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Drug and herbal medicine-induced nephrotoxicity in children; review of the mechanisms

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ABSTRACT

Acute renal failure (ARF) in children can be induced by different chemical and herbal medications. Different drugs mainly antimicrobials, chemotherapeutic agents, and non-steroidal anti-inflammatory drugs (NSAIDs) have all been shown to be involved in drug-induced renal injury in pediatrics. In addition, the nephrotoxic effects of some medical plants particularly in children have been proven, despite the beneficial features. This review aimed to describe how different drugs could induce nephrotoxicity in pediatric population. We searched the current medical literature through different search databases such as PubMed, Scopus, EMBASE, Cochrane central register of controlled trials, EBSCO, and Google Scholar. The results of this study proved that herbal and chemical drugs induce nephrotoxicity in children by different mechanisms. Their toxicity mainly is related to the necrosis and apoptosis induced by these agents or their derivatives in the renal proximal tubular cells. Due to the importance of using these drugs for life-threatening illness in children, new strategies such as co-administration with other agents or developing new formulations are suggested to be investigated.

Implication for health policy/practice/research/medical education:
Drug-induced acute kidney injury in the pediatric patient is a serious issue. This problem remains an adverse effect on a number of both commonly used herbal and some of the drugs in children.

Introduction

Acute renal failure (ARF) can be traditionally defined as a sudden decline in renal for hours to days. Furthermore, the elevation of serum creatinine level has been considered as ARF which recently was classified by the acute dialysis quality initiative (RIFLE) (1). Although this condition overall not well described in pediatric patients, the incidence of ARF in the pediatric intensive care units has been recorded to range from 8% to 30% (2). Because of development of modern medicine and pharmacotherapy, an expanding variety of drugs are used with diagnostic and therapeutic goals, however some of these drugs lead to wide range of side effects attributed to systemic toxicity, and renal dysfunction (3). The kidney as the main organ of drug excretion receives nearly 25% of resting cardiac output. Comparing with some other organs, the kidney has a major role in drug biotransformation after production of electrophilic toxic metabolites and reactive oxygen species (ROS); which increases the risk of oxidative stress induced

damage and possible injury (4).

On the other hand, several physiological differences such as glomerular filtration rate (GFR), volume of distribution and hepatic clearance can be defined between adults and children. Variations in these physiological factors can affect the pharmacokinetics of a drug eventually resulting in variability in renal toxicity among distinct populations (5).

Among different types of drugs, antimicrobials, angiotensin-converting enzyme (ACE) inhibitors, calcineurin inhibitors, chemotherapeutic agents, and non-steroidal anti-inflammatory drugs have all been shown to be implicated in drug-induced renal injury in pediatrics (2). Proven the beneficial effects, using herbal medicine for the treatment of different types of disease deserves more attention in different committees and even in developed countries in recent years. Besides the beneficial features, the nephrotoxic effects of some medical plants particularly in children have been proven (6).

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This review highlights some of the relevant herbal and chemical drugs and/or drug classes inducing nephrotoxicity in children. For this review, we searched current medical literature through different search databases such as PubMed, Scopus, EMBASE, Cochrane central register of controlled trials, EBSCO, and Google Scholar for keywords such as acute renal failure, drugs, glomerular filtration rate (GFR), children, and nephrotoxicity as published in English.

Antimicrobials-induced nephrotoxicity in children

In this section, we reviewed the nephrotoxic effects of different antimonial drugs and their pathological mechanisms in the pediatric population.

Aminoglycosides

Aminoglycosides (AGs) are related to a class of antibiotics mainly used for management of the gram-negative and *Staphylococcus aureus* infections (7). The most common antibiotics of this class used in pediatric clinical practice are amikacin and gentamicin (8). Recent epidemiological studies based on the widely accepted definitions of ARF for pediatrics, have proposed that acute kidney injury can be induced in 20% to 33% of children exposed to AGs (9).

AG-induced renal toxicity has been defined as a direct effect of drugs on the cells of proximal tubule leading to acute tubular necrosis, characterized by loss of glucose, proteins, enzymes, potassium, calcium, and magnesium (10). Despite a rise in serum creatinine, lack of oliguria has been reported in these patients. In some cases progress of ARF to chronic interstitial nephritis has been indicated (11). Uptake of AG by the proximal tubule cells induces nephrotoxicity; since, AG with a positive charge at physiological pH attaches to the anionic phospholipids located in the proximal tubule cell membrane since this phenomenon leads to accumulation of AG within the cells through endocytosis in a megalin-dependent. Subsequently, AG induced cytotoxicity medicated by a variety of mechanisms such as mitochondrial dysfunction, enhanced lysosomal permeability, proteolysis and disrupted protein sorting. All these pathological events lead to tubular cell death through apoptosis and necrosis (12). AGs have also been shown to be in association with the generation of ROS in renal tissue (13).

Vancomycin

In the pediatric intensive care, vancomycin (VCM) as a bactericidal, glycopeptide antibiotic is commonly used for treatment of methicillin-resistant *Staphylococcus aureus* infections. VCM exposure may be related to increased frequency of renal toxicity (14). The early identification and prevention of VCM-induced ARF in patients is important. Despite the known potential nephrotoxicity, the etiology, true incidence, and risk factors of VCM-induced ARF remain uncertain (15). Initially, the reports of VCM-induced ARF were highly related to impurities in the original formulation (16). The incidence of ARF has been reported between 5% to 43% dependent on the methodology of study, population, and the criteria defined for ARF (17). Furthermore, there are conflicting results regarding the effects of VCM serum levels on the progress of ARF in children (18).

VCM can induce the renal toxicity by different mechanisms. According to the literature, oxidative stress has been introduced as a potential mechanism of renal toxicity induced by VCM, which mainly affects the proximal tubule (19). In an experimental model, Sakamoto et al demonstrated that VCM-related apoptosis in renal tubular epithelial cells was induced via mitochondrial production of ROS with peroxidation of the mitochondrial phospholipid cardiolipin (20). In an *in vitro* study by King and Smith, alterations in the mitochondrial function and dose-dependent proliferation of proximal tubule epithelial cells were observed following treatment with VCM (21).

Amphotericin B

Amphotericin B (AmB) is an antifungal agent for treatment of systematic fungal infection. This drug is the first choice in both children and adults suspected fungal infections (22). In the clinic lipid formulations of AmB such as AmB colloidal dispersion, liposomal AmB (l-AmB), and AmB lipid complex are routine rather than conventional AmB (23). Among different adverse effects, renal toxicity is the most clinically significant one for AmB (22). Despite the fact that AmB deoxycholate (d-AMB) has been used as primary drug for management of fungal infections, its administration to children older than neonates is currently arguable because of its renal toxic properties (24). Liposomal formulations of AmB include l-AmB and AmB lipid complex which appear to be less toxic compared to the other types. This consequence is directly due to the absence of deoxycholate in their structure and is believed to target the endoplasmic reticulum organelles of fungi cells, with less distribution to the kidney. The incidence of nephrotoxicity induced by both liposomal formulations is about 13%, which is lesser than other deoxycholate formulations (25). Conversely, compared to the other protocols, patients receiving cumulative low doses of AmB (<1 g) have been less frequently reported to induce ARF. The risk factors for development of ARF are high daily dosing and prolonged duration of treatment, underlying renal insufficiency, and rapid infusion (25). Toxic feature of AmB is frequently associated with rising serum creatinine, hypomagnesemia, hypokalemia, and a non-anion gap metabolic acidosis, and less commonly with hypernatremia (26).

The mechanism of AmB -induced renal toxicity is not yet well understood. As an extremely toxic agent, this drug causes ARF through tubular cell toxicity (27). AmB indirectly causes toxicity by increasing cell permeability.

This pathologic event occurs by inserting the molecules into the cell membranes and forming some pores. Moreover, this agent may also enhance permeability of the macula densa in the renal distal tubular cells resulting in impairment of the tubule-glomerular feedback system (28). Antifungal efficacy in AmB is associated with binding affinity for ergosterol which its cholesterol-binding properties are thought to be the source of injury (29). Furthermore, d-AmB has been suggested to have direct toxic effects on the tubular cells (30). Continued studies are essential to fully investigate the mechanisms of renal toxicity caused by AmB and its lipid-based formulations.

Non-steroidal anti-inflammatory drugs

NSAIDs as over-the-counter (OTC) medications are one of the most commonly used drugs in the United States and around the world and its administration, especially in children, has increased dramatically during recent years (31). The complications associated with NSAIDs in children is rarely reported. However, one of the most important complication is ARF with an incidence of 2.7% in hospitalized adolescents and children (32).

Two pathological mechanisms have been suggested for NSAIDs induced ARF; the first mechanism is due to hemodynamics alterations (78% cases) and the second one is due to acute interstitial nephritis (AIN, 22% cases) (33). Hemodynamic alterations are accompanied by reduced renal plasma flow due to the prostaglandin reduction, which control vasodilation at the glomerular level. Accordingly, NSAIDs induce disruption in the compensatory vasodilation response of prostaglandins to vasoconstrictor hormones. Subsequently, disturbance in the regulation of renal vascular function results in reduction of GFR which leads to renal ischemia and acute tubular necrosis (32).

Additionally, NSAIDs may change the renal hemodynamic by acting as a cyclo-oxygenase (COX) inhibitor. COX is responsible for producing prostaglandins (from arachidonic acid), which have a vasodilating effect on the afferent glomerular arteriole (34). Additionally, AIN as a second mechanism is characterized by the increased infiltration of inflammatory cells into the renal interstitial tissue. This pathological condition is an immunological reaction after about one week of NSAID exposure (35). Furthermore, it seems that inhibition of COX, shunting the arachidonic acid metabolism, toward the leukotrienes producing pathway since this pathway is important in the activation of the inflammatory response (36). Therefore, attempts have been made to develop the NSAIDs with lesser nephrotoxic effects, while to our knowledge no medication is being evaluated as a preventative measure.

Chemotherapy-induced nephrotoxicity in children

In this review, we focused on some of the chemotherapeutic drugs with nephrotoxic characteristics, which are most relevant in children such as methotrexate (MTX), ifosfamide (IFO), and cisplatin.

Methotrexate

In pediatric medication, MTX is considered to be effective for treatment of acute lymphoblastic leukemia (ALL), osteosarcoma, and lymphomas (37). In children, it has been shown that high dose MTX leads to renal injury (38). Cheng et al conducted a study to identify the risk factors in high-dose MTX-induced ARF in childhood ALL. Their results confirmed that increasing age, higher doses of MTX, lower baseline serum protein, and first high-dose MTX course were significant risk factors for developing ARF in childhood ALL. The threshold of 48 hours MTX plasma level, was shown to be valuable to predict ARF in these patients (39).

According to the literature, nephrotoxicity induced by MTX is directly related to the production of ROS resulting in cell death (40). Additionally, crystal-induced nephropathy can occur due to the low-solubility of MTX and its metabolites in an acidic pH, while they can precipitate within the tubules and cause tubular cell death, tubular obstruction and finally decreasing GFR (41). Risk factors include urinary pH (acidic pH) and hydration (dehydration) status which can facilitate the deposition of crystals in the kidney tissue (42). While 90% of MTX is excreted through urine, decreased GFR may reduce the capacity of MTX exertion, which also leads to toxic systemic concentrations. High doses of MTX decrease the levels of folate within normal cells resulting in toxicity (43). Future studies are essential to perform to show the potential long-term outcome of MTX therapy on the kidney tissue and evaluate possible strategies to mitigate the MTX induced nephrotoxicity.

Ifosfamide

In both children and adults, IFO is used for treatment of solid tumors. According to the literature, this drug can induce different degrees of renal impairment in children (less in adults) with high incidence of 30% (34). Risk factors include age, with the greatest risk for children younger than 5 years, administration of high dose of this drug, history of unilateral nephrectomy, and prior or current platinum therapy (44).

To define the pathological mechanisms of IFO, it generally affects the proximal tubules, explaining why the most severely affected children suffer from Fanconi syndrome leading to diminished growth in children (45). Administration of IFO in 30% of children has been reported to affect glomeruli and lead to reduced GFR. Subsequent metabolic consequences such as renal tubule acidosis (both proximal and distal) and electrolyte disorders, hypophosphatemic rickets, hypokalemia, and diabetes insipidus can be observed in this population (46). IFO induced-renal impairment is usually thought to

be related to the oxidative stress caused by the metabolite chloroacetaldehyde (CAA). This metabolite is produced during the IFO renal biotransformation. Due to the renal ontogeny of enzymes involved in IFO metabolism, younger children are at a high risk of renal toxicity. It has been reported that higher levels of cytochrome P4503A (CYP3A) which is responsible for drug metabolism of IFO to CAA have been observed in the age corresponds to toddlerhood in an animal model (47). After entrance of IFO into the proximal tubule through the human organic cation transporter 2 (hOCT2), the toxic concentrations of CAA (50 μM) can be detected (45). These toxic levels affect the renal proximal tubule cells through the generation of oxidative stress. Both the toxic concentration of CAA and generation of ROS may damage DNA and cellular proteins of proximal tube, results in alterations in the intracellular concentrations of sodium and calcium. These proximal tubular dysfunctions may impair the solute reabsorption and affect synthesis of ATP and result in tubular necrosis (48-50). IFO treatment significantly inhibited oxidative phosphorylation in isolated mitochondria of kidney cortex of rats (51). Additionally, it has been suggested that IFO decreases the viability of cells expressing hOCT2 (human organic cation transporter 2) (52).

Cisplatin

Cisplatin (CIS) or cis-diamminedichloroplatinum (II) is a metallic (platinum) coordination compound with a square planar geometry. With a cure rate of 90% for some cancers, unfortunately, CIS can lead to ARF in 20% to 80% of children (53). Risk factors for CIS induced nephrotoxicity are dehydration, administration of high dose of this drug, concomitant use of other nephrotoxic drugs and hypoalbuminemia. Renal damage caused by CIS is typically persistent in children (54). Studies on the mechanisms of CIS induced renal injury have revealed that S3 segment of the proximal tubule is affected by this agent. Thus, the renal toxicity is generally characterized by increased serum creatinine and decreased GFR, as well as hypokalemia and hypomagnesaemia (55). A complex interaction of mechanisms affecting cell structure and cell signaling pathways and leading to inflammation and tubular cell death (56). CIS is taken up by basolateral OCT2, resulting in production of ROS and activation of signaling pathways, mitogen-activated protein kinase (MAPK), P53 and possibly P21, and leading to renal tubular cell death. An inflammatory response also occurs, likely through activation of tumor necrosis factor-α (TNF-α) receptor 2 by intrinsically produced TNF-α. The most frequent event among all the described damaging pathways is the oxidative stress which appears to acts as both a trigger and the consequence (57).

Herbal medicines-induced nephrotoxicity in children

Beyond the beneficial effects of herbal medicine, extensive studies have been designed to extract and identify active substances of medicinal plants in recent years (58). Given the important effects of these plants, their low-price, lower rate of reported side effects, and adaptation to the environment are the main reasons for using herbal medicines. According to the literature, different types of traditional medicine are used for treatment of various diseases in approximately 80% of people from different communities (59). In infants and children medicinal plants are used for management of certain diseases such as malaria and gastrointestinal diseases (60). Despite fewer adverse effects than chemical drugs, medical plants are not all safe for direct administration in humans, particularly in pediatrics (61). The acute poisoning in children is important and particularly neonates while their immune and digestive systems are not fully developed (62). Findings of a research showed that using herbal products may be associated with mortality especially in children. Although the overall rate of mortality related to plants is low, they are considered as an emergent reason for morbidity and mortality (62). Furthermore, as the toxicological information of different herbs is not available and their antidote therapy has not been introduced yet, plant toxicity attracts greater attention (63). The toxic effects of some plants such as Ephedra species, Aconitum species, Datura species, and Lobelia species have been demonstrated in long-term use particularly in the children (64). Toxicological studies of medicinal herbs on animal models have shown that some of these plants such as daouri and juniper tar, typically used to treat chronic eczema and other skin diseases may have nephrotoxicity or hepatotoxicity, suggesting that these plants particularly should be reevaluated in children (6). In addition, two cases with herbal medicine-induced nephrotic syndrome have been introduced. The nephrotoxicity induced by herb medications containing gypsum (hydrated calcium sulfate), ephedra alkaloids, *Ziziphus jujuba* var. *inermis*, and licorice (the root of *Glycyrrhiza glabra*) in first case and citrus peel, *Inula helenium*, dried trifoliate orange, *Cyperus rotundus* (purple nutsedge), licorice, germander, and ginger in the second case (65).

According to the toxicological studies, some herbs consist of toxic substances, which affect different organs specially kidney function. Unadulterated medicinal herbs induce their renal toxicity by aristolochic acid, known as aristolochic acid nephropathy (66). This renal toxicity is accompanied by Fanconi syndrome with tubular atrophy and significant renal interstitial fibrosis. The severity of renal interstitial fibrosis, notably reduces from the outer side of cortex to the inner side (67). Additionally, swelling of endothelial cells with thickening of afferent and interlobular arterioles is often observed. Urothelial carcinoma has been reported particularly with total *Aristolochia fangchi in* excess cumulative dose (200 g) (68). Moreover, sassafras (*Sassafras albidum*) due to the safrole content and coltsfoot (*Tussilago farfara*), borage (*Borago officinalis*), comfrey (*Symphytum* spp.), and life root

(*Senecio aureus*) due to the pyrrolizidine alkaloid content are suggested to be avoided (69). Furthermore, heavy metal poisoning has been reported in children consuming plant product. Additionally, there is a concern that these toxic levels of heavy metal may be associated with chronic kidney disease too (70). Due to the lack of information associated with the mechanisms of nephrotoxicity induced by herbal medicine in children, extensive studies need to be performed.

Conclusion
Drug-induced acute kidney injury in the pediatric patient is a serious issue. This problem remains an adverse effect on a number of both commonly used herbal and some of the drugs in children. Many of the drugs reported above are extremely important agents for treatment of life-threatening diseases. Most drugs affect the kidney mainly through poisoning the proximal tubular cells, accompanied by necrosis and fibrosis. Given the importance of controlling the diseases in children due to high rate of morbidity and mortality in this population, different researches can be continued to investigate the use of co-administered substances to protect against the toxic effects of chemical drugs. On the other hand, new formulations of drugs with equal impact and less toxicity can be developed.

Authors' contribution
MAD and ZS have made substantial *contributions* to conception. MAD and ZS have been involved in drafting the manuscript or revising it critically for important intellectual content. ZS has given final approval of the version to be published.

Conflicts of interest
The authors declared no competing interests.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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