for understanding the pattern of the damage caused by AGs during different stages of kidney development.

Types of injury

Morphological alterations

In utero exposure to even very small amounts of AG has been shown to cause alteration in organogenesis and morphology of the developing kidney [46, 47].

A study of 12 pups born to guina pigs treated with daily injection of gentamicin for 6 days, showed up to 20 and 40% loss in the length of the proximal tubules and glomerular volume of the juxtamedullary nephrons, respectively. Nephrons of the superficial cortex, although they had unchanged length of the proximal tubules, showed up to a 30% decrease in glomerular volume [48].

In a study of newborn rats exposed to high doses of AGs that were administered to their pregnant mothers during the second and third weeks of gestation, changes in birth weight, creatinine clearance or degree of diuresis was observed. The histopathological assessment revealed degenerative changes in the proximal tubules of the juxtamedullary nephrons. Although the prescribed dose of AGs in this study was significantly higher than the doses being used in humans, it was considered to be comparable when corrected for body surface area and glomerular filtration rate differences between fetuses of rats and humans [46]. Furthermore, glomerulogenesis in rats continues until approximately 14 days of life, making the kidney of neonatal rat models similar to that of a 24-week gestation human fetus [49].

Multiple other studies have also shown that administration of AGs to pregnant mothers during the early nephrogenesis period can cause a variable extent of degenerative changes in the glomerular and tubular structure of the developing kidney. Glomerular damage can cause an irreversible reduction in the ultimate number of nephrons [50]. The microscopic evaluation of the kidney of newborn rats exposed to in utero gentamicin, showed a decrease in the mean glomerular volume, the number of differentiated glomeruli and s-shaped bodies. This change was more significant in the nephrons of juxtamedullary zone, which contain more mature structures, and in the kidney of severely growth retarded pups [45].

Functional alterations

The adverse effect of AGs on glomerular and renal tubular function is larger in preterm and small for gestational age infants than in term newborns [29]. The kidney of a premature infant, which is still going through stages of structural and functional development, behaves differently from a mature newborn [7]. Administration of gentamicin, amikacin or netilmicin during the first 10 days of life in premature newborns showed a significant delay in the decline of plasma creatinine, and

alteration in the maturity process of the premature kidney. In contrast, gentamicin was the only AG that had similar effects in full term infants [51, 52]. Gentamicin was found to have a serum peak level-dependent microalbuminuric, natriuric and calciuric effect in preterm neonates, with alteration of sodium, potassium, calcium and magnesium urinary losses immediately after the infusion of the drug [53]. Although these findings could be transient, it is currently unclear if there might be any long-term abnormal functioning of the developing kidney [51, 52]. Furthermore, the functional difference of the premature kidney, with a tendency for loosing salt and the development of negative electrolytes balance adds an additional risk factor for the development of serious functional impairment in the premature newborn.

Long-term effect

Very little is known about the long-term nephrotoxic effect of AGs on the developing kidney. As the structural and functional development of the kidney is an active progress during fetal life and early neonatal period, any exposure to nephrotoxic substances carry the risk of long-term morbidity. The effect of AGs on nephrogenesis and the formation of low nephron endowment has been related to many adult conditions like hypertension, type 2 diabetes mellitus and renal disease. Furthermore, hypertensive individuals are reported to have significantly lower number of nephrons as compared to normotensive controls [54].

Intrauterine growth restricted infants are at particular risk for developmental programming of adult disease. In-utero growth restriction can affect the number of nephrons, the tubular function, the weight of the kidney and its glomerular filtration rate. Small for gestational age infants have also lower drug clearance up to 4 weeks of life as compared to appropriate for gestational age infants [55]. In a study of 69 very low birth weight and extremely low birth weight infants, newborns of extremely low birth weight had significantly lower urinary β_2-microglobulin, a known marker of renal tubular dysfunction, excretion and smaller kidneys compare to extremely low birth weight group [56]. When assessed at pre-school age, the urinary β_2-microglobulin excretion was significantly higher in premature infants who had been treated with AGs immediately after birth [57].

Future data on long-term effect of AGs on the developing kidney can provide us with answers for currently unexplained renal conditions, like kidney failure, chronic mild proteinuria or hypertension that is reported in this vulnerable population later in life [4].

Conclusion

Toxic effect of AGs on the number, size, morphology and function of the glomerular and tubular structure of the developing kidney can interfere with the short- and long-term integrity of the kidney function. The insidious signs and symptoms related to the nephrotoxicity of AGs are often discounted due to the primary complicating clinical scenario of the hospitalized infants. The benefit of AGs administration to pregnant mothers or high-risk infants has to be weighed against the risk of exposure of the developing kidney to its potential adverse effects. Close monitoring of infants with a history of in-utero or early postnatal exposure to AGs is warranted so that early detection of kidney malfunction will be possible. Data is needed to further clarify the extent of short- and long-term morbidities associated with the use of AGs during early life.

Abbreviations

AG: Aminoglycoside; FDA: Food and Drug Administration; NICU: Neonatal Intensive Care Unit; PK: Pharmacokinetics; PD: Pharmacodynamics; MIC: minimum inhibitory concentration; GA: gestational age; ECMO: Extracorporeal Membrane Oxygenation.

Declaration of interest

The Authors declare that they have no conflict of interest to disclose and that they have no financial relationships relevant to this article to disclose.

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