Western University
Scholarship@Western

Paediatrics Publications | Paediatrics Department

10-1-2015

Drug-induced acute kidney injury in children

Lauren N. Faught
Western University

Michael J.E. Greff
Robarts Research Institute

Michael J. Rieder
Western University, mrieder@uwo.ca

Gideon Koren
Western University

Follow this and additional works at: https://ir.lib.uwo.ca/paedpub

Citation of this paper:
Faught, Lauren N.; Greff, Michael J.E.; Rieder, Michael J.; and Koren, Gideon, "Drug-induced acute kidney injury in children" (2015). *Paediatrics Publications*. 1827.
https://ir.lib.uwo.ca/paedpub/1827

British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12554

Drug-induced acute kidney injury in children

Lauren N. Faught,[1,2] Michael J. E. Greff,[3] Michael J. Rieder[1,4,5,6] & Gideon Koren[1,2,4,6,7,8]

[1]Department of Physiology and Pharmacology, Western University, London, Ontario, [2]Ivey Chair in Molecular Toxicology, Schulich School of Medicine and Dentistry, Western University, London, Ontario, [3]Robarts Research Institute, London, Ontario, [4]Department of Pediatrics, Western University, London, Ontario, [5]CIHR-GSK Chair in Paediatric Clinical Pharmacology, Children's Hospital of Western Ontario, London, Ontario, [6]Department of Medicine, Western University, London, Ontario, [7]Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario and [8]Department of Pharmacology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Correspondence
Professor Gideon Koren MD, Department of Pediatrics, Pharmacology, Pharmacy and Medical Genetics, University of Toronto, Toronto, ON M5G 1X8, Canada.
Tel.: 416 813 5781
Fax: 416 813 7562
E-mail: gkoren@sickkids.ca

Keywords
ADR, antimicrobials, chemotherapeutics, drug-induced AKI, NSAID

Received
24 September 2014
Accepted
12 November 2014
Accepted Article Published Online
13 November 2014

Acute kidney injury (AKI) is a serious problem occurring in anywhere between 8 and 30% of children in the intensive care unit. Up to 25% of these cases are believed to be the result of pharmacotherapy. In this review we have focused on several relevant drugs and/or drug classes, which are known to cause AKI in children, including cancer chemotherapeutics, non-steroidal anti-inflammatory drugs and antimicrobials. AKI demonstrates a steady association with increased long term risk of poor outcomes including chronic kidney disease and death as determined by the extent of injury. For this reason it is important to understand the causality and implications of these drugs and drug classes. Children occupy a unique patient population, advocating the importance of understanding how they are affected dissimilarly compared with adults. While the kidney itself is likely more susceptible to injury than other organs, the inherent toxicity of these drugs also plays a major role in the resulting AKI. Mechanisms involved in the toxicity of these drugs include oxidative damage, hypersensitivity reactions, altered haemodynamics and tubule obstruction and may affect the glomerulus and/or the tubules. Understanding these mechanisms is critical in determining the most effective strategies for treatment and/or prevention, whether these strategies are less toxic versions of the same drugs or add-on agents to mitigate the toxic effect of the existing therapy.

Introduction

Acute kidney injury (AKI) can be described as the sudden decrease in renal function over a variable period of time (hours to days) and can be caused by numerous aetiologies [1]. While overall not well defined in children, the incidence of AKI in the paediatric intensive care units is reported to range from 8% to 30% and is thought to occur in roughly 7% of the general paediatric population [2, 3]. Pharmacotherapy is one of the major causes of AKI and may play a causative role in as many as 25% of all cases [4, 5]. Drugs including antimicrobials, chemotherapeutic agents and non-steroidal anti-inflammatory drugs (NSAIDs), among others, have all been implicated in drug-induced renal injury in children [2].

We chose to focus this review on drug-induced toxicity in children as drugs that are renally toxic in children may, but not always, differ from those that are toxic in adults. There are several physiological differences between adults and children that may account for variability in renal toxicity including volume of distribution, glomerular filtration rate (GFR), clearance and expression of hepatic and renal cytochrome P450 enzymes. Variations in these parameters can affect the pharmacokinetics of a drug ultimately resulting in different systemic concentrations of a possible renal toxin among distinct populations. Therefore in some cases this will result in increased exposure to a renal toxin in children increasing their susceptibility to injury, or it may decrease their exposure as compared with adults therefore protecting them [6, 7].

The extent to which drugs play a role in AKI may be explained by the increased vulnerability of the kidney to damage by drugs [4]. The kidney receives nearly 25% of resting cardiac output and is a major organ of drug excretion. It is exposed to a larger proportion and higher concentration of toxic drug than most other organs (due to the concentrating role of the kidney), putting it at greater risk for injury [1, 8, 9]. Additionally, toxicity in the proximal

© 2014 The British Pharmacological Society

tubule specifically may be increased due to its role in both secretion and reabsorption, allowing for accumulation of toxic species within the cell [8]. Adding further to the disadvantage of the kidney compared with some other organs is its major role in drug biotransformation during which electrophilic toxic metabolites and reactive oxygen species (ROS) may be produced; increasing levels of oxidative damage and possible injury [8, 10].

The pathophysiology of AKI is complicated. It can generally be grouped into pre-renal, intrinsic (glomerular, interstitial, vascular and tubular injury) and post-renal causes. The gold standard to diagnose these injuries is kidney biopsy. However, it is not always feasible and the risk might out-weigh the benefits, as it will not always alter the management. By contrast, some tests might help differentiate the causes of renal injuries. For example, nephrotic range proteinuria, haematuria and red blood cell casts are signs of glomerular injury, whereas urinary electrolytes, glucose and protein wasting may be a sign of tubular injury. For example, proximal tubular injury like Fanconi syndrome can lead to sodium, magnesium, phosphate, glucose, uric acid, amino acid and bicarbonate wasting. Other urinary biomarkers, such as β_2-microglobulin and neutrophil gelatinase-associated lipocalin (NGAL) have been investigated extensively in the area of acute tubular necrosis (ATN). Renal injury caused by drugs is complex and may often be a combination of both glomerular and tubular toxicity. It is important to identify the disease early because it might be reversible by stopping the offending agents. Patients who developed AKI are more likely to have increased risk of mortality and increased incidence of chronic kidney disease, and the poor prognostic factor for chronic kidney disease is related to the magnitude and the recurrence of AKI [11]. One of the challenges in AKI is to define the disease and recognize it early.

In an effort to prevent AKI in children an obvious solution would be to avoid the use of renally toxic drugs altogether, particularly in those at high risk of developing renal injury. The answer, however, is not so simple. Many of these drugs are used in the treatment of life-threatening conditions for which no alternative therapies exist. The benefits of these drugs to the patient often outweigh the potential risk and while dose adjustments can be made in an effort to prevent future or continued renal insult other strategies should also be considered. Given the increasing understanding of the underlying mechanisms involved in the toxicity of many of these drugs, one has the ability to develop more effective treatment and prevention strategies, some of which are available or are currently being researched.

This paper reviews some of the relevant drugs and/or drug classes whose adverse effects in children include AKI. We discuss known mechanisms of toxicity, as well as current or experimental treatments and/or prevention strategies.

Cancer chemotherapeutics

Cancer chemotherapeutics are among the most common offenders in drug-induced kidney toxicity [8]. The use of these agents in combination has the potential to potentiate the dangerous effects of typical renal toxic drugs [9, 12]. While the list of chemotherapeutic drugs that have been implicated in renal injury is lengthy, this review will focus on those most relevant in children including ifosfamide, cisplatin and methotrexate [13, 14].

Ifosfamide

Ifosfamide (IFO) is used in the treatment of solid tumours in both children and adults [15–18]. While not necessarily first line, it is included in many paediatric chemotherapy protocols [19–24]. It is particularly relevant in this discussion due to the high incidence of renal impairment seen in children but less commonly in adults, with 30% of children treated with IFO suffering some degree of renal impairment. Generally the proximal tubule is main site of toxicity (Table 1), explaining why the most severely affected children suffer from Fanconi syndrome [25–28]. The glomerulus can also be affected with 30% of children developing reduced GFR [26, 27, 29, 30]. These impairments may lead to clinical manifestations including hypophosphataemic rickets, renal tubule acidosis (both proximal and distal), diabetes insipidus and hypokalaemia [31–34]. Treatment may include renal supportive care such as dialysis and/or renal transplant and in the case of hypophosphataemic rickets supplementation with phosphate and bicarbonate [25]. In the case of IFO renal toxicity, tubulopathies and glomerular toxicity have shown little to no improvement over time [26, 35]. Risk factors include age, with those younger than age 5 years being at the greatest risk, cumulative dose, prior unilateral nephrectomy and importantly, prior or current platinum therapy [9, 12, 36, 37].

Nephrotoxicity caused by IFO is generally believed to be the result of oxidative stress caused by the metabolite chloroacetaldehyde (CAA) produced during its biotransformation in the kidney. Younger children are at a greater risk of kidney toxicity due to the renal ontogeny of those enzymes responsible for IFO metabolism. Higher levels of

Table 1

Classification of acute kidney injury

Drug	Type of injury
Ifosfamide	Direct tubular toxicity
Cisplatin	Direct tubular toxicity
Methotrexate	Obstructive crystal nephropathy and direct tubular toxicity
NSAIDs	Pre-renal and acute interstitial nephritis
Aminoglycosides	Direct tubular toxicity
Amphotericin	Direct tubular toxicity

CYP 3A, which metabolizes IFO to CAA, have been observed in an animal model whose age corresponds to toddlerhood [38, 39]. It appears that IFO enters the proximal tubule via the blood stream through the organic cation transporter 2 (OCT2) resulting in toxic CAA concentrations (50 μM) [40–43]. Toxic levels of CAA have detrimental effects on renal proximal tubule cells likely through the generation of oxidative stress. Both CAA and reactive oxygen species (ROS) may damage cellular proteins and DNA, result in changes in sodium and calcium intracellular concentrations leading to impaired solute reabsorption and necrosis, respectively, affect ATP synthesis and critically, result in a depletion of glutathione [44–48].

With an indication of the mechanisms involved being oxidative damage and glutathione depletion, antioxidants have been assessed as a preventive measure in animal models including l-histidinol, taurine, thymoquinone, resveratrol, melatonin, glycine and N-acetylcysteine (NAC) [45, 47, 49–53]. NAC stands out among the potential therapeutic agents given its clinical use in children for paracetamol (acetaminophen) overdose, providing a wealth of safety data, as well as its documented use to prevent IFO nephrotoxicity in patients [54]. Early *in vitro* and *in vivo* animal studies have shown the effectiveness of NAC in preventing IFO toxicity, as well its lack of interference on the antineoplastic effects of IFO. These findings have been supported by three clinical experiences [45, 55–59], although randomized controlled trials (RCTs) are required to assess the role NAC played in protection of the kidney in the published cases. Given the promise of antioxidants, and in particular NAC, further research needs to be carried out to determine which potential treatments are the most clinically useful.

Cisplatin

With a cure rate of 90% for some cancers, cisplatin (CIS) is an effective paediatric chemotherapeutic agent that has clear benefits [60–62]. However, AKI, present in 20%–80% of children treated with CIS, is an adverse effect that may limit its tolerable dose levels [61, 63]. CIS affects the S3 segment of the proximal tubule and nephrotoxicity is generally marked by increased serum creatinine and a decreased GFR, along with hypomagnesaemia and hypokalaemia [13, 63–65]. Risk factors include cumulative dose, dehydration, concomitant use of other nephrotoxic drugs and hypoalbuminemia. Renal damage caused by CIS is typically persistent in children [13, 66]. Treatment includes general supportive care for AKI and magnesium supplementation in the case of hypomagnesaemia [67].

The study of CIS renal injury has revealed a complex interaction of mechanisms affecting cell structure and cell signalling pathways [61]. Simply put, CIS is taken up by basolateral OCT2, resulting in production of ROS and activation of signalling pathways, mitogen-activated protein kinase (MAPK), P53 and possibly P21, leading to renal tubular cell death. An inflammatory response also occurs, likely through activation of tumour necrosis factor-α (TNF-α) receptor 2 by intrinsically produced TNF-α. Oxidative stress appears to be both the driving force and end result of some of these changes [61, 68].

Identifying these targets has allowed for evaluation of a number of compounds in preventing this nephrotoxicity. Cimetidine has been assessed in an attempt to prevent renal transport and accumulation of CIS, as has erythropoietin to block apoptosis and quercetin to prevent inflammation [61, 68]. However, the most exploited mechanism in attempts to prevent CIS nephrotoxicity, is oxidative stress. Numerous anti-oxidants have been assessed to thwart the effects of oxidative stress caused by CIS including, but not limited to, amifostine, NAC, sodium thiosulfate and theophylline [69–73]. While NAC and sodium thiosulfate have not been assessed in RCTs, both amifostine and theophylline have. Theophylline was effective in some trials but not in others [69, 74]. Similarly, amifostine was effective in reducing nephrotoxicity from 30% to 10% in a trial of women with ovarian cancer but not so in a trial assessing CIS-induced nephrotoxicity in children with osteosarcoma [70, 71]. Guidelines of the American Society of Clinical Oncology support the use of amifostine in ovarian or non-small cell lung cancers treated with CIS, but not for other types of cancer [75].

Methotrexate

The nephrotoxic drug methotrexate (MTX) has a wide range of use owing not only to its anti-proliferative but also its immunomodulating effects. It is particularly important for children as an effective treatment for acute lymphoblastic leukemia [2, 76–78]. It is used in either low or high dose regimens, with only high dose regimens resulting in AKI. The overall incidence of AKI caused by high dose MTX is around 2% [79, 80].

Mechanistically AKI caused by high dose MTX is similar to CIS and IFO in that direct drug toxicity is also thought to occur via ROS resulting in cellular damage [78, 80, 81]. However MTX is distinct in that it may also result in crystal nephropathy. MTX and its metabolites can precipitate within the tubules due to their low solubility in an acidic pH resulting in tubular obstruction, leading to decreased GFR and tubular cell death [8, 80, 82, 83]. Risk factors include hydration status and urinary pH, with those who are dehydrated or have an acidic pH being at greatest risk. Unilateral nephrectomy and concomitant use of renal toxic drugs are also risk factors [8, 14].

With respect to long term consequences, MTX AKI is completely reversible and therefore the primary concern with its use may not be its transient renal effects but rather the effect of decreased GFR on MTX renal clearance rate and serum concentrations. High MTX concentrations reduce folate concentrations within normal cells resulting in toxicity [8, 78]. 90% of MTX is excreted renally and therefore decreased GFR diminishes the capacity to excrete MTX, resulting in toxic systemic concentrations. Prolonged

transient effects increase the risk of organ damage. However, the long term effects on the kidney have yet to be properly evaluated and may be cause for concern, as well [8, 78].

With respect to prevention and treatment strategies, AKI caused by MTX can be reduced, although not completely mitigated with hydration and urine alkalinization strategies [80, 84]. These strategies prevent the concentration of MTX from becoming too high in the tubules, as well as increase its solubility, which is pH dependent. Toxic systemic concentrations of MTX, brought on by AKI must also be addressed. Currently leucovorin is routinely administered approximately 24–36 h after MTX, allowing for rescue of normal tissues from MTX toxicity by replenishing folate concentrations [79, 80]. Glucarpidase has also recently been approved for use in patients with elevated MTX plasma concentrations. This agent cleaves MTX into two non-toxic metabolites and can decrease its concentration by more than 95% in a mere 15 min. It does not, however, have any effect on intracellular concentrations of MTX [79]. While the current means of reducing AKI and systemic toxicity caused by MTX are quite effective, future research is necessary to address both the possible long term outcome of MTX therapy on the kidney, as well as possible strategies allowing for complete mitigation of its renal toxicity.

NSAIDS

NSAIDS are commonly used in children as analgesics, antipyretics and anti-inflammatory medications. Indomethacin, in particular, is an important treatment for patent ductus arteriosis in infants [85, 86]. NSAIDS are widely available putting large numbers of people at risk for their adverse effects. One such adverse effect is AKI, with an incidence of 2.7% in hospitalized children and adolescents [87].

There are two mechanisms through which NSAIDs cause AKI, changes in haemodynamics and acute interstitial nephritis (AIN). The former is thought to account for 78% of cases of AKI, while the latter accounts for 22% [87]. NSAIDs may alter haemodynamics by acting as cyclooxygenase (COX) inhibitors. COX is responsible for producing prostaglandins (from arachidonic acid), which have a vasodilating effect on the afferent glomerular arteriole. While it is unlikely that prostaglandins have much impact on children with normal circulating volume, in individuals with volume depletion, their role as vasodilators becomes more important to maintain adequate renal perfusion. Blocked prostaglandin synthesis leads to unchecked vasoconstriction of the afferent arteriole, resulting in reduced GFR and eventually renal ischaemia and acute tubular necrosis [2, 87–89].

AIN it thought to occur as a result of COX inhibition shunting the metabolism of arachidonic acid to the pathway producing leukotrienes, which are involved in the activation of the inflammatory response [90]. Along with AKI, patients may also, although rarely, present with manifestations of systemic hypersensitivity reactions. Children receiving NSAIDs may also present with nephrotic syndrome [91, 92]. Treatment of haemodynamically driven AKI includes normal supportive care, while corticosteroid treatment may be used in AIN. While patients generally recover, one study has shown approximately 30% of children have persistent mild chronic kidney damage [91]. Preventative strategies include avoiding NSAIDs and/or monitoring those at high risk, including children with volume depletion, pre-existing renal disease, or concomitant use of other nephrotoxic drugs [85]. While attempts have been made to develop NSAIDs that are less nephrotoxic, to our knowledge no pharmacotherapy is being evaluated as a preventative measure.

Antimicrobials

A variety of different antimicrobials can cause AKI, in particular aminoglycosides and amphotericin B.

Aminoglycosides

Aminoglycosides (AGs) are a class of antibiotics used in the treatment of Gram negative and *Staphylococcus aureus* infections [93, 94]. They include antibiotics such as gentamicin and amikacin. In children they are implicated in AKI at a rate of 10% to 30% [1, 95]. There are conflicting reports as to whether neonates are at an increased or decreased risk for AG nephrotoxicity [2, 96]. Patients may present with oliguric AKI, along with proximal tubule dysfunction, resulting in loss of enzymes, proteins, glucose, calcium, potassium and magnesium. Most patients may recover but some progress to chronic interstitial nephritis [97]. Risk factors for AKI resulting from AGs are underlying renal insufficiency, duration of therapy greater than 10 days, trough concentrations greater than 2 $\mu g\ ml^{-1}$, concomitant liver disease and hypoalbuminaemia [98].

AG-induced renal toxicity occurs as a result of its uptake by the proximal tubule cells. With a positive charge at physiological pH AGs bind anionic phospholipids within the proximal tubule cell membrane. AGs are endocytosed in a megalin-dependent fashion resulting in accumulation within the cell. With accumulation primarily in the S1 and S2 segments [2, 99], AKI occurs via tubular cytotoxicity caused by a variety of routes including increased lysosomal permeability, mitochondrial dysfunction, proteolysis and disrupted protein sorting leading to death via both apoptosis and necrosis [1]. AGs have also been implicated in the production of ROS. Cytosolic AGs act on mitochondria directly and indirectly, and thus activate the intrinsic apoptotic pathways, interrupt the respiratory chain, impair ATP production and produce oxidative stress by increasing superoxide anions and hydroxyl radicals

[100–102]. Renal toxicity associated with various AGs is correlated with the affinity of each drug for the proximal tubule cell [103–105].

Prevention strategies for AG AKI include using extended dosing intervals, administering during active periods of the day, limiting the duration of therapy, monitoring serum drug concentrations and renal function two to three times per week and maintaining trough concentrations of less than or equal to 1 $\mu g\ ml^{-1}$ [98]. While not currently used clinically, several compounds have been assessed in the prevention of AG renal toxicity. Anionic polyamino acids are able to interfere with AG's binding to the proximal tubule cell, while several antioxidants including selenium, vitamin A and vitamin C have been successful in mitigating AG toxicity in experimental models. More research is necessary to determine the potential clinical usefulness of these strategies [106, 107].

Amphotericin B

Amphotericin B (AmB) is an antifungal agent, which is the drug of choice in immuno-compromised children [2]. While extremely toxic to the kidney, causing AKI via tubular cell toxicity, its common use for life-threatening fungal infections contributes to its mainstay in antifungal therapy [108]. Some degree of decreased renal function has been reported in up to 80% of patients undergoing therapy and the reported incidence of AmB-induced AKI increases with the cumulative dose delivered [109, 110]. On the contrary patients receiving cumulative low doses of AmB of less than 1 g have been reported to develop renal failure less frequently. Risk factors for AmB-induced AKI include underlying renal insufficiency, rapid infusion, large daily dosing and prolonged duration of therapy [109].

The mechanism by which AmB exerts is toxicity is not well understood. AmB can increase cell permeability by inserting itself into membranes and forming pores. It may also increase permeability in the macula densa of the distal tubule resulting in dysregulation of the tubuloglomerular feedback system. Deoxycholate, a component of AmB is also thought to be responsible for direct toxicity to the tubules [98, 111–113]. Prevention strategies include saline hydration before and after drug administration, use of liposomal formulations, limiting the duration of therapy, and considering a continuous low dose infusion over a 24 h period rather than a large dose at set intervals [98].

Liposomal formulations include liposomal AmB and AmB lipid complex. Lipid formulations appear to be less renally toxic as they do not contain deoxycholate and are thought to preferentially target fungi within the endoplasmic reticulum, with less delivery to the kidney. The rate of nephrotoxicity by both AmB lipid complex and liposomal AmB is approximately 13%, which is considerably lower than formulations with deoxycholate [109, 114]. Continued research is necessary in order to mitigate fully renal toxicity caused by AmB and its lipid based formulations.

Conclusion

Drug-induced AKI is a serious problem. As outlined above, it remains a side effect for a number of both commonly used and important drugs for children. While ultimately avoidance of renally toxic drugs, especially in those most at risk, is best, it is also unlikely. Many of the drugs presented above are extremely effective agents for potentially life-threatening illnesses and unfortunately alternative therapies do not always exist. There are, however, other options to this dilemma. We can continue the research and use of other co-administered agents, which will protect against the toxic effects of some drugs. Alternatively, developing newer formulations with equal effectiveness but less toxicity may be the best approach. Examples of both have been described above. In either scenario, an understanding of the mechanisms underlying the toxicity caused by these drugs is our best hope in developing successful treatment and prevention strategies. While for some drugs we have begun to understand even the most complex mechanisms at play, others still remain unclear. Continued research in the area surrounding mechanisms of adverse drug reactions is imperative to our advancement in continuing to predict, treat and ultimately prevent these serious adverse events.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work and no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. LNH, MJR and GK have carried out and published work regarding the protective role of N-acetylcysteine for ifosfamide-induced AKI.

We would like give special thanks to nephrologist Dr Susan Huang for providing us with feedback for this paper.

REFERENCES

1 Tiong HY, Huang P, Xiong S, Li Y, Vathsala A, Zink D. Drug-induced nephrotoxicity: clinical impact and preclinical *in vitro* models. Mol Pharm 2014; 11: 1933–48.

2 Patzer L. Nephrotoxicity as a cause of acute kidney injury in children. Pediatr Nephrol 2008; 23: 2159–73.

3 Chan JC, Williams DM, Roth KS. Kidney failure in infants and children. Pediatr Rev 2002; 23: 47–60.

4 Decloedt EM, Maartens G. Drug-induced renal injury. CME 2011; 29: 252–5.

5 Bentley ML, Corwin HL, Dasta J. Drug-induced acute kidney injury in the critically ill adult: recognition and prevention strategies. Crit Care Med 2010; 38: (6 Suppl.): S169–74.

6 Chen N, Aleksa K, Woodland C, Rieder M, Koren G. Ontogeny of drug elimination by the human kidney. Pediatr Nephrol 2006; 21: 160–8.

7 Routledge PA. Pharmacokinetics in children. J Antimicrob Chemother 1994; 34: (Suppl. A): 19–24.

8 Perazella MA, Moeckel GW. Nephrotoxicity from chemotherapeutic agents: clinical manifestations, pathobiology, and prevention/therapy. Semin Nephrol 2010; 30: 570–81.

9 Goren MP, Wright RK, Pratt CB, Horowitz ME, Dodge RK, Viar MJ, Kovnar EH. Potentiation of ifosfamide neurotoxicity, hematotoxicity, and tubular nephrotoxicity by prior cis-diamminedichloroplatinum(II) therapy. Cancer Res 1987; 47: 1457–60.

10 Lohr JW, Willsky GR, Acara MA. Renal drug metabolism. Pharmacol Rev 1998; 50: 107–41.

11 Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012; 81: 442–8.

12 Rossi R, Godde A, Kleinebrand A, Riepenhausen M, Boos J, Ritter J, Jurgens H. Unilateral nephrectomy and cisplatin as risk factors of ifosfamide-induced nephrotoxicity: analysis of 120 patients. J Clin Oncol 1994; 12: 159–65.

13 Fujieda M, Matsunaga A, Hayashi A, Tauchi H, Chayama K, Sekine T. Children's toxicology from bench to bed–Drug-induced renal injury (2): nephrotoxicity induced by cisplatin and ifosfamide in children. J Toxicol Sci 2009; 34: (Suppl. 2): SP251–7.

14 Jones DP, Spunt SL, Green D, Springate JE, Children's Oncology Group. Renal late effects in patients treated for cancer in childhood: a report from the Children's Oncology Group. Pediatr Blood Cancer 2008; 51: 724–31.

15 de Kraker J. Ifosfamide in pediatric oncology. Anticancer Drugs 1991; 2: 339–41.

16 Nattional Cancer Institute. PDQ Adult Soft Tissue Sarcoma Treatment. Bethesda, MD: National Cancer Intitute, Date last modified 02/28/ 2014 Available at http://www.cancer.gov/cancertopics/pdq/treatment/adult-soft-tissue-sarcoma/Patient/page1 (last accessed 3 January 2014).

17 Dechant KL, Brogden RN, Pilkington T, Faulds D. Ifosfamide/mesna. A review of its antineoplastic activity, pharmacokinetic properties and therapeutic efficacy in cancer. Drugs 1991; 42: 428–67.

18 Tascilar M, Loos WJ, Seynaeve C, Verweij J, Sleijfer S. The pharmacologic basis of ifosfamide use in adult patients with advanced soft tissue sarcomas. Oncologist 2007; 12: 1351–60.

19 Breitfeld PP, Lyden E, Raney RB, Teot LA, Wharam M, Lobe T, Crist WM, Maurer HM, Donaldson SS, Ruymann FB. Ifosfamide and etoposide are superior to vincristine and melphalan for pediatric metastatic rhabdomyosarcoma when administered with irradiation and combination chemotherapy: a report from the Intergroup Rhabdomyosarcoma Study Group. J Pediatr Hematol Oncol 2001; 23: 225–33.

20 Cairo MS. The use of ifosfamide, carboplatin, and etoposide in children with solid tumors. Semin Oncol 1995; 22: (3 Suppl. 7): 23–7.

21 Granowetter L, Womer R, Devidas M, Krailo M, Wang C, Bernstein M, Marina N, Leavey P, Gebhardt M, Healey J, Shamberger RC, Goorin A, Miser J, Meyer J, Arndt CA, Sailer S, Marcus K, Perlman E, Dickman P, Grier HE. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. J Clin Oncol 2009; 27: 2536–41.

22 Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, Gebhardt MC, Dickman PS, Perlman EJ, Meyers PA, Donaldson SS, Moore S, Rausen AR, Vietti TJ, Miser JS. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003; 348: 694–701.

23 Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, Swift P, Shimada H, Black CT, Brodeur GM, Gerbing RB, Reynolds CP. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. N Engl J Med 1999; 341: 1165–73.

24 Sandler E, Lyden E, Ruymann F, Maurer H, Wharam M, Parham D, Link M, Crist W. Efficacy of ifosfamide and doxorubicin given as a phase II 'window' in children with newly diagnosed metastatic rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. Med Pediatr Oncol 2001; 37: 442–8.

25 Loebstein R, Koren G. Ifosfamide-induced nephrotoxicity in children: critical review of predictive risk factors. Pediatrics 1998; 101: E8.

26 Skinner R. Chronic ifosfamide nephrotoxicity in children. Med Pediatr Oncol 2003; 41: 190–7.

27 Prasad VK, Lewis IJ, Aparicio SR, Heney D, Hale JP, Bailey CC, Kinsey SE. Progressive glomerular toxicity of ifosfamide in children. Med Pediatr Oncol 1996; 27: 149–55.

28 Rossi R, Godde A, Kleinebrand A, Rath B, Jurgens H. Concentrating capacity in ifosfamide-induced severe renal dysfunction. Ren Fail 1995; 17: 551–7.

29 Skinner R, Pearson AD, English MW, Price L, Wyllie RA, Coulthard MG, Craft AW. Risk factors for ifosfamide nephrotoxicity in children. Lancet 1996; 348: 578–80.

30 Ashraf MS, Skinner R, English MW, Craft AW, Pearson AD. Late reversibility of chronic ifosfamide-associated nephrotoxicity in a child. Med Pediatr Oncol 1997; 28: 62–4.

31 Smeitink J, Verreussel M, Schroder C, Lippens R. Nephrotoxicity associated with ifosfamide. Eur J Pediatr 1988; 148: 164–6.

32 Ashraf MS, Brady J, Breatnach F, Deasy PF, O'Meara A. Ifosfamide nephrotoxicity in paediatric cancer patients. Eur J Pediatr 1994; 153: 90–4.

33 DeFronzo RA, Abeloff M, Braine H, Humphrey RL, Davis PJ. Renal dysfunction after treatment with isophosphamide (NSC-109724). Cancer Chemother Rep 1974; 58: 375–82.

34 Elias A, Ryan L, Sulkes A, Collins J, Aisner J, Antman KH. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. J Clin Oncol 1989; 7: 1208–16.

35 Skinner R, Parry A, Price L, Cole M, Craft AW, Pearson AD. Glomerular toxicity persists 10 years after ifosfamide treatment in childhood and is not predictable by age or dose. Pediatr Blood Cancer 2010; 54: 983–9.

36 Loebstein R, Atanackovic G, Bishai R, Wolpin J, Khattak S, Hashemi G, Gobrial M, Baruchel S, Ito S, Koren G. Risk factors for long-term outcome of ifosfamide-induced nephrotoxicity in children. J Clin Pharmacol 1999; 39: 454–61.

37 Skinner R, Cotterill SJ, Stevens MC. Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. United Kingdom Children's Cancer Study Group. Br J Cancer 2000; 82: 1636–45.

38 Aleksa K, Halachmi N, Ito S, Koren G. Renal ontogeny of ifosfamide nephrotoxicity. J Lab Clin Med 2004; 144: 285–93.

39 Aleksa K, Woodland C, Koren G. Young age and the risk for ifosfamide-induced nephrotoxicity: a critical review of two opposing studies. Pediatr Nephrol 2001; 16: 1153–8.

40 Ciarimboli G, Holle SK, Vollenbrocker B, Hagos Y, Reuter S, Burckhardt G, Bierer S, Herrmann E, Pavenstadt H, Rossi R, Kleta R, Schlatter E. New clues for nephrotoxicity induced by ifosfamide: preferential renal uptake via the human organic cation transporter 2. Mol Pharm 2011; 8: 270–9.

41 Woodland C, Ito S, Granvil CP, Wainer IW, Klein J, Koren G. Evidence of renal metabolism of ifosfamide to nephrotoxic metabolites. Life Sci 2000; 68: 109–17.

42 Aleksa K, Ito S, Koren G. Renal-tubule metabolism of ifosfamide to the nephrotoxic chloroacetaldehyde: pharmacokinetic modeling for estimation of intracellular levels. J Lab Clin Med 2004; 143: 159–62.

43 Springate J, Chan K, Lu H, Davies S, Taub M. Toxicity of ifosfamide and its metabolite chloroacetaldehyde in cultured renal tubule cells. In Vitro Cell Dev Biol Anim 1999; 35: 314–7.

44 Chen N, Aleksa K, Woodland C, Rieder M, Koren G. The effect of N-acetylcysteine on ifosfamide-induced nephrotoxicity: *in vitro* studies in renal tubular cells. Transl Res 2007; 150: 51–7.

45 Chen N, Aleksa K, Woodland C, Rieder M, Koren G. N-Acetylcysteine prevents ifosfamide-induced nephrotoxicity in rats. Br J Pharmacol 2008; 153: 1364–72.

46 Benesic A, Schwerdt G, Mildenberger S, Freudinger R, Gordjani N, Gekle M. Disturbed Ca^{2+}-signaling by chloroacetaldehyde: a possible cause for chronic ifosfamide nephrotoxicity. Kidney Int 2005; 68: 2029–41.

47 Sener G, Sehirli O, Yegen BC, Cetinel S, Gedik N, Sakarcan A. Melatonin attenuates ifosfamide-induced Fanconi syndrome in rats. J Pineal Res 2004; 37: 17–25.

48 Eiam-ong S, Spohn M, Kurtzman NA, Sabatini S. Insights into the biochemical mechanism of maleic acid-induced Fanconi syndrome. Kidney Int 1995; 48: 1542–8.

49 Sehirli O, Sakarcan A, Velioglu-Ogunc A, Cetinel S, Gedik N, Yegen BC, Sener G. Resveratrol improves ifosfamide-induced Fanconi syndrome in rats. Toxicol Appl Pharmacol 2007; 222: 33–41.

50 Badary OA. Taurine attenuates fanconi syndrome induced by ifosfamide without compromising its antitumor activity. Oncol Res 1998; 10: 355–60.

51 Badary OA. Thymoquinone attenuates ifosfamide-induced Fanconi syndrome in rats and enhances its antitumor activity in mice. J Ethnopharmacol 1999; 67: 135–42.

52 Badary OA. L-Histidinol attenuates Fanconi syndrome induced by ifosfamide in rats. Exp Nephrol 1999; 7: 323–7.

53 Nissim I, Weinberg JM. Glycine attenuates Fanconi syndrome induced by maleate or ifosfamide in rats. Kidney Int 1996; 49: 684–95.

54 Algren A, ed. Review of N-acetylcysteine for the treatment of acetaminophen (paracetamol) toxicity in paediatrics. Secon meeting of the subcommittee of the expert committee on the selection and use of essential medicines; 2008 September 29–October 3rd, 2008; Geneva.

55 Chen N, Aleksa K, Woodland C, Rieder M, Koren G. Prevention of ifosfamide nephrotoxicity by N-acetylcysteine: clinical pharmacokinetic considerations. Can J Clin Pharmacol 2007; 14: e246–50.

56 Chen N, Hanly L, Rieder M, Yeger H, Koren G. The effect of N-acetylcysteine on the antitumor activity of ifosfamide. Can J Physiol Pharmacol 2011; 89: 335–43.

57 Hanly L, Figueredo R, Rieder MJ, Koropatnick J, Koren G. The effects of N-acetylcysteine on ifosfamide efficacy in a mouse xenograft model. Anticancer Res 2012; 32: 3791–8.

58 Hanly L, Rieder MJ, Huang SH, Vasylyeva TL, Shah RK, Regueira O, Koren G. N-acetylcysteine rescue protocol for nephrotoxicity in children caused by ifosfamide. J Popul Ther Clin Pharmacol 2013; 20: e132–45.

59 Hanly LN, Chen N, Aleksa K, Cutler M, Bajcetic M, Palassery R, Regueira O, Turner C, Baw B, Malkin B, Freeman D, Rieder MJ, Vasylyeva TL, Koren G. N-acetylcysteine as a novel prophylactic treatment for ifosfamide-induced nephrotoxicity in children: translational pharmacokinetics. J Clin Pharmacol 2012; 52: 55–64.

60 Pritchard J, Brown J, Shafford E, Perilongo G, Brock P, Dicks-Mireaux C, Keeling J, Phillips A, Vos A, Plaschkes J. Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach–results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol 2000; 18: 3819–28.

61 Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney Int 2008; 73: 994–1007.

62 Douglass EC, Reynolds M, Finegold M, Cantor AB, Glicksman A. Cisplatin, vincristine, and fluorouracil therapy for hepatoblastoma: a Pediatric Oncology Group study. J Clin Oncol 1993; 11: 96–9.

63 Arany I, Safirstein RL. Cisplatin nephrotoxicity. Semin Nephrol 2003; 23: 460–4.

64 Gonzales-Vitale JC, Hayes DM, Cvitkovic E, Sternberg SS. The renal pathology in clinical trials of cis-platinum (II) diamminedichloride. Cancer 1977; 39: 1362–71.

65 Kintzel PE. Anticancer drug-induced kidney disorders. Drug Saf 2001; 24: 19–38.

66 Brock PR, Koliouskas DE, Barratt TM, Yeomans E, Pritchard J. Partial reversibility of cisplatin nephrotoxicity in children. J Pediatr 1991; 118: (4 Pt 1): 531–4.

67 Hirai S, Kaida S, Ito T, Hasebe S, Ueno M, Udagawa H, Hayashi M. [Magnesium premedication prevents Cisplatin-induced nephrotoxicity in patients with esophageal and hypopharyngeal cancer]. Gan To Kagaku Ryoho 2013; 40: 743–7.

68 dos Santos NA, Carvalho Rodrigues MA, Martins NM, dos Santos AC. Cisplatin-induced nephrotoxicity and targets of nephroprotection: an update. Arch Toxicol 2012; 86: 1233–50.

69 Mousavi SS, Zadeh MH, Shahbazian H, Khanzadeh A, Hayati F, Ghorbani A, Golzari K, Valavi E, Motemednia F, Mousavi MB. The protective effect of theophyline in cisplatin nephrotoxicity. Saudi J Kidney Dis Transpl 2014; 25: 333–7.

70 Gallegos-Castorena S, Martinez-Avalos A, Mohar-Betancourt A, Guerrero-Avendano G, Zapata-Tarres M, Medina-Sanson A. Toxicity prevention with amifostine in pediatric osteosarcoma patients treated with cisplatin and doxorubicin. Pediatr Hematol Oncol 2007; 24: 403–8.

71 Kemp G, Rose P, Lurain J, Berman M, Manetta A, Roullet B, Homesley H, Belpomme D, Glick J. Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. J Clin Oncol 1996; 14: 2101–12.

72 Dickey DT, Muldoon LL, Doolittle ND, Peterson DR, Kraemer DF, Neuwelt EA. Effect of N-acetylcysteine route of administration on chemoprotection against cisplatin-induced toxicity in rat models. Cancer Chemother Pharmacol 2008; 62: 235–41.

73 Dickey DT, Wu YJ, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in *vivo* levels. J Pharmacol Exp Ther 2005; 314: 1052–8.

74 Benoehr P, Krueth P, Bokemeyer C, Grenz A, Osswald H, Hartmann JT. Nephroprotection by theophylline in patients with cisplatin chemotherapy: a randomized, single-blinded, placebo-controlled trial. J Am Soc Nephrol 2005; 16: 452–8.

75 Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, Cohen GI, Emami B, Gradishar WJ, Mitchell RB, Thigpen JT, Trotti A 3rd, von Hoff D, Schuchter LM. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol 2009; 27: 127–45.

76 Larsen El S, Devidas W, Nachman M, Raetz J, Loh E, Heerema M, Carroll N, Gastier-Foster A, Borowitz J, Wood M, Willman B, Winick C, Hunger N, Carroll W. Comparison of high-dose methotrexate (HD-MTX) with Capizzi methotrexate plus asparaginase (C-MTX/ASNase) in children and young adults with high-risk acute lymphoblastic leukemia (HR-ALL): a report from the Children's Oncology Group Study AALL0232. J Clin Oncol 2011; 29: 3.

77 Jolivet J, Cowan KH, Curt GA, Clendeninn NJ, Chabner BA. The pharmacology and clinical use of methotrexate. N Engl J Med 1983; 309: 1094–104.

78 Lameire N, Kruse V, Rottey S. Nephrotoxicity of anticancer drugs–an underestimated problem? Acta Clin Belg 2011; 66: 337–45.

79 Ahmed HH, Hasan Y. Prevention and management of high dose methotrexate toxicity. J Cancer Sci Ther 2013; 5: 106–12.

80 Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. Oncologist 2006; 11: 694–703.

81 Chabner B, Longo DL. Cancer Chemotherapy and Biotherapy : Principles and Practice, 5th edn. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011; xv.

82 Widemann BC, Balis FM, Adamson PC. Dihydrofolate reductase enzyme inhibition assay for plasma methotrexate determination using a 96-well microplate reader. Clin Chem 1999; 45: 223–8.

83 Widemann BC, Sung E, Anderson L, Salzer WL, Balis FM, Monitjo KS, McCully C, Hawkins M, Adamson PC. Pharmacokinetics and metabolism of the methotrexate metabolite 2, 4-diamino-N(10)-methylpteroic acid. J Pharmacol Exp Ther 2000; 294: 894–901.

84 Baer DM, Dito WR. Interpretations in Therapeutic Drug Monitoring. Chicago: Educational Products Division, American Society of Clinical Pathologists, 1981; xiii.

85 Gazarian MG, Graudins V. Safe use of NSAIDs in infants and children. Med Today 2008; 7: 71–3.

86 Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2011; (7)CD004213.

87 Misurac JM, Knoderer CA, Leiser JD, Nailescu C, Wilson AC, Andreoli SP. Nonsteroidal anti-inflammatory drugs are an important cause of acute kidney injury in children. J Pediatr 2013; 162: 1153–9. 9 e1.

88 Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet 2005; 365: 417–30.

89 Taber SS, Mueller BA. Drug-associated renal dysfunction. Crit Care Clin 2006; 22: 357–74.

90 Pirani CL, Valeri A, D'Agati V, Appel GB. Renal toxicity of nonsteroidal anti-inflammatory drugs. Contrib Nephrol 1987; 55: 159–75.

91 Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. Nat Rev Nephrol 2010; 6: 461–70.

92 Alper AB, Jr, Meleg-Smith S, Krane NK. Nephrotic syndrome and interstitial nephritis associated with celecoxib. Am J Kidney Dis 2002; 40: 1086–90.

93 Gilbert DN. Aminoglycosides. In: Principle and Practise of Infectious Disease, 6th edn, eds Mandell GL, Bennett JE, Dolin R. New York: Churchill Livingstone, 2005; 328.

94 Kumana CR, Yuen KY. Parenteral aminoglycoside therapy. Selection, administration and monitoring. Drugs 1994; 47: 902–13.

95 Zappitelli M, Moffett B, Hyder A, Goldstein SL. Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study. Nephrol Dial Transplant 2010; 23: 144–50.

96 Koren G, Klein J, MacLeod SM. The dissociation between aminoglycoside serum concentrations and nephrotoxicity. Life Sci 1988; 43: 1817–23.

97 Singh NP, Ganguli A, Prakash A. Drug-induced kidney disease. JAPI 2003; 41: 970–9.

98 Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician 2008; 78: 743–50.

99 Quiros Y, Vicente-Vicente L, Moralesm A, López-Novoa J, López-Hernández F. An integrative overview on the mechanisms underlying the renal tubular cytotoxicity of gentamicin. Toxicol Sci 2010; 119: 245–56.

100 Morales AI, Detaille D, Prieto M, Puente A, Briones E, Arevalo M, Leverve X, Lopez-Novoa JM, El-Mir MY. Metformin prevents experimental gentamicin-induced nephropathy by a mitochondria-dependent pathway. Kidney Int 2010; 77: 861–9.

101 Cuzzocrea S, Mazzon E, Dugo L, Serraino I, Di Paola R, Britti D, De Sarro A, Pierpaoli S, Caputi A, Masini E, Salvemini D. A role for superoxide in gentamicin-mediated nephropathy in rats. Eur J Pharmacol 2002; 450: 67–76.

102 Simmons CF, Jr, Bogusky RT, Humes HD. Inhibitory effects of gentamicin on renal mitochondrial oxidative phosphorylation. J Pharmacol Exp Ther 1980; 214: 709–15.

103 Smith CR, Baughman KL, Edwards CQ, Rogers JF, Lietman PS. Controlled comparison of amikacin and gentamicin. N Engl J Med 1977; 296: 349–53.

104 Smith CR, Lipsky JJ, Laskin OL, Hellmann DB, Mellits ED, Longstreth J, Lietman PS. Double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin. N Engl J Med 1980; 302: 1106–9.

105 Williams PD, Bennett DB, Gleason CR, Hottendorf GH. Correlation between renal membrane binding and nephrotoxicity of aminoglycosides. Antimicrob Agents Chemother 1987; 31: 570–4.

106 Williams PD, Hottendorf GH, Bennett DB. Inhibition of renal membrane binding and nephrotoxicity of aminoglycosides. J Pharmacol Exp Ther 1986; 237: 919–25.

107 Ali BH. Agents ameliorating or augmenting experimental gentamicin nephrotoxicity: some recent research. Food Chem Toxicol 2003; 41: 1447–52.

108 Bates DW, Su L, Yu DT, Chertow GM, Seger DL, Gomes DR, Platt R. Correlates of acute renal failure in patients receiving parenteral amphotericin B. Kidney Int 2001; 60: 1452–9.

109 Safdar A, Ma J, Saliba F, Dupont B, Wingard JR, Hachem RY, Mattiuzzi GN, Chandrasekar PH, Kontoyiannis DP, Rolston KV, Walsh TJ, Champlin RE, Raad II. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. Medicine 2010; 89: 236–44.

110 Pathak A, Pien FD, Carvalho L. Amphotericin B use in a community hospital with sepcial emphasis on side effects. Clin Infect Dis 1998; 26: 334–8.

111 Zager RA, Bredl CR, Schimpf BA. Direct amphotericin B-mediated tubular toxicity: assessments of selected cytoprotective agents. Kidney Int 1992; 41: 1588–94.

112 Branch RA. Prevention of amphotericin B-induced renal impairment. A review on the use of sodium supplementation. Arch Intern Med 1988; 148: 2389–94.

113 Heidemann HT, Gerkens JF, Spickard WA, Jackson EK, Branch RA. Amphotericin B nephrotoxicity in humans decreased by salt repletion. Am J Med 1983; 75: 476–81.

114 Alexander BD, Wingard JR. Study of renal safety in amphotericin B lipid complex-treated patients. Clin Infect Dis 2005; 40: (Suppl. 6): S414–21.