SECTION 17

Drugs and renal disease

CHAPTER 362

Drug-induced nephropathies

Anushree Shirali and Mark A. Perazella

Scope of the problem

Humans are exposed to significant numbers of medications and drugs on a regular basis. In general, most drugs are well tolerated; however, a subgroup of patients can and do develop adverse renal effects. As will be discussed subsequently, nephrotoxicity can result from categories of agents. These include therapeutic and diagnostic agents, herbal, alternative, and natural substances, and environmental exposures (Perazella, 2010, 2011). In addition, these substances can cause a number of kidney injuries that can be broadly classified into the following syndromes: (1) acute kidney injury (AKI), (2) parenchymal kidney disease, (3) tubulopathies, and (4) chronic kidney disease (CKD) (Perazella, 2010, 2011).

While drugs are not an uncommon cause of community-acquired kidney injury, they are a much more frequent cause in hospitalized patients. In this setting they share the spotlight with renal ischaemia as the leading cause of AKI, and often act together with ischaemia to cause AKI. In general, the incidence of hospital-acquired AKI caused by drugs is estimated to be as high as 40%, with various other series noting incidences ranging from 17% to 35% (Hou et al., 1983; Baraldi et al., 1998; Obialo et al., 2000; Nash et al., 2002; Sesso et al., 2004). It appears that agents such as intravenous radiocontrast and various antibiotics are the major contributors to nephrotoxic AKI in the hospital (Hou et al., 1983; Nash et al., 2002), whereas non-steroidal anti-inflammatory drugs (NSAIDs) are the most common culprits in the outpatient arena (Baraldi et al., 1998).

In addition to causing AKI, drugs can promote isolated tubular injury at various nephron segments, causing clinically recognized tubulopathies. The proximal tubules are most often involved, while the loop of Henle, and distal nephron may also be affected by drug toxicity. Medications may target the glomerulus and cause various types of glomerulopathies with proteinuria. Nephrotic syndrome with high-grade proteinuria, nephritic syndrome with low-grade proteinuria and haematuria, or some combination of the two can result from drug-related injury. Several drugs can directly (drug or metabolite) or indirectly (metabolic disturbances) cause nephrolithiasis. Finally, CKD can ensue from drug injury with resulting chronic interstitial nephritis and fibrosis or glomerulosclerosis.

Vulnerability of the kidney to nephrotoxic drugs

The kidney serves many roles and performs a number of essential bodily functions. It clears endogenous waste products, controls volume status through balanced excretion of sodium and water, modulates electrolyte and acid–base balance, and acts as an endocrine organ. Other major functions are the metabolism and excretion of exogenously administered therapeutic and diagnostic agents as well as substances that humans are exposed to in the environment. In its role as the primary eliminator of exogenous drugs and toxins, the kidney is vulnerable to develop various forms of injury and loss of renal function leads to a number of clinical problems. The kidney is exposed to a number of important nephrotoxins that induce injury and result in renal disease. There are several factors that increase vulnerability of the kidney to these potential toxins, which can target one or more of the renal compartments. This can ultimately lead to various clinical renal syndromes.

Nephrotoxic drugs

Adequate exposure to an offending agent is the first step in the development of drug-induced nephrotoxicity. In fact, humans are exposed to a variety of potential nephrotoxic substances on a rather frequent basis (Table 362.1). Several therapeutic agents are known nephrotoxins and cause various forms of kidney injury. Classic examples include several chemotherapeutic agents, antimicrobial agents, certain analgesics, and immunosuppressive agents (Elseviers and DeBroe, 1999; Kintzel, 2001; Gambaro and Perazella, 2003; Rougier et al., 2003; Izzedine et al, 2005; Lameire et al., 2005; Perazella, 2005; Schetz et al., 2005). While most of these agents are prescribed by practitioners, many others are available as over-the-counter preparations to the general population. Importantly, new drugs are being released for use into clinical practice at a rapid rate, exposing at-risk patients to drugs with unknown toxic potential. Furthermore, agents utilized for diagnostic purposes, such as iodinated radiocontrast and high-dose intra-arterial gadolinium, are another common source of nephrotoxin exposure (Briguori et al., 2005; Ergün et al., 2006).

Alternative and complementary products, which include herbal remedies, natural products, and nutritional supplements that are widely available at most health food stores, are another important and currently unregulated source of potentially nephrotoxic substances (Isnard et al., 2004; Blowey, 2005). Of significant concern are the harmful contaminants and chemicals contained in the products that are not listed on the label (Isnard et al., 2004; Blowey, 2005). In addition to direct nephrotoxicity, interaction of herbal products with conventional drugs is also a potential source of renal toxicity. Examples of nephrotoxic alternative products include aristolochic acid, *Ephedra* species, and *Glycyrrhiza* species (Isnard et al., 2004; Blowey, 2005). Adulteration of herbal products with dichromate, cadmium, and phenylbutazone also causes significant renal injury (Isnard et al., 2004; Blowey, 2005). An example of adulteration involving infant and baby formula is worth mentioning. To falsely elevate protein content, melamine was added to formula,

Table 362.1 Commonly encountered nephrotoxic agents and exposures

Therapeutic agents	Alternative products	Diagnostic agents	Environmental exposures
Antimicrobial	**Herbal remedies**	**Radiocontrast**	**Heavy metals**
Aminoglycosides	Aristolochic acid	High osmolar	Lead
Antiviral agents	*Ephedra* sp.	Low osmolar	Mercury
Amphotericin B	*Glycyrrhiza* spp.	Iso-osmolar	Cadmium
Colistin	*Datura* spp.		Uranium
Sulphadiazine	*Taxus celebica*	**Other agents**	**Copper**
Ciprofloxacin	*Uno degatta* *Cape aloes*	Gadolinium (in Bismuth high dose)	Bismuth
Chemotherapy		Oral NaP solution (colonoscopy prep)	**Solvents**
Platins	**Adulterants**		**Hydrocarbons**
Ifosfamide	Mefenamic acid		
Mitomycin	Dichromate		*Other toxins*
Gemcitabine	Cadmium		Silicon
Methotrexate	Phenylbutazone		Germanium
Pentostatin	Melamine		
Interleukin 2			
Anti-angiogenesis agents			
Analgesics			
NSAIDs			
Selective COX-2 inhibitors			
Phenacetin analgesic combinations			
Immunosuppressives			
Calcineurin inhibitors			
Sirolimus			
Other			
ACEIs/ARBs			
Methoxyflurane			
Sucrose, hydroxyethyl starch, mannitol			
Pamidronate, zoledronate			
Topiramate, zonisamide			
Orlistat			
Statins			
Mesalamine			

ACEIS = angiotensin-converting enzyme inhibitors; ARBs = angiotensin-receptor blockers; NaP = sodium phosphate; NSAIDs = non-steroidal anti-inflammatory drugs.

which was noted to cause AKI and nephrolithiasis in neonates (Wang et al., 2009).

Adverse kidney effects can also develop in the setting of environmental exposure to various nephrotoxic substances (Van Vleet and Schnellmann, 2003; Brewster and Perazella, 2004; Yu et al., 2004). Nephrotoxins such as lead, cadmium, mercury, copper, uranium, and bismuth are but a few of the known culprit agents. A classic and well-described nephrotoxic concern is lead exposure, which may be harmful even at levels that are considered safe and acceptable to governmental agencies. For example, low-level lead exposure exacerbates underlying both diabetic and non-diabetic CKD, which can lead to more rapid progression to advanced stages of CKD and end-stage renal disease (ESRD) requiring renal replacement therapy (Van Vleet and Schnellman, 2003; Brewster and Perazella, 2004; Yu et al., 2004).

Nephrotoxic risk factors

In order to fully understand and simplify the approach to the kidney's vulnerability to nephrotoxic drugs, classification of risk factors is divided into three major categories: (1) patient-specific, (2) kidney-specific, and (3) drug-specific factors (Table 362.2). Each category or specific risk factor individually contributes to the enhanced development of renal injury; however, often more than one of the risk factors is acting to promote nephrotoxicity. Most often at least two or all three of these factors conspire to cause various forms of clinical kidney disease (Table 362.3). Furthermore, it is these factors that also explain the variability and heterogeneity seen with drug-induced kidney disease.

Table 362.2 Risk factors which increase renal vulnerability to nephrotoxins

Patient-specific factors	Female sex
	Old age (>65 years)
	Nephrotic syndrome
	Cirrhosis/obstructive jaundice
	Acute/chronic kidney disease
	True or effective volume depletion:
	◆ Decreased glomerular filtration rate
	◆ Enhanced proximal tubular toxin reabsorption
	◆ Sluggish distal tubular urine flow rates
	Metabolic perturbations:
	◆ Hypokalaemia, hypomagnesaemia, hypercalcemia
	◆ Alkaline or acid urine pH
	Immune response genes
	Pharmacogenetics favouring drug toxicity:
	◆ Gene mutations in hepatic and renal P450 system
	◆ Gene mutations in renal transporters and transport proteins
Kidney-specific factors	High rate of blood delivery (20–25% of cardiac output)
	Increased toxin concentration in renal medulla and interstitium
	Biotransformation of substances to reactive oxygen species
	High metabolic rate of tubular cells (loop of Henle)
	Proximal tubular uptake of toxins:
	◆ Apical uptake via endocytosis/pinocytosis
	◆ Basolateral transport via OAT and OCT
Drug-specific factors	Prolonged dosing periods and toxin exposure
	Potent direct nephrotoxic effects of the drug or compound
	Combinations of toxins/drugs promoting enhanced nephrotoxicity
	Competition between endogenous and exogenous toxins for transporters, increasing toxin accumulation within the tubular cell
	Insoluble parent compound and metabolite with intratubular crystal precipitation

OAT = organic anion transporters; OCT = organic cation transporters.

Patient-specific risk characteristics

An important risk category for drug-induced nephrotoxicity is the underlying patient-specific characteristics (Fig. 362.1, Table 362.2). Exposure to drugs and other substances increases risk for kidney injury when certain underlying factors, which predispose to nephrotoxicity, are present. Factors such as older age and female gender, which are non-modifiable, enhance renal risk through the following: (1) changes in total body water, which is reduced in setting of decreased lean body mass and leads to drug overdose; (2) unrecognized lower and glomerular filtration rate (GFR) despite normal serum creatinine concentration; and (3) reduced drug binding to proteins due to hypoalbuminaemia, which results in increased free drug concentrations (Jerkic et al., 2001; Guo and Nzerue, 2002; Singh et al., 2003; Evenepoel, 2004). In addition, the elderly also have an increased propensity to vasoconstriction from excessive angiotensin II and endothelin and have higher levels of oxidatively modified biomarkers, which are injurious to the kidney (Jerkic et al., 2001). These factors combine to expose the patient to excess drug concentrations and risk of nephrotoxicity. Also, underlying both AKI and CKD are important risk factors for increasing renal vulnerability to nephrotoxic injury through multiple mechanisms (Guo and Nzerue, 2002; Singh et al., 2003; Evenepoel, 2004). Excessive drug dosing for the level of kidney function, exposure of a reduced number of functioning nephrons to toxic drugs, ischaemia

Table 362.3 Clinical renal syndromes caused by nephrotoxins

Tubulopathies	Renal tubular acidosis/Fanconi syndrome
	Sodium wasting
	Potassium wasting
	Nephrogenic diabetes insipidus
Nephrotic syndrome/ proteinuria	Glomerular disease:
	◆ Minimal change glomerulonephritis
	◆ Focal segmental glomerulosclerosis
	◆ Membranous glomerulonephritis
	◆ Other
	Thrombotic microangiopathy:
	◆ HUS/TTP
Acute kidney injury	Haemodynamic disturbances
	Parenchymal kidney disease
	Collecting system disease
Chronic kidney disease	Analgesic nephropathy
	Chronic tubulointerstitial nephritis
	Secondary progression of toxin-induced kidney disease

HUS = haemolytic uraemic syndrome; TTP = thrombotic thrombocytopenic purpura.

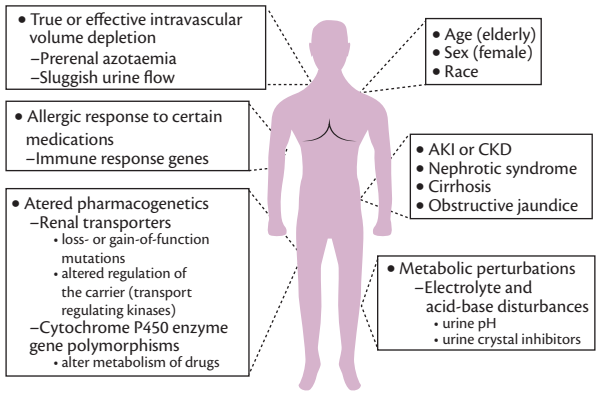

Fig. 362.1 Patient-specific risk factors for drug-induced nephrotoxicity.

preconditioned tubular cells, and more robust renal oxidative injury response to toxins are all contributors in these settings.

Underlying disease states such as cirrhosis and nephrotic syndrome raise risk through multiple mechanisms that include altered renal perfusion from reduced effective circulating blood volume, hypoalbuminaemia with increased free circulating drug, and unrecognized renal impairment (Guo and Nzerue, 2002; Singh et al., 2003; Evenepoel, 2004; Wyatt et al., 2006). The last point cannot be overemphasized, as serum creatinine concentration is often low or normal in these patients, despite the presence of significant kidney impairment. Obstructive jaundice also enhances toxicity to certain drugs, such as the aminoglycosides through altered haemodynamics characterized by decreased renal blood flow and direct tubular injury from bile salts (Lucena et al., 1995). Volume depletion from vomiting, diarrhoea, diuretics, and other sources of salt and water loss increase renal vulnerability to various agents by inducing renal hypoperfusion. Similarly, effective volume depletion from congestive heart failure, liver disease with ascites, and sepsis promote renal hypoperfusion and prerenal azotaemia. Taken together, these underlying processes enhance the nephrotoxic potential of many drugs and substances. In particular, reduced renal perfusion increases adverse renal effects of the following drugs: (1) drugs excreted primarily by the kidney by causing excessive drug dosing, (2) drugs handled (reabsorbed or secreted) by the proximal tubule can cause excessive intracellular concentrations, and (3) drugs that tend to be insoluble in the urine where crystal precipitation occurs within distal tubular lumens with sluggish flow (Guo and Nzerue, 2002; Singh et al., 2003; Evenepoel, 2004; Markowitz and Perazella, 2005; Wyatt et al., 2006).

Metabolic perturbations also enhance renal vulnerability to certain drugs. Electrolyte and divalent ion disorders such as hypokalaemia, hypomagnesaemia, and hypocalcaemia can increase the nephrotoxicity associated with aminoglycosides (Guo and Nzerue, 2002; Singh et al., 2003; Evenepoel, 2004). Through direct renal effects, severe hypercalcemia increases risk for drug-induced nephrotoxicity by inducing afferent arteriolar vasoconstriction and renal sodium and water wasting, which leads to prerenal physiology. Certain metabolic disorders that alter urine pH increase risk for intratubular crystal deposition when certain drugs and substances precipitate within tubular lumens in the distal nephron (Perazella and Brown, 1994; Markowitz and Perazella, 2005). For example, systemic metabolic acidosis or alkalosis may decrease or increase urine pH, while proximal and distal renal tubular acidoses are associated with alkaline urine due to impaired renal ability to excrete H^+ ions. Drugs such as sulphadiazine, methotrexate, and triamterene, which are insoluble in a low pH environment, are more likely to form intratubular crystals in acidic urine (pH < 5.5) (Perazella and Brown, 1994; Markowitz and Perazella, 2005). Alkaline urine (pH > 6.0) increases crystal precipitation within tubular lumens from drugs such as indinavir, atazanavir, oral sodium phosphate solution, and ciprofloxacin (Perazella and Brown, 1994; Markowitz and Perazella, 2005; Stratta et al., 2007). Finally, drugs such as topiramate, zonisamide, and acetazolamide alkalinize the urine through inhibition of carbonic anhydrase and promote precipitation of calcium phosphate within tubules, thereby enhancing renal stone formation (Vega et al., 2007; Wroe, 2007).

The host's underlying genetic makeup can also enhance or reduce the kidney's vulnerability to potential nephrotoxic medications (Ciarimboli et al., 2005; Harty et al., 2006; Ulrich et al., 2006). For example, the patient's response to a drug or its metabolite that has formed adducts that modify their physical structure makes them more immunogenic. In this circumstance, there is significant heterogeneity in the response of patients to drugs and exogenous exposures. One obvious example is the heightened allergic response of some individuals as compared with others. Innate host immune response genes often differ and can predispose certain patients to develop an allergic response to a substance. The variability of immune responses is evident in a patient who develops drug-induced interstitial nephritis, which appears to be a T-cell driven process, while another exposed to the same drug does not (Spanou et al., 2006). This translates into enhanced vulnerability to an allergic response in the kidney and development of an acute interstitial nephritis (AIN) and associated renal impairment.

The role of pharmacogenetics as an explanation for the heterogeneous response of patients to drugs as it relates to efficacy and toxicity is a better-studied area and a focus of research (Ciarimboli et al., 2005; Harty et al., 2006; Ulrich et al., 2006). The hepatic cytochrome P450 (CYP450) enzyme system has been well studied as it relates to drug metabolism. In fact, several CYP450 enzyme gene polymorphisms are associated with reduced metabolism and subsequent end-organ toxicity. Like the liver, the kidney also possesses CYP450 enzymes that participate in drug metabolism (Harty et al., 2006; Ciarimboli et al., 2005; Ulrich et al., 2006). Gene polymorphisms favouring reduced drug metabolism would similarly be expected to increase nephrotoxic risk. Polymorphisms of genes encoding proteins involved in the metabolism and subsequent renal elimination of drugs have been described and are correlated with various levels of drug sensitivity. Specific to the discussion of nephrotoxicity, loss-of-function mutations in apical secretory transporters, which reduce cell drug efflux into the urine, and mutations in kinases that regulate drug carrier proteins can impair drug elimination and promote toxicity by increasing intracellular drug concentrations (Ciarimboli et al., 2005). As research continues to advance in this area, more information on how patients differ in the function and regulation of channels, transporters, and carriers that regulate elimination of drugs and other compounds cleared by the kidney will become available. Tenofovir-induced Fanconi syndrome is an example of this type of research (Izzedine et al., 2006a). In HIV patients exposed to tenofovir who developed Fanconi syndrome, a single nucleotide polymorphism (1249 G→A SNP) was present in the gene coding the multidrug-resistant protein-2 (MRP2) efflux transporter, which transports tenofovir out of the cell. In contrast,

tenofovir exposed patients without Fanconi syndrome did not have the noted polymorphism.

Kidney-specific risk factors

The kidney metabolizes and excretes various drugs and toxins, making it an obvious target of injury (Fig. 362.2). Exposure of the kidney to drugs, toxins, and other substances occurs due to the high rate of drug and toxin delivery to this excretory organ. In fact, renal blood flow approaches 25% of cardiac output. Many renal cells are predisposed to drug injury as a result of their high metabolic rates and the relatively hypoxic environment they reside in (Cummings and Schnellmann, 2001; Kaloyanides et al., 2001). Tubular cells in the loop of Henle are an example where high metabolic rates occur due to the active transport of many solutes by Na^+-K^+-ATPase. This excess cellular workload and hypoxic environment promotes increased sensitivity to injury when exposure to potentially nephrotoxic substances occurs (Cummings and Schnellmann, 2001; Kaloyanides et al., 2001). The development of a high concentration of parent compounds and their metabolites in the renal medulla and interstitium from the enormous concentrating ability of the kidney further enhances renal nephrotoxicity (Cummings and Schnellmann, 2001; Kaloyanides et al., 2001). The resulting excessive tissue concentration of these compounds and metabolites promotes injury through direct toxicity and ischaemic damage, the end result of reduced prostaglandin and increased thromboxane concentrations.

Drug metabolism in the kidney is another source of injury. Multiple renal enzyme systems, including CYP450 and flavin-containing monooxygenases promote the formation of toxic metabolites and reactive oxygen species, both which are injurious to renal cells (Cummings and Schnellmann, 2001; Kaloyanides et al., 2001; Aleksa et al., 2005). These by-products of biotransformation tilt the balance in favour of oxidative stress, outstripping natural antioxidants and increasing renal injury via nucleic acid alkylation or oxidation, protein damage, lipid peroxidation, and DNA strand breaks (Cummings and Schnellmann, 2001; Kaloyanides et al., 2001; Aleska et al., 2005).

The proximal tubular cells are a target of drug toxicity by virtue of their extensive cellular uptake of potential toxins and drugs by both apical and basolateral transport systems. Apical membrane uptake of substances occurs via endocytosis and other transport pathways (Fanos and Cataldi, 2001; Nagai and Takano, 2004; Orbach et al., 2004; Ciarimboli et al., 2005; Enomoto and Endou, 2005). Polycationic aminoglycosides (Fig. 362.3), heavy metals, and various complex sugars and starches such as sucrose and hydroxyethyl starch (Fig. 362.4) are examples of substances taken up by this pathway. Following endocytosis of aminoglycosides, which involves megalin, the endocytic receptor for cationic ligands, these drugs are translocated into the lysosomal compartment. These drugs accumulate and subsequently form myeloid bodies, which are membrane fragments and damaged organelles formed as a consequence of aminoglycoside inhibition of lysosomal enzymes (Cummings and Schnellmann, 2001; Kaloyanides et al., 2001; Nagai and Takano, 2004). This apical pathway of uptake leads to accumulation of a critical aminoglycoside concentration within cells, triggering an injury cascade that causes cell injury and death. Basolateral delivery of drugs that are either organic anions or cations by peritubular capillaries is another pathway by which proximal tubular cell toxin exposure occurs (Enomoto and Endou, 2005; Ciarimboli et al., 2005). Drug delivery via peritubular capillaries is followed by uptake into proximal tubular cells via a family of transporters, including human organic anion (HOAT) and cation (HOCT) transporters (Enomoto and Endou, 2005; Ciarimboli et al., 2005). A number of drugs are delivered to the proximal tubular cells via this pathway with classic examples including the acyclic nucleotide phosphonates, which are transported via HOAT (Enomoto and Endou, 2005), and cisplatin, which is transported via HOCT. Once within the cells, drugs traverse the intracellular space via various regulated carrier proteins, and subsequently exit from the cells via apical transport proteins (Ciarimboli et al., 2005).

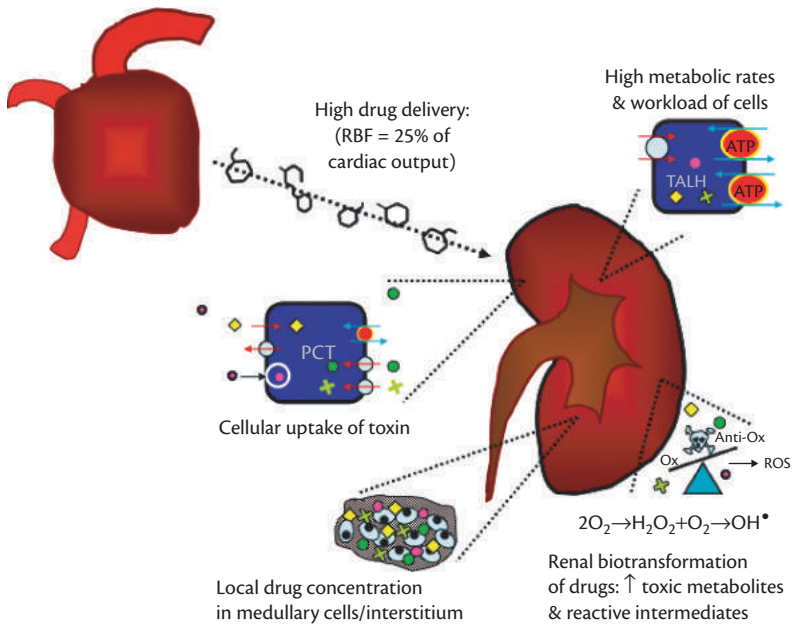

Fig. 362.2 Kidney-specific risk factors for drug-induced nephrotoxicity.

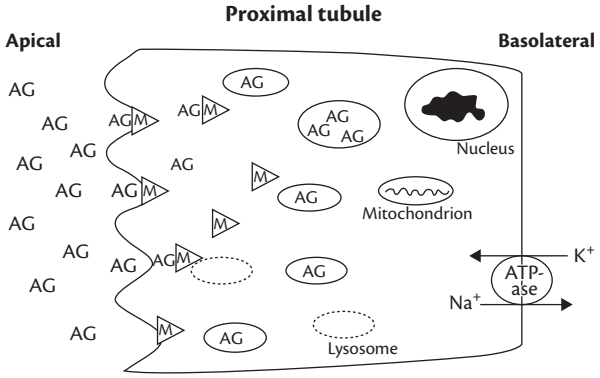

Fig. 362.3 Uptake of aminoglycoside (AG) by the proximal tubule via initial binding to megalin (M) in the apical membrane followed by fusion with lysosomes. Once inside the cell, AG induces cellular injury through multiple mechanisms.

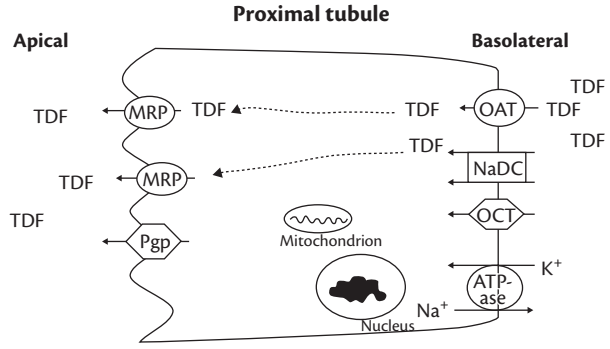

Fig. 362.5 Uptake of tenofovir (TDF) by the proximal tubule. TDF is transported into the cell by organic anion transporters and into the urine via various efflux transporters. TDF can cause cellular injury when it accumulates in the cell, often targeting the mitochondrion.

Loss-of-function mutations in and competition for apical secretory transporters (Lang, 2005), which reduces drug efflux from cell into urine, enhance accumulation of these agents within proximal tubular cells and causes cellular injury via apoptosis or necrosis (Fig. 362.5). It is this extensive trafficking of drugs through the cells that increases renal tubular exposure and risk for elevated concentration of toxin when other risk factors supervene.

Drug-specific risk factors

Not surprisingly, the underlying drug characteristics also play an important role in the development of adverse renal effects (Fig. 362.6). Prolonged therapy with high doses of a nephrotoxic agent enhances kidney injury based on excessive renal exposure, even in the absence of other risk factors. Aminoglycosides with more positive charge are more likely to cause nephrotoxicity, perhaps due to enhanced interactions with negatively charged membrane phospholipids and megalin (Rougier et al., 2003; Nagai and Takano, 2004). This is reflected by the greater nephrotoxicity observed with neomycin as compared with amikacin. Drug combinations also raise risk of nephrotoxicity; aminoglycosides and cephalothin, NSAIDs and radiocontrast, and cisplatin and aminoglycosides, are a few examples of this enhanced nephrotoxic risk (Guo and Nzerue, 2002; Singh et al., 2003; Evenepoel, 2004; Wyatt et al., 2006). As mentioned previously, various drugs can compete for transport proteins in the proximal tubular cells, thereby reducing renal elimination and increasing intracellular drug concentration (Izzedine et al., 2005; Markowitz and Perazella, 2005; Perazella, 2005; Schetz et al., 2005). This favours renal injury and the development of nephrotoxicity. Various drugs and their metabolites that are insoluble in human urine may also cause renal injury. In addition to drug characteristics that induce insolubility, factors such as urine pH, sluggish tubular urine flow rates, and rapid parenteral or excessive dosing (high peak serum and urine concentrations) enhances risk for precipitation and crystal formation in distal nephron tubular lumens (Guo and Nzerue, 2002; Singh et al., 2003; Wyatt et al., 2006). Commonly used medications such as aciclovir, methotrexate, sulphadiazine, indinavir, ciprofloxacin, atazanavir, and oral sodium phosphate solution are examples.

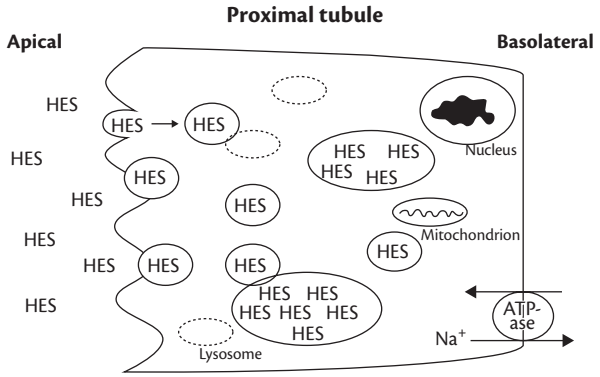

Fig. 362.4 Uptake of hydroxyethyl starch (HES) by the proximal tubule via pinocystosis followed by fusion with lysosomes. Lysosomes become packed with HES, which cannot be degraded, causing cell swelling and injury.

Several medications are highly nephrotoxic and can promote kidney injury, even with brief and/or low-level exposure. Examples include the aminoglycosides, in particular neomycin, amphotericin B, the polymyxins, zoledronate, and the antiviral agents, adefovir and cidofovir (Gambaro and Perazella, 2003; Markowitz et al., 2003; Rougier et al., 2003; Izzedine et al., 2005; Perazella, 2005; Alexander and Wingard, 2005; Schetz et al., 2005; Falagas and Kasiakou, 2006). As such, aminoglycosides are a classic group of nephrotoxins. Accumulation of high concentrations within lysosomes and release into the cell cytoplasm promotes phospholipid membrane interruption, oxidative stress, and mitochondrial injury that cause proximal tubular cell apoptosis and necrosis, leading to isolated tubulopathies or full-blown AKI. Intravenous amphotericin B, including its lipid and liposomal formulations to a lesser degree, disrupt tubular cell membranes and increase their permeability to cations, resulting in tubular dysfunction (Alexander and Wingard, 2005). Colistin and polymyxin B are extremely nephrotoxic antimicrobials with a very narrow therapeutic window. The nephrotoxicity of these drugs appears to be due to the D-amino content and fatty acid component, which increase membrane permeability and influx of cations (Falagas and Kasiakou, 2006). Tubular cell swelling and cell lysis develops. The acyclic nucleotide phosphonates enter the cell via basolateral human OAT-1 and promote cellular injury through multiple mechanisms. Mitochondrial injury occurs with adefovir through inhibition of DNA polymerase gamma, which is the sole DNA polymerase in mitochondria (Izzedine et al., 2005; Perazella, 2005). Cidofovir, which forms

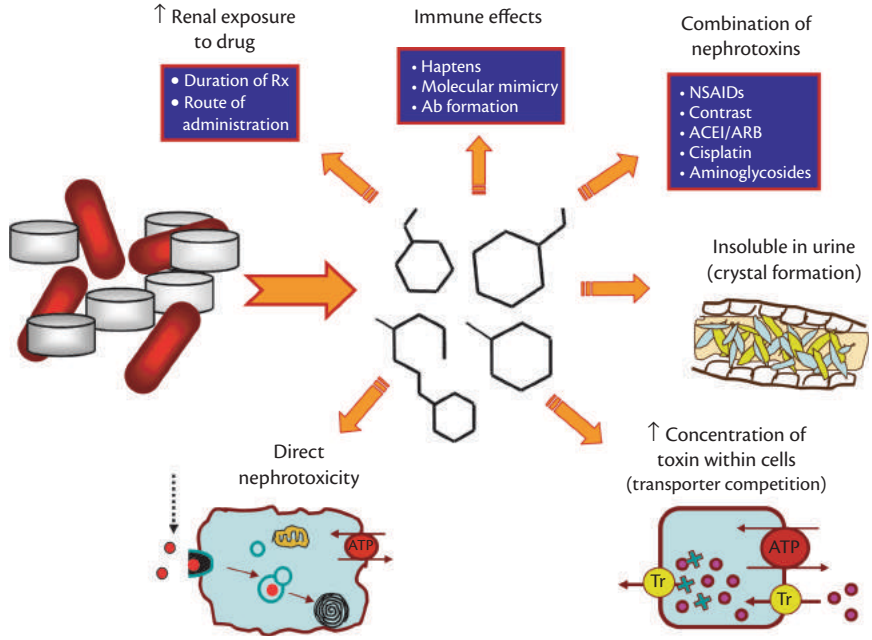

Fig. 362.6 Drug-specific risk factors for drug-induced nephrotoxicity.

cidofovir-phosphocholine within cells, interferes with synthesis and/or degradation of membrane phospholipids, resulting in proximal tubular injury (Izzedine et al., 2005; Perazella, 2005). It is likely that it also injures the mitochondria. Tenofovir also impairs cellular energetics through mitochondrial disruption as manifested by swelling and loss of cristae (Izzedine et al., 2005; Markowitz and Perazella, 2005; Perazella, 2005).

Anti-angiogenesis therapy is associated with nephrotoxicity (Yang et al., 2003; Eremina et al., 2008). Vascular endothelial growth factor (VEGF) maintains normal fenestrated endothelial function and health, especially in glomerular basement membrane (Sugimoto et al., 2003). Therapy with this class of drugs is associated with hypertension, proteinuria, and kidney injury. These drugs cause a number of kidney lesions, however, glomerular endothelial injury and thrombotic microangiopathy are the most common (Eremina et al., 2008; Gurevich and Perazella, 2009).

Classification of drug-induced nephropathies

Renal function is determined by a series of events that starts with the delivery of blood from the renal arteries to the glomeruli. Pressure-driven filtration within the glomerulus produces an ultrafiltrate, which is refined by solute and water reabsorption within the renal tubules to form the final effluent of urine. The urogenital system allows urine to flow from the kidney to the bladder for excretion. Therapeutic drugs can induce renal dysfunction by acting on any of these steps, including disruption of renal blood flow (RBF), GFR, injury to the renal parenchyma, and interruption of urinary flow. Thus, one useful classification system divides drug-induced nephrotoxicity into prerenal, intrarenal, or postrenal mechanisms of injury. Most drugs have a unique mechanism of injury, although some can affect the kidney via multiple pathways. Lastly, depending on drug characteristics and cumulative drug exposure, kidney injury can result acutely (AKI) or progress over time to chronic kidney disease (CKD). The following sections will expand upon the different types of drug-induced nephropathies, with examples of the most commonly encountered drugs in each category.

Pseudo-renal failure

A discussion on drug-induced renal injury necessarily includes pseudo-renal failure, during which serum creatinine may increase without a true loss of GFR. The mechanism for this, which is common to trimethoprim and cimetidine, is inhibition of the organic ion transporter that mediates tubular secretion of creatinine. The rise in creatinine is usually mild and entirely reversible upon drug discontinuation.

Prerenal azotaemia

Drugs that reduce RBF and GFR (Table 362.4) may cause AKI by disturbing renal haemodynamics. Patients display features that are typical of renal hypoperfusion, including: (1) inactive urine

Table 362.4 Drug-induced prerenal azotaemia

Afferent vasoconstrictors	Calcineurin inhibitors
	NSAIDs
	COX-2 selective inhibitors
	Radiocontrast agents
	Vasopressors
Efferent vasodilators	Direct renin inhibitors
	ACEIs
	ARBs

ACEIs = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; COX-2 = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory agents.

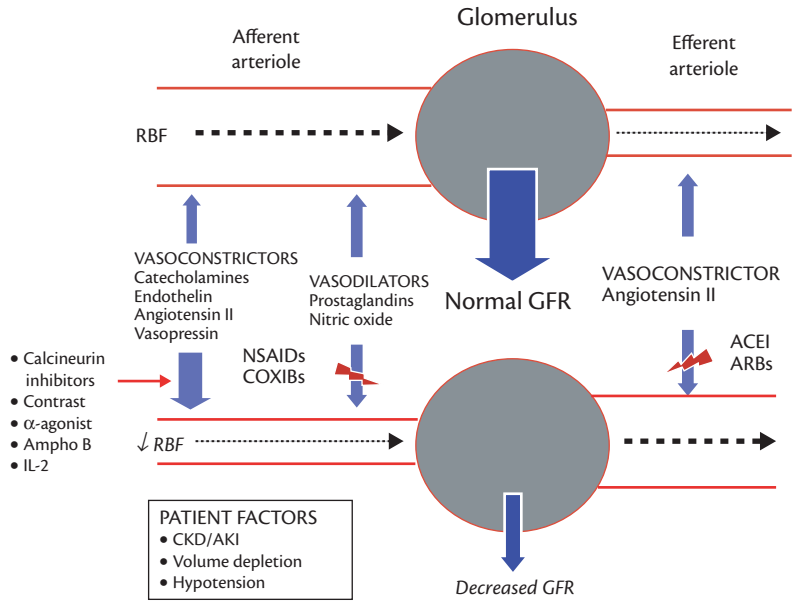

Fig. 362.7 Normal glomerular filtration rate (GFR) is maintained by a balance of vasoconstrictors and vasodilators. Certain drugs can offset the balance via effects on the afferent and efferent arterioles in at risk patients, thereby reducing GFR and causing prerenal acute kidney injury (AKI).

sediment and (2) avid urine sodium (UNa^+) reabsorption with UNa^+ concentration < 20 mEq/L, and fractional excretion (Fe) of Na^+ < 1%. In patients receiving diuretics, Fe urea < 35% is a more useful marker of prerenal azotaemia, as diuretic therapy can increase urine Na^+ excretion independently of volume status. Drugs that cause systemic hypoperfusion can indirectly decrease RBF, but direct reduction of RBF and GFR occurs via modulation of the vascular tone of afferent and efferent renal arterioles (Fig. 362.7).

Afferent arteriolar vasoconstrictors

Cyclooxygenase inhibitors (NSAIDs)

Cyclooxygenase (COX) enzyme metabolism is essential to prostaglandin synthesis. COX inhibitors such as traditional NSAIDs, which inhibit both the constitutive (isoform 1) and inducible forms (isoform 2) of the enzyme, prevent prostaglandin-mediated autoregulation of RBF (Smyth et al., 2009). As prostaglandins mediate vasodilation of the afferent arteriole in the presence of vasoconstrictive agents such as angiotensin II (ATII), norepinephrine (noradrenaline), vasopressin, and endothelin, they provide critical counterbalance to the vasoconstriction that predominates in hypovolaemic states. Thus, the risk of renal ischaemia with NSAID therapy is particularly pronounced in patients who have decreased true or effective circulating volume that predisposes to renal vasoconstriction. CKD patients with their reduced renal reserve are also at higher risk for NSAID nephropathy, which most commonly produces prerenal azotaemia but can also cause intrinsic renal disease. Discontinuation of drug usually reverses the prerenal azotaemia; however, prolonged therapy in high-risk patients may induce ischaemic ATN.

COX-2 isoform specific inhibitors were developed with the goal of minimizing gastrointestinal (GI) toxicity of NSAIDs. While the use of these drugs has decreased due to increased adverse cardiovascular outcomes, their pharmacology underscores the importance of COX metabolism to tissue homeostasis. As previously noted, COX-1 is constitutively expressed in various tissues, including the GI tract, where it is plays a cytoprotective role (Smyth et al., 2009). Basal COX-2 expression is lower compared to COX-1 and responds to inflammatory stimuli that release cytokines and growth factors (Harris, 2006). Thus, COX-2 inhibitors dampen inflammation mediated COX-2 expression while avoiding GI toxicity that occurs with inhibition of constitutive COX-1 expression. This principle, however, does not apply to renal COX-2, which plays an integral role in maintaining RBF and GFR when intravascular volume is compromised (Harris, 2006). Thus, COX-2-specific inhibition may not be less toxic to the kidney. Indeed, while COX-2 inhibitors such as celecoxib, valdecoxib, and rofecoxib have demonstrated reduced GI toxicity versus COX-1 inhibitors, their nephrotoxic profile is similar to traditional NSAIDs (Harris and Breyer, 2006).

Calcineurin inhibitors

Potent immunosuppression by calcineurin inhibitors (CNIs) is critical to preventing rejection of solid organ and bone marrow transplants. The two CNIs in clinical use, ciclosporin and tacrolimus, utilize different pathways that converge to inhibit calcineurin, a phosphatase that activates transcription factors for genes involved in T-cell division. Within the kidney, they promote afferent arteriolar vasoconstriction by enhancing the release of vasoconstrictors such as ATII and endothelin, while inhibiting the secretion of vasodilators such as nitric oxide and prostaglandins (Naesens et al., 2009). These effects are dose-dependent and can be modulated by lowering drug doses or by avoiding medications that interfere with metabolism of CNIs. Similar to COX inhibitors, the risk for CNI nephrotoxicity is increased in patients who have intravascular volume depletion or CKD.

Efferent arteriolar vasodilators

The angiotensin II type 1 (AT_1) receptor on the efferent arteriole constricts in response to ATII binding. Thus, drugs that inhibit the renin–angiotensin–aldosterone system (RAAS) by lowering ATII

levels, such as angiotensin-converting enzyme inhibitors (ACEIs), or by blocking the AT_1 receptor (ARBs) result in vasodilation of the efferent arteriole. The resulting decrease in intraglomerular pressure transiently reduces GFR. The compensatory response is vasodilation of the afferent arteriole to increase RBF and maintain glomerular perfusion pressure, but this response is blunted when RBF is impaired in clinical situations of intravascular volume depletion, bilateral or critical renal artery stenosis, and advanced CKD. When compensatory afferent arteriolar vasodilation is intact, however, there is compelling indication for RAAS blockade in patients with renal disease and heart failure. Thus, minimal decline in GFR may be tolerated if there is a clinical indication for ACEI/ARB use (Bakris and Weir, 2000). More often, hyperkalaemia rather than increased creatinine prompts withdrawal of these agents.

Intrinsic kidney disease

Drug-induced intrinsic kidney disease refers to injury to compartments within the renal parenchyma. Thus, insults in this broad category can be further subdivided according to the compartments they affect, that is, vascular, glomerular, tubular, and interstitial.

Vascular injury

The renal vasculature is susceptible to drug-induced injury by a variety of mechanisms (Table 362.5). The injury may result from events proximal to the downstream kidney, as is seen with atheroembolic disease (AED), or from direct injury to renal endothelia from thrombotic microangiopathy (TMA), hyalinosis, and vasculitis. AKI is common, particularly with AED, TMA, and vasculitis, whereas hyalinosis from long-term CNI use typically results in CKD. Thus, clinicians may note either rapid or slow but progressive decline in renal function. Urinalysis varies according to the type of injury. An active urine sediment with red blood cells (RBCs) and/or RBC casts in combination with low-grade proteinuria should prompt consideration of vasculitis (or glomerulonephritis). AED and vasculitis may include systemic inflammatory signs such as fever and arthralgias. Skin lesions of AED and vasculitis include petechiae, purpura, and livedo reticularis. The 'blue-toe' syndrome in AED reflects distal limb ischaemia induced by microemboli. Laboratory abnormalities such as anaemia, thrombocytopenia, and increased lactate dehydrogenase are apparent in TMA. Peripheral eosinophilia is an uncommon feature of AED, but in association with unexplained renal failure, should prompt diagnostic consideration.

Table 362.5 Drug-induced vascular injury

Hyaline arteriolopathy	Calcineurin inhibitors
Thrombotic microangiopathy	Chemotherapeutic agents:
	◆ Mitomycin C
	◆ Gemcitabine
	◆ Cisplatin
	◆ Bleomycin
	◆ 5-Fluorouracil
	Calcineurin inhibitors
	Contraceptives
	Ticlopidine
	Radiation therapy
	Quinine
	IFN-α
Vasculitis	Penicillamine
	PTU
	Levamisole
	Hydralazine
	Anti-TNFα agents
	Allopurinol
Cholesterol emboli (atheroemboli)	Thrombolytic agents
	Heparin
	Warfarin

IFN = interferon; PTU = propylthiouracil; TNF = tumour necrosis factor.

Thrombotic microangiopathy

TMA associated with pharmaceutical agents is usually caused by the thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome (TTP-HUS) spectrum of disorders. TMA classically presents with microangiopathic haemolytic anaemia, thrombocytopenia, and reduced GFR. It is a rare but serious consequence of several drugs (Table 362.5), including CNIs, oral contraceptives, antiplatelet agents, antibodies directed against VEGF and its receptor (anti-VEGF), and gemcitabine. The common feature of all these agents is endothelial injury, which may be a direct action of the drug or an indirect action via increased intravascular thrombi. The TTP variant displays reduced level or activity of a von Willebrand factor (vWF) cleaving protein (referred to as 'a disintegrin and metalloprotease with thrombospondin type 1 repeat' or ADAMTS13) that cleaves pro-thrombotic large vWF to prevent platelet activation and aggregation. The TMA associated with antiplatelet agents may be due to antibody generation against ADAMTS13 (Zakarija et al., 2009). Quinine use may also enhance antibody formation against endothelia, platelets, and lymphocytes that leads to an acute onset of TTP-HUS. Renal histology reveals platelet thrombi within arterioles and within the glomerular capillaries. The injured glomerulus often demonstrates capillary hyaline microthrombi with associated endothelial cell swelling and mesangiolysis (Fig. 362.8).

Gemcitabine-associated TMA may be the result of direct endothelial injury (Izzedine et al., 2006b). Several other anticancer agents have also been implicated, including mitomycin C, cisplatin, and 5-fluorouracil, calling into question whether the drug or underlying malignancy is the primary predisposing risk factor for development of TMA. In contrast to quinine-associated TMA, the disease seen with gemcitabine may have a slow and insidious onset In addition, new-onset hypertension or exacerbation of existing hypertension is common (Humphreys et al., 2004). An ischaemic skin rash may also develop with gemcitabine-associated TMA (Zemtsov et al., 2011).

Anti-angiogenesis therapy, with drugs such as bevacizumab, sunitinib, and sorafenib, are other recognized causes of kidney injury and nephrotoxicity (Yang et al., 2003; Eremina et al., 2008). VEGF, produced by adjacent podocytes (visceral epithelial cells), maintains normal fenestrated endothelial function and health. VEGF

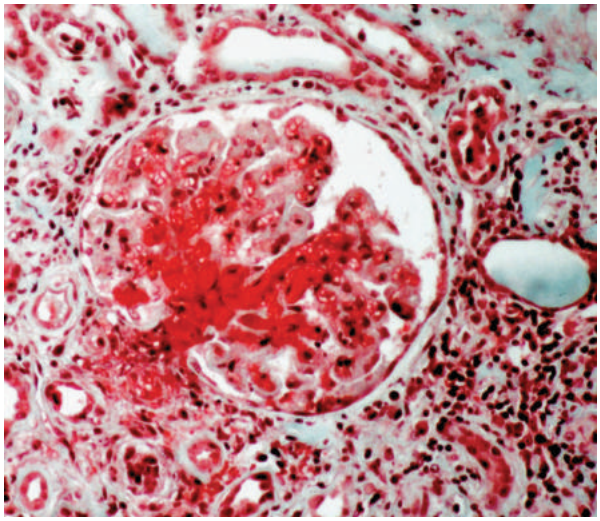

Fig. 362.8 Thrombotic microangiopathy is seen in this glomerulus as manifested by mesangiolysis, endothelial cell swelling, and capillary loop thrombi.

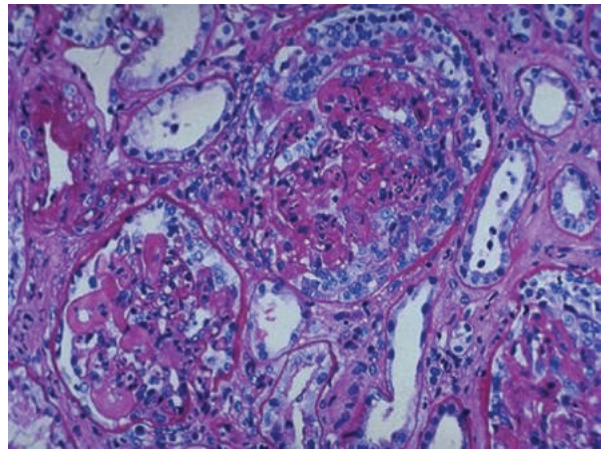

Fig. 362.9 Crescentic glomerulonephritis is seen in these glomeruli. Cellular crescent formation is noted with destruction of the associated glomeruli.

is particularly important for normal functioning of the glomerular basement membrane (Sugimoto et al., 2003). Reduction in VEGF, blockade of its receptor, or blunting of its intracellular signalling pathways by the various anti-angiogenic drugs leads to loss of the healthy fenestrated endothelial phenotype and promotes microvascular injury and TMA (Sugimoto et al., 2003). Clinically, these drugs are associated with hypertension, proteinuria, and kidney injury. Studies have shown a dose-related increase in blood pressure and proteinuria with these agents (Yang et al., 2003; Eremina et al., 2008). Reduced nephrin expression in the slit diaphragms from these drugs may further contribute to proteinuria (Sugimoto et al., 2003). While these drugs have been described to cause a number of kidney lesions, glomerular endothelial injury and TMA are the most commonly noted (Yang et al., 2003; Gurevich and Perazella, 2009).

Treatment of drug-induced TMA includes removal of agent whenever possible. In cases where reduced levels of ADAMTS13 are demonstrated to be the cause of TMA, plasma exchange is useful treatment. In the absence of reduced protease levels, such as in cases linked to gemcitabine, this treatment approach has not been successful (Humphreys et al., 2004).

Vasculitis

Some drugs induce a hypersensitivity reaction that results in vascular inflammation that affects multiple organs. Skin manifestations, such as a leucocytoclastic rash, are common. Other inflammatory signs such as fever, arthralgias, and myalgias may also be present. Renal involvement typically presents as rapidly progressive renal failure with haematuria and proteinuria. Urine sediment may display red cells, sometimes organized into casts. Renal biopsy typically displays inflamed vessels and necrotizing glomerulonephritis, often with crescent formation (Fig. 362.9). Serological workup may reveal positive antineutrophil cytoplasmic antibodies (ANCA), particularly against myeloperoxidase (MPO). Some drugs induce a syndrome that shares features with systemic lupus erythematosus (DIL). These drugs, particularly hydralazine, may be associated with ANCA. However, antibodies against other nuclear components, such as anti-histone antibodies, are more likely. Many drugs have been associated with vasculitis, but a causal role has been difficult to establish.

Certain drugs, however, are well established as aetiologic agents including penicillamine and propylthiouracil (PTU). Levamisole, originally developed as an antiparasitic agent but now banned in several countries because of serious side effects, is used as a cutting agent in preparing cocaine. Such adulterated preparations are thought to increase cocaine-induced psychotropic effects and have been associated with severe vasculitis and renal failure. Both levamisole and PTU are associated with ANCA-positive serology (Simms et al., 2008; Zwang et al., 2011). As previously mentioned, hydralazine exposure may be associated with DIL. Anti-tumour necrosis factor-alpha (TNFα) antibody drugs utilized to treat a number of disease states have been associated with ANCA-positive serology and an associated necrotizing and crescentic GN (Simms et al., 2008; Dedeoglu, 2009). Several mechanisms have been proposed for the autoimmunity induced by anti-TNFα antibodies, including increased apoptosis of cells and release of nuclear antigens as well as cytokine shifts to a T-helper cell type 2 profile (Dedeoglu, 2009).

Atheroemboli

Renal AED occurs when cholesterol crystals break off from atherosclerotic plaques and lodge within end-organ small vessels, including renal arterioles, causing tissue ischaemia. This also initiates an inflammatory cascade, which results in an influx of polymorphonuclear leucocytes, giant cells, and eosinophils (Fig. 362.10). Over time, the inflamed blood vessels may become hyperplastic and occluded. With sustained tissue ischaemia and the associated interstitial inflammation, interstitial fibrosis and glomerular sclerosis are late-stage findings. Spontaneous cases have been reported, but more commonly, procedures that can potentially disrupt and dislodge atherosclerotic plaques such as coronary angiography and vascular procedures precipitate development of renal failure. Paradoxically, the use of anticoagulants including heparin, warfarin, and tissue plasminogen activator, is linked with development of renal AED. Because anticoagulants dissolve the clots that develop over and stabilize ruptured plaques, their use may cause greater propensity to dislodge and shower downstream, including into renal vessels.

Renal AED often occurs in the setting of systemic AED (rash/livedo reticularis, retinal ischaemia, GI bleed, pancreatitis, severe

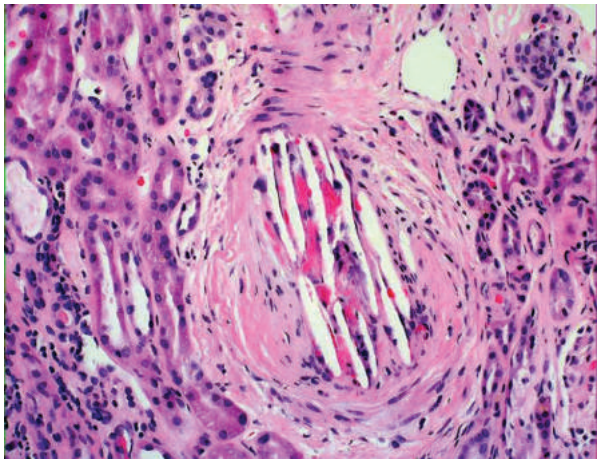

Fig. 362.10 Renal atheroemboli is manifested as biconcave clefts and intimal hyperplasia and giant cell reaction noted in the arteriole.

hypertension, peripheral eosinophilia/hypocomplementaemia, etc.) mimicking other diseases such as vasculitis, or present in isolation with kidney injury. In the end, renal AED may cause AKI, a subacute, stuttering course of kidney injury, or CKD leading to ESRD.

Hyalinosis

Hyaline deposition in endothelial cells with progressive arteriolar thickening is a pathognomonic lesion for vascular injury from calcineurin inhibitors (Liptak and Ivanyi, 2006). Hyalinosis represents the end stage of a process that begins with vacuolization of endothelial cells and vascular smooth muscle cells. As damaged cells die off, they are replaced by extracellular matrix and insudated plasma proteins that have a characteristic smooth, pink-coloured appearance (hyaline) on light microscopy. Eventually, hyaline deposition can completely occlude the vascular lumen and result in tissue ischaemia and sclerosis.

Glomerular injury

Therapeutic agents can also cause various glomerular patterns of injury (Table 362.6). Most of these agents disrupt podocyte integrity and function. Thus, with injury to the filtration barrier, patients present with proteinuria, often in the nephrotic range. Other manifestations of nephrotic syndrome including hypoalbuminaemia, hyperlipidaemia, and oedema may also be present. Serum creatinine may be increased, representing drug-induced haemodynamic, tubular or interstitial injury, rather than a pure glomerular lesion. Urinary sediment is generally bland, though microscopic haematuria may be present in cases of membranous glomerulonephritis. Three types of histological lesions are most commonly seen in drug-induced glomerulopathies: minimal change disease (MCD), focal and segmental glomerulosclerosis (FSGS), and membranous glomerulonephritis (MGN).

Minimal change disease

MCD is characterized by normal light microscopy and immunofluorescence, but complete podocyte effacement on electron microscopy (EM). Many drugs are associated with this lesion, but the most common offenders are NSAIDs, including the selective COX inhibitors. Patients present with an insidious onset of heavy proteinuria and not uncommonly, renal failure. Interstitial inflammation with T cells and B cells may be apparent on histopathological examination. NSAID discontinuation typically reverses the renal failure. In contrast to primary MCD, steroids do not have a proven role in treating NSAID-induced MCD. Other agents linked to development of MCD include penicillamine, interferon, gold, and pamidronate.

Table 362.6 Drug-induced glomerulonephritides

Minimal change disease	COX inhibitors: NSAIDs and COX-2 selective agents
	IFN-α
	Lithium
	Quinolones
	Penicillins
	Traimethadione
Focal and segmental glomerulosclerosis	Pamidronate
	Lithium
	Heroin
	IFNs: alpha, beta, and gamma
Membranous glomerulonephritis	Gold
	NSAIDs and COX-2 selective inhibitors
	Penicillamine, bucillamine
	Captopril

COX-2 = cyclooxygenase; IFN = interferons; NSAIDs = non-steroidal anti-inflammatory agents.

Focal and segmental glomerulosclerosis

Some of the same agents that are linked to MCD lesions are also associated with FSGS, including lithium and interferons. Another prime example is pamidronate, a bisphosphonate used in the treatment of osteoporosis, hypercalcemia, and lytic bone lesions. Pamidronate was first linked to a collapsing variant of FSGS in several patients who received higher than standard doses of intravenous pamidronate, suggesting a dose-dependent effect (Markowitz et al., 2001). Months after sustained exposure to pamidronate, the majority of patients presented with renal failure and nephrotic range proteinuria (Markowitz et al., 2001). Histological examination revealed features typical to FSGS, with negative or non-specific immunofluorescence staining but severe sclerosis of the glomerular tuft and diffuse podocyte injury on EM (Markowitz et al., 2001). As seen in Fig. 362.11, collapsing FSGS is characterized by an exuberant number of visceral epithelial cells forming a pseudo-crescent around the collapsed and shrunken glomerulus. Other studies support a link between pamidronate and FSGS, with collapsing as well as other variants (Bodmer et al., 2007). Other bisphosphonates including zoledronate have also been linked to FSGS lesions, but much less frequently (Bodmer et al., 2007).

Collapsing FSGS has also been reported in a cohort of patients with chronic anabolic androgen use for bodybuilding purposes (Herlitz et al., 2010). Androgens may cause FSGS through multiple mechanisms including the induction of hyperfiltration, upregulation of the RAAS, and direct injury to the glomerular podocyte.

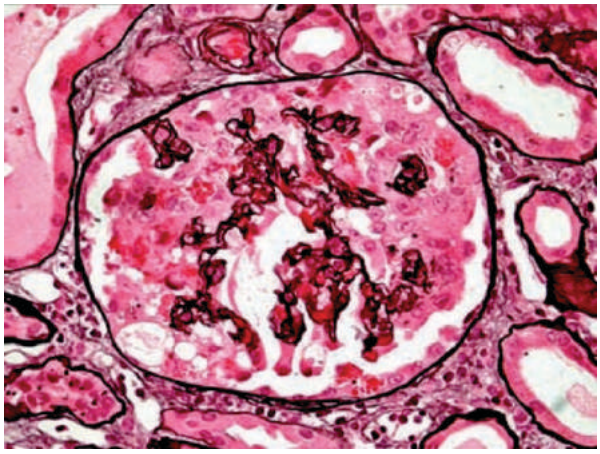

Fig. 362.11 Collapsing focal and segmental sclerosis (FSGS) is noted. The glomerulus is severely collapsed and significant visceral cell hyperplasia is present.

In addition, all forms of interferon (alpha, beta, and gamma) have been associated with development of FSGS, including collapsing FSGS (Markowitz et al., 2010). The mechanism of injury is unclear but may be through direct and indirect effects. Interferon may bind podocyte receptors and alter cellular proliferation and metabolism, induce oxidative stress and increase MHC class II antigen expression. Indirect effects include macrophage activation (as in haemophagocytic syndrome which is associated with FSGS) or stimulation of pathogenic cytokine synthesis (interleukin (IL)-6, IL-13), which are permeability factors in FSGS and MCD (Markowitz et al., 2010).

Membranous glomerulonephritis

MGN is an immune-complex GN characterized by diffuse glomerular basement membrane thickening with no hypercellularity on LM (Fig. 362.12). Immunofluorescence examination shows diffuse, granular IgG staining along the glomerular capillary wall. Ultrastructural details include subepithelial deposits with 'spike'-like extensions. Drugs most often implicated in MGN lesions include those used for treatment of rheumatological diseases, such as penicillamine, bucillamine, and gold. These drugs may act as haptens that induce formation of autoreactive lymphoid cells. NSAIDs and selective COX inhibitors have also been described to cause MGN. However, this occurs less commonly when compared with NSAID-associated MCD. Patients present with heavy proteinuria and renal failure, which often reverses with cessation of drug therapy. Crescentic GN has been noted with penicillamine therapy and renal recovery may be prolonged (Mathieson et al., 1996).

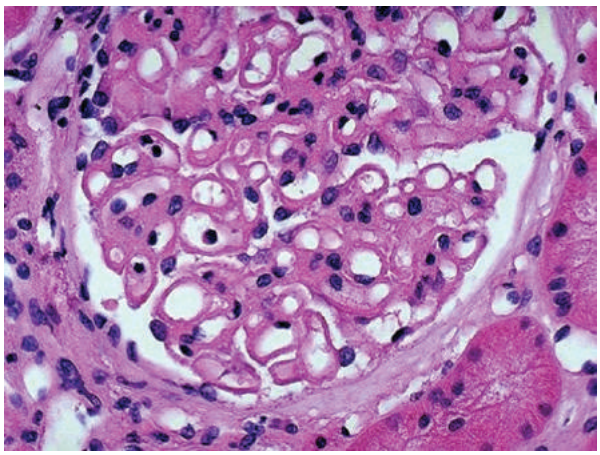

Fig. 362.12 Glomerular capillary loop thickening is noted and consistent with membranous glomerulonephritis.

Acute tubular necrosis

Tubular injury resulting in acute tubular necrosis (ATN) is a common mechanism for drug-induced nephrotoxicity. An extensive number of drugs are associated with ATN, and the more common of these agents are listed in Table 362.7. Pharmaceutical agents can either directly or indirectly injure the renal tubule. For example, tubules are not sensitive to statins per se, but rather to the rhabdomyolysis and myoglobinuria that statins may induce and subsequently lead to haem pigment nephropathy. Furthermore, while some drugs may have an intrinsically high nephrotoxic potential, clinical risk factors are the most important predictors for renal injury. Patients may have baseline CKD or they may be receiving certain nephrotoxic agents because of malignancy or infection, and these disease states render greater vulnerability to renal tubular injury. Thus, while the severity of drug-induced ATN is generally dose dependent, a lowered drug burden may still induce significant injury in vulnerable patients.

Table 362.7 Drug-induced acute tubular necrosis

Antibiotics, antiviral, and antifungal agents	Aminoglycosides: gentamicin > amikacin > tobramycin
	Cephalosporins (select): cefazolin > cephalexin, ceftazidime
	Polymixins: colistin, polymyxin B
	Vancomycin
	Pentamidine
	Foscarnet
	Nucleotide analogues: cidofovir, tenofovir, adefovir
Chemotherapeutic agents	Cisplatin > carboplatin
	Ifosfamide
	Methotrexate (high dose)
	Pemetrexed
	Imatinib
	Pentostatin
Contrast agents	Hyperosmolar > low osmolar > iso-osmolar radiocontrast
	Gadolinium-based contrast
Miscellaneous	Statins (via rhabdomyolysis)
	Zoledronate
	Warfarin (macroscopic haematuria)
	Cocaine, amphetamines, bath salts

Nephrotoxic ATN can affect any part of the tubule but characteristically injures the proximal tubule (PT), as it is the first renal segment to be exposed to a potentially nephrotoxic concentration of drug, either at the apical side from glomerular filtrate or on the basolateral side from peritubular capillaries. The high metabolic activity of the PT makes it particularly sensitive to cellular injury, and injury can diminish its re-absorptive capacity for sodium and other electrolytes. Thus, patients with ATN may display urine $Na^+ > 20$ and Fe NA > 2% and with injury at particular sites in the tubule, urinary magnesium, phosphorous, and glucose wasting may be evident. Proteinuria is generally mild and urine sediment may contain renal tubular epithelial (RTE) cells, RTE casts, or granular casts with classic 'muddy-brown' appearance (Fig. 362.13). Patients suspected of ATN rarely undergo kidney biopsy, as the diagnosis is usually clinically apparent. However, when tissue is obtained in this setting, it often reveals dilated tubules, flattened epithelium with blebbing and tubular simplification and atrophy with a small amount of interstitial oedema and few inflammatory cells (Fig. 362.14). Depending on the agent and severity of injury, renal failure may be either non-oliguric or oliguric and may require supportive care with haemodialysis, as kidney injury may persist even after drug withdrawal.

The pharmacological agents, listed by their drug class in Table 362.7, may disrupt tubular integrity via a variety of mechanisms including mitochondrial dysfunction, free radical generation, disruption of transcellular ionic gradients, and inflammatory cytokine release.

Antibacterial agents

Among antibiotics, aminoglycosides carry the greatest risk of nephrotoxicity because they are excreted primarily by the kidney. The exact mechanism of injury is not known but the cationic and amphophilic properties of aminoglycosides suggest a binding affinity for PT membranes, likely via the megalin receptor (Schmitz et al., 2002). Nephrotoxicity appears to track with charge—the more cationic (neomycin > gentamicin > amikacin), the more likely the drug will interact with PT apical membranes and induce injury. Thus, the PT readily absorbs and accumulates these agents within intracellular lysosomes. Upon accumulating within lysosomes, myeloid bodies are noted to develop. These structures are membrane fragments and damaged organelles formed as a consequence of aminoglycoside inhibition of lysosomal enzymes. Within the PT epithelial cell, they disrupt the activity of subcellular organelles, induce oxidative stress, and promote mitochondrial dysfunction. Decreased drug load and reduced frequency of administration can avoid the toxic peak levels, which are associated with increased PT uptake. Antagonizing megalin binding is an attractive target for prevention of aminoglycoside nephrotoxicity.

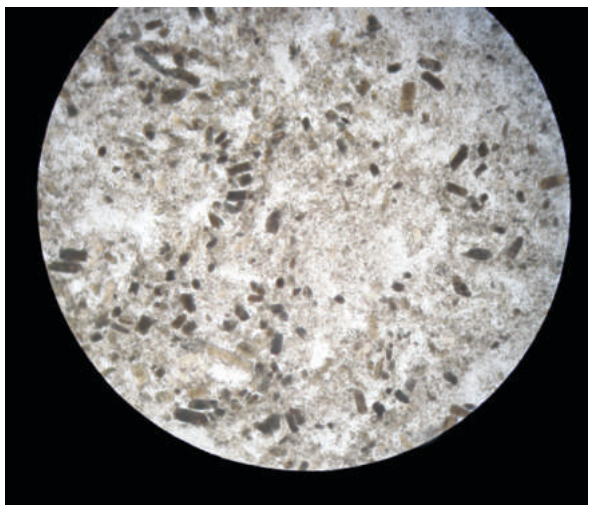

Fig. 362.13 Urine microscopy reveals a larger number of granular casts, consistent with severe acute tubular necrosis.

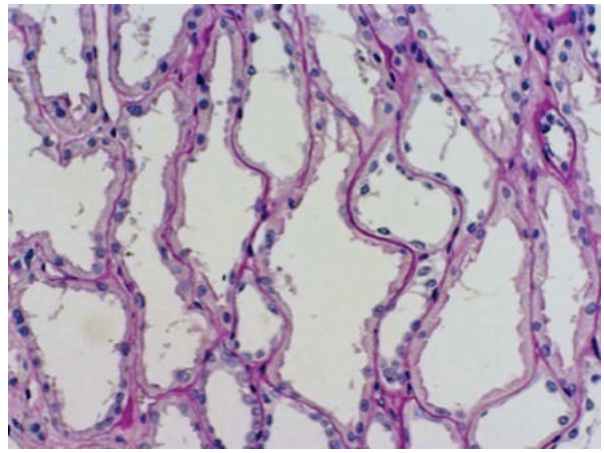

Fig. 362.14 Renal biopsy reveals severe acute tubular necrosis as manifested by tubular dilatation and flattening of epithelial cells, tubular cell dropout with epithelial simplification, and tubular cell apical blebbing.

Cephalosporins are another class of agents that are implicated in renal injury. While classically associated with AIN, certain cephalosporins, particularly agents such as cephaloglycin and cefaclor, are an infrequent cause of ATN. The risk for ATN increases with concomitant use of other nephrotoxic agents, such as NSAIDs and aminoglycosides.

Other nephrotoxic antibiotic agents include colistin, a polymixin, and vancomycin, which promotes renal injury when very high concentrations develop. Colistin and polymyxin B are polymixin antimicrobials that are extremely nephrotoxic. These agents possess a very narrow therapeutic window and their nephrotoxicity is related to their D-amino content and fatty acid component, which increases tubular cell membrane permeability and influx of cations (Falagas et al., 2005). Vancomycin is typically a well-tolerated drug, however, it can induce AKI via two mechanisms. One is idiosyncratic through induction of AIN, while the other is direct tubular toxicity when excessive serum concentrations develop (Bergman et al., 1988; Shah-Khan et al., 2011). Renal biopsies in patients with AKI associated with toxic vancomycin concentrations have demonstrated ATN (Shah-Khan et al., 2011).

Chemotherapeutic agents

Many widely used oncological drugs with tumouricidal activity are also nephrotoxic. Cisplatin, for example, is associated with a high incidence of non-oliguric ATN, chiefly because hydrolysis of a chloride ion on the parent molecule releases hydroxyl radicals that mediate tubular injury. Cisplatin gains entry into renal tubular cells in part through the organic cation transporter-2 (OCT-2) (Pabla and Dong, 2008). Other pathways of tubular injury caused

by cisplatin include renal vascular injury with associated tubular ischaemia, increased TNFα production with inflammation, and increased signalling via MAP kinases and p53, all which promote renal tubular cell apoptosis and death (Fig. 362.15). Carboplatin and oxaloplatin, also platinum-based agents, are less nephrotoxic than cisplatin but do have a risk of nephrotoxicity at high doses (Hartmann and Lipp, 2003). This decrease in toxicity relates in part to the lack of the chloride ion and the absence of OCT-2 transport into cells (Ciarimboli et al., 2005). Platin-related kidney injury may be reduced by provision of amifostine (glutathione analogue), sodium thiosulphate, and other antioxidants (Pabla and Dong, 2008). However, use of these drugs is complicated by adverse effects and reduced tumouricidal properties. Prevention of cisplatin toxicity is treated primarily with saline and hypertonic saline and correction of electrolyte disturbances.

The alkylating agent ifosfamide is a synthetic analogue that is unique from the parent molecule, cyclophosphamide, in inducing ATN. This difference in nephrotoxicity from ATN between the drugs is likely related to overproduction of toxic metabolites such as chloroacetaldehyde (Zhang, 2005). Another potential explanation is that like cisplatin, ifosfamide enters proximal tubular cells vis OCT-2, whereas cyclophosphamide does not (Zhang, 2005). Aside from vigorous saline administration, there are no defined prophylactic measures to reduce ifosfamide nephrotoxicity.

Other agents cause PT injury that is usually limited to high doses. These include the antimetabolite methotrexate and its derivative pemetrexed. Interestingly, they appear to cause tubular injury via separate mechanisms. Methotrexate, as discussed later, causes AKI primarily through precipitation of insoluble drug crystals within tubular lumens, while recent cases report direct renal tubular toxicity with pemetrexed (Glezerman et al., 2011). These patients had been exposed to other chemotherapeutic agents with nephrotoxic potential prior and had underlying risk factors such as hypertension, diabetes mellitus, ACEI therapy, and diuretics. This agent is taken up into tubular cells receptors located on the apical (folate receptor-alpha) and basolateral cell membranes (reduced folate carrier). Once inside the cell, pemetrexed is polyglutaminated and trapped within the cell. As a result of high tubular cytoplasmic concentrations, pemetrexed impairs RNA and DNA synthesis via its antifolate effect and causes tubular injury. Renal histology in patients with pemetrexed-induced AKI revealed tubular injury and atrophy along with associated interstitial fibrosis (Glezerman et al., 2011). Thus, use of this drug in patients with risk factors for AKI must be monitored closely for nephrotoxicity.

Antifungal agents

The antifungal activity of amphotericin B depends on insertion into fungal cell walls, which results in pore formation and disruption of cell membrane integrity and transmembrane ionic gradients (Perazella, 2005). This same mechanism is postulated to cause tubular membrane injury, which results in characteristic urinary potassium and magnesium wasting in addition to acute cellular necrosis. Additionally, amphotericin B preparation requires solubilization by deoxycholate, which also possesses nephrotoxic potential. Nephrotoxicity may be acute, due to afferent arteriolar vasoconstriction or subacute/chronic due to dose-related cellular injury. Prevention of nephrotoxicity consists primarily of saline infusion during amphotericin B administration, alternate day dosing when serum creatinine rises, and, if possible, substitution with a non-nephrotoxic agent. The liposomal and lipid complex formulations have reduced nephrotoxicity, in part because they do not require deoxycholate for solubilization. However, with increasing doses, these agents also cause AKI over time, especially in patients with underlying risk factors (Alexander and Wingard, 2005). Most other antifungal agents are, for the most part, considered to have low nephrotoxic potential.

Antiviral agents

Several antiviral agents that are integral to treatment of viral infections, including the human immunodeficiency virus (HIV) and the hepatitis viridae can cause tubular injury. Tenofovir, for example, is a nucleoside reverse transcriptase inhibitor (NRTI) with potent anti-HIV activity. Similar to other NRTIs, including cidofovir and

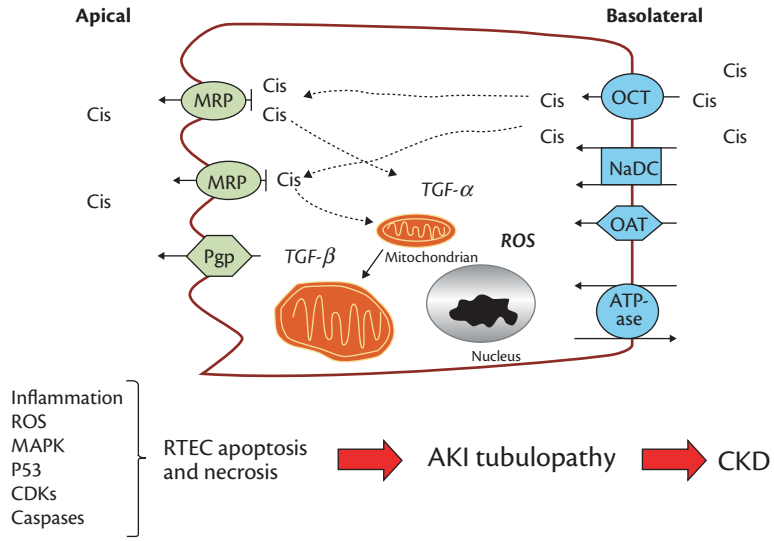

Fig. 362.15 Cisplatin (Cis) nephrotoxicity is in part related to its uptake by proximal tubular cells. Cis enters cells via organic cation transporters (OCT) and when it accumulates within cells, causes cell injury via multiple mechanisms. Apoptosis and necrosis of tubular cells result and cause clinical acute kidney injury (AKI) and tubulopathy. Not uncommonly, chronic kidney disease (CKD) may develop following cisplatin therapy.

adefovir, PT epithelial cells avidly take up tenofovir via organic anion transporters on the basolateral membrane (Perazella, 2005). Thus, drugs enter the renal circulatory system via peritubular capillaries and accumulate inside PT cells to cause mitochondrial toxicity. As discussed previously, this is particularly true for patient with underlying kidney disease and patients with a single nucleotide polymorphism in the gene coding the MRP2 efflux transporter for tenofovir. One way to counteract these effects of tenofovir is reduced dosing or avoidance of drug in patients with advanced kidney disease. Another approach, based on the OAT uptake of tenofovir, is co-administration with probenecid, a competitive inhibitor of the OAT (Perazella, 2005).

Other antiviral agents implicated in renal dysfunction include foscarnet and aciclovir (discussed later), which cause tubular injury in part due to intratubular crystal formation and deposition. Foscarnet has been described to cause both direct renal tubular injury as well as precipitate in glomerular capillaries, an unusual form of crystal-related injury.

Rhabdomyolysis

Myotoxic drugs induce ATN primarily by indirect mechanisms. Such drugs, which include statins, fibrates, and drugs associated with neuroleptic malignant syndrome, cause muscle injury and release of the haem-containing protein myoglobin. Myoglobin is nephrotoxic by a variety of mechanisms including vasoconstriction of renal blood vessels, tubular obstruction by cast formation, and direct proximal tubule injury (haem-induced oxidative injury). Thus, in addition to evidence of tubular necrosis, renal biopsy may even show tubular haemosiderin deposition, reflecting uptake of haem pigment by epithelial cells. Treatment of rhabdomyolysis includes aggressive intravascular volume repletion to maintain high urine flow rates and to prevent precipitation of myoglobin.

Radiocontrast-induced nephropathy

The frequent use of computed tomography (CT) scans as a diagnostic modality and other radiocontrast-based diagnostic and therapeutic interventions (angiography) has resulted in increased prevalence of radiocontrast-induced nephropathy (RCIN). RCIN commonly refers to the direct tubular injury induced by contrast, but it should be noted that there is a haemodynamic component that may be mediated by decreased renal blood flow. Thus, an ischaemic component may also be present. The mechanism of direct tubular injury is thought to be multifactorial: (1) oxidative stress from increased production of free oxygen radicals, and (2) osmotic cellular injury, which is supported in part by the observation that the risk of RCIN is highest with high osmolar contrast. This is supported by the decreased incidence of AKI noted with reduced dye volume as well as low or iso-osmolar contrast. In patients receiving radiocontrast agents, preventive treatment with isotonic fluids prior to radiocontrast exposure is standard therapy. There is consensus that isotonic fluids are preferred volume expanders, but the utility of adding bicarbonate to intravenous fluids is less clear. While some studies have shown an added benefit to urinary alkalinization, others have demonstrated equal efficacy. These disparate results probably reflect differences in study design and patient populations. Thus, one acceptable approach would use either isotonic saline or isotonic bicarbonate, but forego bicarbonate use in those patients for whom it is contraindicated (concomitant hypocalcaemia, metabolic alkalosis, etc.)

Similar to bicarbonate fluid administration, *N*-acetyl cysteine (NAC) use to prevent CIN has also yielded mixed results. Most of these studies have been small and not adequately powered to study hard clinical endpoints. The Acetylcysteine for Contrast-induced Nephropathy Trial (ACT), which included 2308 patients, documented no benefit with NAC therapy as RCIN developed in 12.7% of NAC-treated and placebo patients (ACT Investigators, 2011). Thus, while NAC is safe and inexpensive, it appears to offer no protection against RCIN and probably should be abandoned as therapy. However, correction of volume depletion as well as use of low volume and iso-osmolar contrast carries the greatest renal benefit for all patients.

Warfarin-related nephropathy

Recently, a relatively new form of AKI has been described in patients treated with warfarin (Brodsky et al, 2009). It has been described in patients with and without CKD who are over-anticoagulated (international normalized ratio > 3). The mechanism appears to be as follows: excessive anticoagulation leads to glomerular haemorrhage, often in patients with an underlying glomerulopathy (immunoglobulin A (IgA) nephropathy), with subsequent obstruction of tubules with RBC casts (Fig. 362.16). The cause of AKI is not clearly known, but may be related to tubular obstruction and/or haem-related tubular injury from lysosomal overload and oxidative damage (Brodsky et al, 2009). Therapy consists of reversal of anticoagulation initially, followed by more judicious anticoagulation in those who truly require it (e.g. prosthetic valves). Unfortunately, many patients do not recover from AKI and are left with CKD, sometimes requiring chronic dialysis.

Treatment of all forms of drug-induced ATN includes removal of the offending agent, correcting volume depletion, avoiding other nephrotoxin exposure, and appropriate drug dosing, but renal recovery may not immediately follow. In addition, clinical situations may sometimes require continuation of drug if its overall benefit to the patient outweighs the risk of renal injury. Prevention of nephrotoxic ATN by modification of risk factors, therefore, is paramount to preventing adverse renal outcomes. Care must be taken in all patients and particularly in those with CKD or other risk

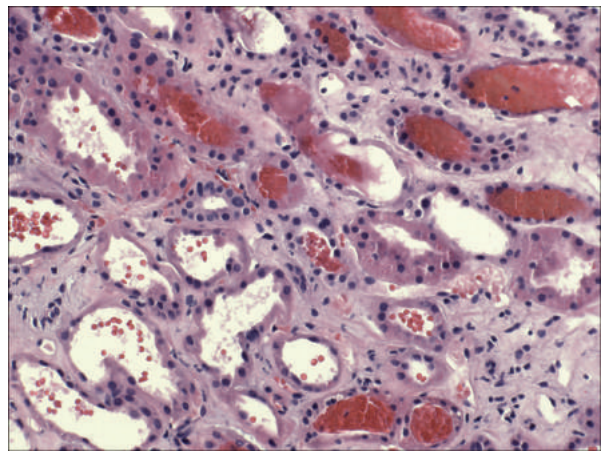

Fig. 362.16 Severe acute tubular injury and tubular lumens filled with red blood cell casts are noted. This entity is known as 'warfarin nephropathy' and occurs in the setting of over-anticoagulation in a patient with underlying kidney disease, such as IgA nephropathy.

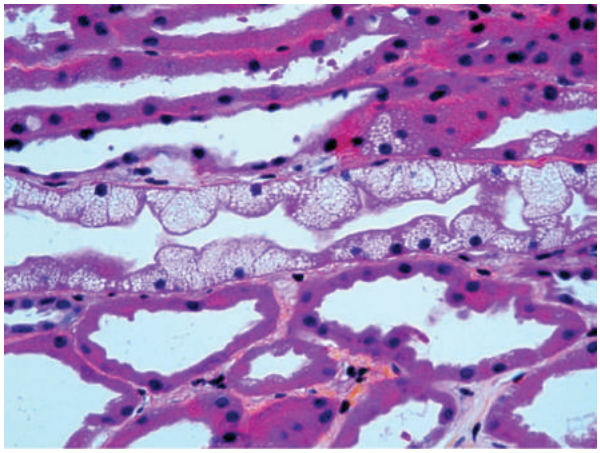

Fig. 362.17 Osmotic nephropathy is noted. Uptake of various substances, such as sucrose, hydroxyethyl starch, and dextran overload lysosomes, causing tubular cell swelling and acute kidney injury.

factors for AKI, to avoid NSAIDs and to treat pre-existing volume depletion.

Osmotic nephropathy

Osmotic nephropathy refers to the type of injury seen when certain macromolecules enter proximal tubule cells via pinocytosis or other forms of endocytosis. The first description of this pattern of injury dates back to animal studies from the 1940s undertaken after death from renal failure was reported in patients given intravenous sucrose (Anderson and Bethea, 1940). These studies noted that sucrose infusion results in tubular epithelial cell swelling and the degree of swelling correlates with renal dysfunction (Anderson and Bethea, 1940). Similar results were later described with other agents such as mannitol and dextran, and more recently, with intravenous immunoglobulin (IVIG) and hydroxyethyl starch (HES) (Perazella, 2005). This suggests a common mechanism of injury that begins with drug entry into the tubular cell. As these agents are not further metabolized, they accumulate within lysosomes (Fig. 362.17), causing tubular epithelia to swell and form vacuoles. These structural responses disrupt cellular integrity and if tubular swelling is severe, obstruct tubular lumens to occlude urine flow and cause AKI. Renal biopsy reveals characteristic histopathologic lesions such as swollen, oedematous tubules often filled with cytoplasmic vacuoles. With severe injury, tubules may appear degraded, similar to dense ATN (Perazella, 2005).

Intravenous immunoglobulin

The major IVIG preparation commonly linked to osmotic-related renal injury contains sucrose as a stabilizing agent (Chapman et al., 2004). Thus, osmotic nephropathy from IVIG likely reflects injury directly mediated by sucrose, as described above. Indeed, histological lesions in IVIG-suspected nephropathy are similar to those seen with sucrose-mediated AKI (Perazella, 2005). Non-sucrose containing forms of IVIG that contain other carbohydrate stabilizers are available. The use of these agents has not been linked to AKI and thus, is ideal therapy for patients who are at higher risk for osmotic nephrosis, including those with pre-existing CKD.

Hydroxyethyl starch

Hydroxyethyl starch (Hetastarch; HES) is a potent volume expander whose use in particularly favoured in the surgical field. The HES product consists of an amylopectin chain with hydroxyethyl substitutions of varying degrees. By generating oncotic pressure within the vasculature, HES encourages plasma volume refilling. Increased hydroxyethyl substitution results in higher molecular weight HES that provides greater volume expansion. However, these forms are less easily metabolized and more prone to causing AKI, particularly in patients with underlying kidney disease (Davidson, 2006). Similar to previously discussed agents, HES-induced renal injury has features typical of osmotic nephrosis such as tubular cell oedema and vacuolization.

Dextran

Dextran is another volume expander that has long been linked to osmotic-related kidney injury in both animal models as well as clinical studies. While not as prevalent as HES in use as a colloid agent, dextran has antiplatelet properties that have made it useful prophylaxis against thrombotic events during surgery. Thus, it should be noted that in cases of unexplained postoperative AKI, a thorough examination of perioperative medications including dextran is warranted.

Therapy for this renal lesion centres primarily on discontinuation of suspected agents. Unfortunately, while many cases recover from AKI, patients who develop severe AKI require support with either continuous renal replacement therapy or acute haemodialysis. Prevention of or prophylaxis against osmotic nephropathy requires avoiding concomitant administration of other nephrotoxic agents, maintaining euvolaemia, and avoiding their use in high-risk individuals. As such, avoidance of these drugs should be strongly considered in patients who have reduced renal reserve at baseline from other forms of kidney disease or have sepsis (especially relevant to HES).

Table 362.8 Drug-induced crystal nephropathy

Sulphonamides
Aciclovir
Methotrexate
Indinavir/atazanavir
Triamterene
Ciprofloxacin
Nitrofurantoin
Sodium phosphate purgative

Crystal nephropathy

Intratubular crystal precipitation can occur with administration of several drugs (Table 362.8). Depending on the clinical situation and specific agent, AKI may result and occasionally require institution of dialysis.

Indinavir and atazanavir

Protease inhibitors such as indinavir, and more recently atazanavir are important in treatment against the human immunodeficiency virus (HIV). Both agents, however, may precipitate within renal tubules to form crystals (Fig. 362.18) and in the collecting system to form stones. The risk appears to be slightly higher with indinavir, although both agents have a greater propensity to

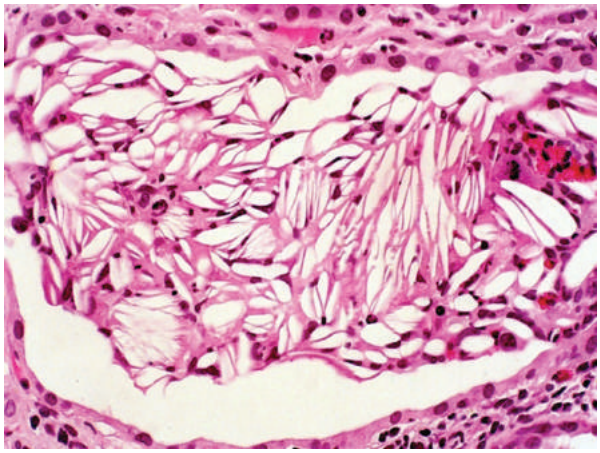

Fig. 362.18 Crystal nephropathy from indinavir therapy is noted. The insoluble indinavir crystals can precipitate within distal tubular lumens and cause acute kidney injury. Other drugs such as aciclovir, sulphadiazine, ciprofloxacin, and atazanavir may also cause crystal nephropathy.

cause crystalluria and stone disease than other anti-HIV medications (Atta et al., 2008). These protease inhibitors are maximally soluble in urine only when pH decreases below 4.0 (Yarlagadda and Perazella, 2008). Since the kidney cannot acidify urine to such a level, treatment must focus on copious fluid intake. Other risks for crystal precipitation and stone formation are volume depletion, underlying kidney or liver disease, and for indinavir, treatment with trimethoprim-sulfamethoxazole. Treatment consists of drug discontinuation, volume repletion, and in the setting of obstructing stones, urologic interventions. In general, 25% of patients are unable able to take indinavir due to recurrent renal toxicity (Yarlagadda and Perazella, 2008).

Aciclovir

Crystal deposition with aciclovir depends on the rate of delivery. When delivered via intravenous bolus at 500 mg/m^2, aciclovir is excreted in urine via rapid filtration and tubular secretion (Yarlagadda and Perazella, 2008). Combined with inherently low solubility, intratubular deposition of characteristic needle-shaped aciclovir crystals may occur, particularly in states of volume depletion. Oral aciclovir has reduced rate of absorption and delivery for renal excretion, which is a probable explanation for why oral drug dosing carries little risk of crystalluria. However, excessive doses of oral valacyclovir, which is metabolized to aciclovir, in patients with risk factors (volume depletion, underlying kidney disease) can cause crystal nephropathy (Roberts et al., 2011). Ganciclovir, which is structurally related to aciclovir, does not appear to cause crystalluria.

Aciclovir-induced crystal nephropathy is often associated with nausea, flank pain, pyuria with crystalluria, and AKI. Renal failure can be severe and may require dialysis treatment for uraemia and/or neurotoxicity. However, with drug withdrawal, renal function generally returns to baseline. Treatment of aciclovir crystalluria focuses on saline diuresis. Loop diuretics can assist with maintaining high urine flow rates, but the fluid rate should be increased to prevent diuretic-induced volume contraction. Pre-hydration should be standard prophylaxis for high-risk patients, particularly those who have previously exhibited adverse renal effects from aciclovir therapy. In these patients, dose reduction of drug is ideal when rechallenge is necessary.

Sulphadiazine

Sulphonamide antibiotics such as sulphadiazine are poorly soluble, particularly when used at the high doses needed for treatment of toxoplasmosis (Yarlagadda and Perazella, 2008). An acidic urine with pH < 5.5 and intravascular volume depletion also increase the risk for forming urine crystals. Urinary sulphadiazine crystal may assume several shapes but commonly appear as needles, rosettes, or shocks of wheat (Yarlagadda and Perazella, 2008). Patients may also develop stones or smaller nephroliths, but this is a fairly rare occurrence. Preventative measures include increased fluid intake or intravenous isotonic sodium bicarbonate to maintain high urine flow rates and alkalinize the urine. If crystals are already present, alkalinization to raise urine pH above 7 decreases further precipitation of crystals and aggregation into nephroliths.

Triamterene

The potassium-sparing diuretic triamterene is often combined with thiazides for the treatment of hypertension. It has a number of underappreciated renal side effects, including crystalluria. In fact, urinary crystals containing triamterene and its metabolites can be seen following ingestion of clinical doses even in healthy volunteers, reflecting the extensive renal excretion and poor solubility of the drug (Fairley et al., 1986). The crystals are usually brown, spherical, and may appear as Maltese crosses under polarized light. Brown casts can also be seen alongside triamterene crystals, reflecting tubular injury from obstructing crystals. Urinary alkalinization is one approach to prevent crystalluria in patients who require triamterene therapy (e.g., patients with Liddle syndrome). Potassium citrate may be the preferred method as it avoids the sodium load of usual bicarbonate preparations.

Oral sodium phosphate solution

Various oral sodium phosphate solutions (OSPS) are employed as popular pre-surgical and pre-colonoscopy purgatives. In general, these agents are safe and effective, but in patients with a certain risk profile, they are associated with AKI, or acute phosphate nephropathy, that occurs within a few days following exposure to OSPS. Reports of AKI detected several weeks to months after OSPS dosing have also been described (Markowitz et al., 2005). It is now accepted that OPSP can lead to both AKI and CKD. In addition, hyperphosphataemia and hypocalcaemia may accompany or precede development of renal injury, but it may not be present in all cases (Markowitz et al., 2005). Patients often have bland urine sediments and low level or tubular proteinuria. Renal histopathology in cases of AKI has demonstrated tubular necrosis and atrophy and impressive calcium phosphate deposition within tubules and interstitium of the distal nephron (Markowitz et al., 2005). It appears that older women, those with underlying kidney disease, and especially those on ACEIs, ARBs, or diuretics, are at highest risk of OSPS-associated crystal nephropathy (Markowitz et al., 2005).

Orlistat

The use of orlistat as a weight-loss aid is based on its ability to reduce dietary fat absorption via specific inhibition of gastric and pancreatic lipase. However, despite its utility as a weight loss agent, use of this drug has also been tied to increased incidence of AKI (Weir et al., 2011). The mechanism of renal injury associated with

orlistat appears to be increased intestinal oxalate absorption and hyperoxaluria (enteric hyperoxaluria). Orlistat induces an intentional fat malabsorption syndrome with unabsorbed fat remaining in the intestines. Dietary calcium forms complexes with this fat and is unavailable to bind to intestinal oxalate. As a result, free oxalate is increased and facilitates intestinal absorption, particularly in the colon. Renal biopsies in the setting of orlistat-associated AKI note calcium oxalate crystal deposition within tubular lumens (Singh et al., 2007).

Ciprofloxacin

Quinolone antibiotics such as ciprofloxacin are widely used in current clinical practice. Despite its prevalence, crystalluria and crystal nephropathy are rare adverse events. Crystalluria was described in animal studies and in human subjects, but clinical kidney injury was not noted. However, in at risk patients such as the elderly, those with underlying kidney disease or volume depletion, and excessive drug dosing, AKI has occurred (Yarlagadda and Perazella, 2008). In neutral or alkaline pH, ciprofloxacin is insoluble and forms crystals within renal tubular lumens. Clinically, ciprofloxacin displays crystals of various shapes in alkaline urine. When AKI from ciprofloxacin-related AKI develops, the drug should be discontinued and intravenous normal saline to induce euvolaemia and high urinary flow rates should be administered. Kidney function typically recovers with these interventions.

Methotrexate

Several malignancies can be successfully treated with methotrexate, which is a dihydrofolate reductase inhibitor. A limiting adverse effect is AKI, which occurs with high-dose therapy (1–12 g/m^2) for cancer (Yarlagadda and Perazella, 2008). Methotrexate (MTX) and its metabolite, 7-OH methotrexate, are filtered by the glomerulus and secreted by the proximal tubules. Once in the urine, they can precipitate within distal tubular lumens, especially in acidic urine and with sluggish urine flow. In general, AKI from crystal-associated tubular injury develops in approximately 2–12% of patients exposed. Unsurprisingly, underlying kidney disease (GFR < 60 mL/min/1.73 m^2), acid urine, and volume depletion are risk factors for MTX-induced crystal nephropathy. Prevention requires interventions to raise urine pH (>7.1) and increase urine flow rates (intravenous sodium bicarbonate). If AKI develops following MTX exposure, the drug should be discontinued, leucovorin should be administered, and in extreme cases of toxicity, glucarpidase should be considered. Glucarpidase, which is available only by compassionate protocol, cleaves MTX to non-toxic metabolites, but must be initiated early for a beneficial effect (Widemann et al., 2010). High-flux haemodialysis clears MTX from plasma (~75%), but is associated with significant post-dialysis rebound. Thus, it has a smaller role in MTX toxicity and AKI.

Acute interstitial nephritis

The hallmark of classic AIN is rapid onset of AKI after the initiation of a suspect drug. Renal injury is usually non-oliguric but severe AKI cases may result in the need for dialytic therapy. The time course between exposure and onset of renal injury is generally within 2 weeks, though prior exposure to an agent may result in more rapid onset. Some drugs, such as NSAIDs and proton pump inhibitors (PPIs), especially when administered to the elderly, may take many months to cause clinically obvious AIN. Numerous drugs have been associated with AIN (Table 362.9), but those common to clinical use include antibiotics, NSAIDs, PPIs, and diuretics. Given their near-ubiquitous clinical use, PPIs are the most common drugs implicated in AIN cases currently (Brewster and Perazella, 2007). Among the agents listed in Table 356.9, beta-lactams and sulpha antibiotics classically induce a systemic response including fever, rash, and peripheral eosinophilia. Other drugs associated with AIN do not commonly elicit these signs, but do display a hypersensitivity reaction in the kidney typified by AKI, low-grade proteinuria, haematuria, and sterile pyuria. Urine sediment may show red blood cells, white blood cells, renal tubular cells, granular casts, and white blood cell casts, but as frequently as 25% of the time urine microscopy can be bland.

Diagnosis is based on clinical evidence, but uncertain diagnoses may call for further workup. Standard renal imaging such renal ultrasound or CT scanning may show renal enlargement, but this is not specific for AIN. Similarly, a positive test on gallium scintigraphy is neither sensitive nor specific for AIN, but may be useful to exclude ATN as a competing aetiology for AKI in situations where definitive diagnosis by renal biopsy is not feasible. Recently, FDG-PET-CT scan was shown to be positive in patients with AKI and AIN (biopsy proven) and negative in a patient with AKI from crescentic GN (Katagiri et al., 2010). Interestingly, the gallium scan was negative. Renal biopsy may not be necessary if clinical suspicion is high for AIN. However, it is particularly useful if withdrawal of a culprit drug in suspected AIN is not clinically desirable or steroid therapy is being considered in a high-risk patient. While AIN is found in <3% of all renal biopsies, the number increases to 6–27% with biopsies performed in the setting of AKI (Markowitz

Table 362.9 Drug-induced acute interstitial nephritis

Analgesics	NSAIDs
	COX-2 selective agents
Antibiotics/antiviral agents	β-lactams
	Quinolones
	Rifampin
	Sulphonamides
	Vancomycin
	Aciclovir, atazanavir, indinavir
GI agents	Proton pump inhibitors:
	◆ Omeprazole
	◆ Lansoprazole
	◆ Others
	H_2 blockers
Diuretics	Loop diuretics: furosemide, bumetanide, torsemide
	Thiazide diuretics
Miscellaneous	Allopurinol
	5-Aminosalicylic acid
	Phenytoin
	Phenindione

COX-2 = cyclo-oxygenase-2; NSAIDs = non-steroidal anti-inflammatory agents.

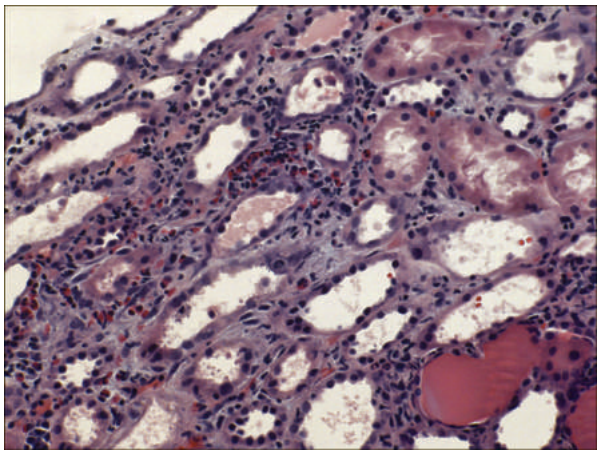

Fig. 362.19 Acute interstitial nephritis (AIN) is noted. Many drugs can cause AIN, which is characterized by a cellular interstitial infiltrate (eosinophils, lymphocytes, polymorphonuclear cells, plasma cells), tubulitis, and varying degrees of interstitial oedema (early) and fibrosis (late).

and Perazella, 2010). Typical biopsy features include an inflammatory interstitial infiltrate that is usually T lymphocyte and monocyte predominant, but may also include eosinophils (Fig. 362.19). Interstitial oedema and tubulitis are also cardinal features on renal biopsy. Interstitial fibrosis may be seen if the course of renal failure from AIN is prolonged, or in cases of underlying CKD.

As exemplified in Table 362.9, AIN is not limited to any particular class of drugs. Rather, a wide spectrum of agents can induce a hypersensitivity reaction in the kidney, reflecting possible common mechanisms for AIN. Proposed mechanisms include molecular mimicry or direct binding of the drug to the tubular basement membrane. In the latter case, the drug may act as a hapten that confers immunogenicity to normal tubular components (Markowitz and Perazella, 2010). Treatment for AIN begins with withdrawal of the causative agent, which may be difficult to pinpoint in the hospitalized patient receiving multiple medications. A stepwise withdrawal of agents, beginning with the most common offending agent, is prudent. If recovery of kidney function does not begin within several days and AIN is definitely the cause, a course of steroids is often contemplated. Corticosteroid therapy is a consideration given the inflammatory nature of AIN, though there are no randomized, controlled trials to support their use. Steroids may, in certain cases, be beneficial with faster renal recovery, fewer instances of CKD, and reduced dialysis requirement. Studies where steroids lacked benefit generally had more severe kidney injury at the time of biopsy and initiation of therapy than patients who received conservative treatment, and steroids were typically administered late in the course of disease. In one large study that showed a beneficial effect of steroids, the severity of AKI at the time of biopsy and initiation of steroid therapy were similar between the treatment groups and steroids were administered early in the course of disease (Gonzalez et al., 2008). Clarkson et al., who found no benefit with steroid treatment, reported a wide time range from symptoms to kidney biopsy (2–6 weeks) and the authors do not provide information on withdrawal of the causative drug (Clarkson et al., 2004). Gonzalez and co-workers, in contrast, do not provide data on length of time from symptoms to kidney biopsy, but do note that culprit drugs were withdrawn (Gonzalez et al., 2008). Yet with the limitations of these retrospective studies aside, it appears that steroids are most effective when initiated early in the disease course and when advanced renal failure or significant interstitial fibrosis on renal biopsy is not present.

Postrenal kidney injury

Postrenal kidney disease is an underappreciated aspect of drug-induced nephropathies. Drugs that cause postrenal injury (Table 362.10) obstruct urinary flow via structural perturbations such as stone disease and retroperitoneal fibrosis or functional dysfunction such as urinary retention. The resulting AKI can be oliguric, especially if the obstruction is bilateral or unilateral with a solitary kidney. Diagnosis of obstructive uropathy is acquired by renal ultrasound, which shows dilation of the renal pelvis (hydronephrosis) or dilation of the ureter (hydroureter). Volume depletion with decreased urine output may result in false negative ultrasound testing. Retroperitoneal fibrosis can also result in obstructive uropathy without dilation of the collecting system. In cases where obstruction is suspected despite negative ultrasound findings, retrograde pyelography may be considered. Identification of a specific cause for obstructive uropathy requires further imaging, usually a non-contrast CT scan. Bladder ultrasound scanning may demonstrate a significant volume of urine indicative of structural or functional outlet obstruction. Urine examination typically shows bland urine sediment, with the exception of haematuria and crystalluria that may be evident in stone disease. FeNa is unhelpful and may be either < 1% or > 2%.

Table 362.10 Postrenal injury from nephrotoxic agents

Retroperitoneal fibrosis	Beta blockers
	Methysergide
	Dopaminergic agents: pergolide, cabergoline, pramipexole
Nephrolithiasis	Antibacterials:
	◆ Sulphonamides
	◆ Aminopenicillins
	◆ Ciprofloxacin
	◆ Nitrofurantoin
	Protease inhibitors:
	◆ Indinavir
	Diuretics:
	◆ Triamterene
Urinary retention	Antihistamines
	Anticholinergics
	Opioids
	Alpha-adrenergic agents
	Beta-adrenergic agents
	Dopaminergic drugs
	Muscle relaxants

Stone disease

Drugs play a causal role in 1–2% of all renal stones (Daudon and Jungers, 2004). Agents that are frequently implicated in stone disease include sulphonamides and indinavir. While other drugs are also associated with stone formation (Table 362.10), these agents are among the most prevalent.

Sulphonamides

As mentioned in the discussion on crystal nephropathy, sulpha drugs readily form crystals within the tubule. Factors that promote precipitation of crystals and aggregation of crystals into calculi will result in drug-induced nephrolithiasis. In the case of sulphadiazine, high total drug dose combined with an acidic (pH < 5.5) urine and volume depletion puts patients at particular risk. This is because of the inherent insolubility of the drug as well as its high rate of urinary excretion. Thus, high-dose sulpha treatment, as required in treatment of cerebral toxoplasmosis, should receive prophylactic volume repletion and urinary alkalinization.

Indinavir

The propensity of indinavir to form nephroliths composed of the parent drug and its metabolites stems from its crystalluric potential. Unfortunately, this potential exists because indinavir is poorly soluble in the usual human urine pH range between 5.5 and 7.0. In fact, solubility is not readily achieved until urine pH reaches 3.5. Urinary acidification to this extent is potentially harmful and is not recommended. Rather, volume expansion that maintains high urine flow rate can prevent crystal deposition and stone formation. Stone formation with atazanavir, another protease inhibitor, may also occur although at a lower prevalence than indinavir. Renal insufficiency due to indinavir stone disease is generally reversible, though some cases evolve into CKD, which is thought to be a manifestation of interstitial fibrosis (Yarlagadda and Perazella, 2008). Acute management of indinavir stone disease is usually conservative, with fluids to maintain high urine flow rate and analgesics. As mentioned previously, urinary acidification is not recommended. Lastly, while urologic interventions such ureteral stenting may be employed if conservative management fails, lithotripsy is not likely to succeed because of the gelatinous composition of these stones.

Antiepileptic drugs

Topiramate and zonisamide are used in the treatment of several processes including seizure disorders, migraine headaches, and mood disorders. They have both been linked with an increased incidence of calcium phosphate kidney stones in both children and adults. The incidence has ranged between 1% and 2% in trials with long-term follow-up (Daudon and Jungers, 2004). The proposed mechanism for the nephrolithogenic effects of these drugs is inhibition of carbonic anhydrase. This prevents proximal tubular bicarbonate reabsorption and results in an acquired type 2 renal tubular acidosis. Synergistic use of these agents as well concomitant use of other carbonic anhydrase inhibitors such as acetazolamide should be avoided, as it will theoretically increase the propensity for stone formation.

Retroperitoneal fibrosis

Certain drugs elicit an inflammatory reaction in the retroperitoneal (RP) space that leads to fibrous tissue deposition. If extensive, the fibrosis can encapsulate organs and structures within the RP space, including the ureters. This may lead to urinary retention and renal failure via ureteral obstruction. Drugs that have been more commonly associated with this rare condition include ergot alkaloids such as methysergide and dopamine agonists such as methyldopa and pergolide, though other agents such as opioid analgesics and beta blockers may also play a role particularly with excess use. Signs and symptoms may not manifest until the RP fibrosis is advanced, which explains the high degree of ureteral obstruction seen with this disease. Treatment begins with drug withdrawal but if the fibrosis is advanced, resolution of the disease may only be partial. In the primary or idiopathic forms of RP fibrosis, corticosteroids are employed as first-line drugs to counter the immune reactions that are thought to be the pathological mechanism. However, there are no data to support the routine use of immune suppressants in drug-induced RP fibrosis.

Urinary retention

Prolonged interruption of bladder function can lead to obstructive nephropathy from urinary retention. While bladder function can be compromised with ageing or in patients with neurological diseases, drugs are also a common cause of urinary retention, particularly in the postoperative or hospital setting. Table 362.10 lists the broad categories of agents linked with urinary retention. These drugs may have varied effects on overall bladder function, including decreased detrusor muscle contractility and reduced sphincter relaxation. For example, antihistamines exert an anticholinergic effect that diminishes detrusor function. Other agents, such as alpha blockers increase the tone of the urethral internal sphincter. Regardless of the mechanism of urinary retention, patients may present with decreased urine output and, if bladder sensation is intact, suprapubic discomfort. Urinary retention is reversible with drug withdrawal, but may require temporary bladder decompression with a urinary catheter.

Tubulopathies

Certain drugs (Table 362.11) extend their deleterious effects on the renal tubules to beyond reduced GFR. Most of these adverse effects, collectively referred to as tubulopathies, involve derangements of mineral and water homeostasis at various tubular segments along the nephron.

Proximal tubule

Several drugs are directly toxic to the proximal tubule. In addition to causing ATN, these drugs also induce proximal tubulopathies such as Fanconi syndrome. Since the proximal tubule is a principal site of reabsorption of filtered bicarbonate, glucose, and amino acids, phosphate, uric acid, and other substances, the clinical features of this syndrome include renal tubular acidosis and hypophosphataemia. Urine studies may indicate wasting of phosphorus, glucose, amino acids, and uric acid, although incomplete proximal tubulopathies may occur. The drugs most frequently associated with proximal tubulopathies include tenofovir, cisplatin, ifosfamide, and gentamicin.

Tenofovir is a classic example of a drug causing a proximal tubulopathy, with partial or full-blown Fanconi syndrome (Perazella, 2010). As noted, tenofovir enters PT cells via the human OAT, accumulates within the cytoplasm when there is reduced apical efflux transport out of the cell (MRP transporter mutation or drug competition), and ultimately injures cells primarily by inducing

Table 362.11 Tubulopathies

Proximal tubule	Tenofovir
	Ifosfamide
	Gentamicin
	Cisplatin
Loop of Henle	Cisplatin:
	◆ Salt wasting
	Gentamicin:
	◆ Bartter like syndrome
Distal tubule	Nephrogenic diabetes insipidus:
	◆ Lithium
	◆ Foscarnet
	◆ Amphotericin B
	◆ Demeclocycline
	◆ Cidofovir
	◆ Tenofovir
	Hyperkalaemia:
	◆ Decreased aldosterone synthesis
	Direct renin inhibitors
	ACEIs
	ARBs:
	◆ Direct aldosterone blockers: spironolactone, eplerenone, drospirenone
	◆ ENaC antagonists
	Triamterene, amiloride, pentamidine, trimethoprim
	Magnesium wasting
	EGFR antibodies:
	◆ Cetuximab
	◆ Panitumumab

ACEI = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; EGFR = epidermal growth factor receptor; ENaC, epithelial sodium channel.

mitochondrial dysfunction (Fig. 362.5). This leads to loss of apical transport properties with wasting of glucose, phosphate, uric acid, amino acids, protein, and loss of bicarbonate reclamation. Clinically this is diagnosed as Fanconi syndrome.

Loop of Henle

In addition to nephrotoxicity secondary to ATN, cisplatin may induce a renal sodium-wasting syndrome characterized by polyuria and increased urinary sodium. These signs highlight the renal toxicity of cisplatin: (1) polyuria secondary to tubular injury at the loop of Henle, which impairs water absorption and urine concentrating ability, and (2) impaired sodium and water reabsorption secondary to proximal tubule damage (Perazella and Moeckel, 2010). Since the loop of Henle is also a primary site for magnesium reabsorption via paracellular mechanisms, hypomagnesaemia may also be a feature of cisplatin-induced injury (Arany and Safirstein, 2003).

Gentamicin and other aminoglycosides have also been described to cause an acquired Bartter-like syndrome (Chen et al., 2009). These agents are thought to induce hypokalaemia, metabolic alkalosis, hypomagnesaemia, hypocalcaemia, and sodium wasting by activating the calcium-sensing receptor in the thick ascending loop of Henle cells, thereby causing dysfunction of apical ROMK and inhibition of NKCC2 transport function. This reduces the development of a positive lumen potential, thereby causing increased urinary excretion of sodium, calcium, and magnesium.

Distal nephron/collecting duct

Magnesium wasting

In addition to the loop of Henle, the distal nephron also contributes to magnesium reabsorption, mostly via transcellular transport mediated by the epithelial channel transient receptor potential M6 (TRPM6). Activation of this channel is dependent upon epithelial growth factor receptor (EGFR) signalling (Groenestege et al., 2007). There are accumulating data implicating novel monoclonal antibodies that target EGFR, including cetuximab and panitumumab, in inducing renal magnesium wasting. These agents cause magnesium wasting by binding the EGF receptor (100-fold greater affinity than endogenous EGF), and inhibiting the signalling pathway that would normally enhance TRPM6 channel function and absorption of magnesium from the urinary space (Fig. 362.20).

In initial colorectal trials, a 1.8–5.8% incidence of hypomagnesaemia was noted. However, with closer monitoring and measurement of magnesium, the incidence of combined grade 2–4 hypomagnesaemia approaches 43% (Fakih et al., 2006). The incidence and severity of hypomagnesaemia increases with longer

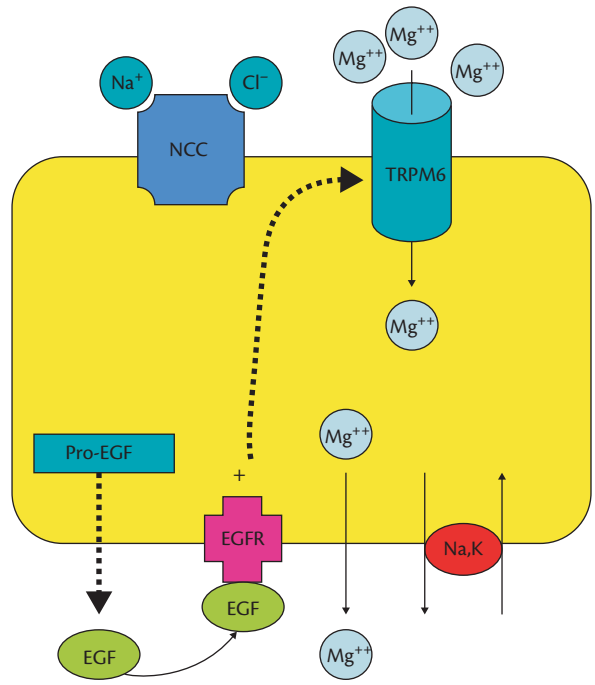

Fig. 362.20 The effect of epidermal growth factor (EGF) binding its receptor (EGFR) and stimulating magnesium reabsorption in the distal convoluted cell (DCT) is shown. EGFR activation is associated with magnesium absorption via TRPM6 (transient receptor potential M6) in the apical membrane. Cetuximab causes renal magnesium wasting by competing with EGF for its receptor.

durations of cetuximab exposure. As these agents are used as cancer therapeutics, it is critical to monitor serum magnesium levels in patients receiving these agents so that hypomagnesaemia may be anticipated and treated early.

Treatment may include oral or intravenous repletion and depends on the grade of toxicity. In general, intravenous repletion is required as oral therapy is ineffective and poorly tolerated. If other factors that influence serum magnesium levels, such as diarrhoea, poor oral intake, or malabsorption are present, more intensive repletion may be necessary. Often, hypocalcaemia and hypokalaemia accompany severe hypomagnesaemia and also require repletion. In general, the renal magnesium wasting abates 4–6 weeks after discontinuing cetuximab.

Renal magnesium wasting may also be seen with calcineurin inhibitors, particularly ciclosporin, which decreases *in vitro* and *in vivo* expression of TRPM6 (Ikari et al., 2008; Ledeganck et al., 2011). Thus, transplant patients should be monitored for this disorder and undertake magnesium repletion as needed. The platinum drugs are also associated with renal magnesium wasting and patients frequently require intravenous repletion to maintain normal serum magnesium concentrations.

Hyperkalaemia

Potassium regulation in the distal nephron is tightly coupled to the collecting duct epithelial Na channel (ENaC) that is highly expressed on the luminal cell surface. Sodium is reabsorbed into the cell via these channels and this process is critical to generating an electronegative tubular lumen (depolarizes the apical membrane). This creates an electrochemical gradient which favours potassium secretion into the tubular lumen via the potassium channel ROMK. Thus, agents that directly close or bind ENaC such as amiloride, triamterene, trimethoprim or pentamidine may lead to decreased potassium secretion and hyperkalaemia in at risk patients (CKD, AKI, hyporeninaemic hypoaldosteronism, other drugs impairing potassium homeostasis) (Fig. 362.21).

Aldosterone is the major regulator of renal potassium excretion; it performs this task by increasing expression of ENaC and ROMK (apical potassium channels) on connecting segment and collecting duct cells, and stimulating the Na-K-ATPase pump. All of these effects promote potassium secretion into the urinary space. Thus, direct aldosterone antagonists such as spironolactone and eplerenone or drugs that decrease aldosterone synthesis, such as ACEIs, ARBs, or direct renin inhibitors, can lead to hyperkalaemia by dampening the stimulatory signal for ENaC expression. Again, as with the ENaC antagonists, hyperkalaemia develops with these drugs when risk factors for impaired potassium excretion are present (Fig. 362.21). Drospirenone, a weak aldosterone antagonist, used in combination with ethinyl oestradiol for contraception, postmenstrual syndrome and postmenopausal osteoporosis maintains theoretical risk for hyperkalaemia when used in high-risk patients. Studies have shown an increase in plasma potassium concentration with drospirenone, but only a small number of patients develop hyperkalaemia (K > 5.5 mEq/L) (Preston et al., 2005).

Nephrogenic diabetes insipidus

Vasopressin (or antidiuretic hormone, ADH) is the major regulator of water handling in the collecting tubules. Binding of vasopressin to its receptor vasopressin 2 (V2) generates a series of events beginning with activation of adenylate cyclase that results in an increased number of water channels in the luminal membrane. These channels allow water to move along an osmotic gradient from the tubular lumen into collecting duct cells. From there, water then moves across the freely permeable basolateral membrane for eventual absorption into the systemic circulation. Thus, drugs that interfere with the actions of ADH on the collecting duct inhibit water reabsorption, resulting in decreased urinary concentrating ability, polyuria, and polydipsia. If urinary water losses are not matched by oral intake, hypernatremia may also result. Chronic lithium use has been commonly linked to nephrogenic diabetes insipidus (NDI) via several mechanisms, including reduced V2 expression (Apurv, 2006). Other drugs, however, are also associated with development of NDI, including foscarnet, amphotericin B, demeclocycline, cidofovir, and tenofovir (Apurv, 2006). Withdrawal of drug may reverse NDI, except in cases of chronic lithium use. In these cases, pharmacologic approaches such as thiazide diuretics and amiloride may be necessary to reduce polyuria.

Chronic kidney disease

Sustained exposure to drugs that cause AKI or other forms of cumulative renal injury over time may result in CKD. Any drug

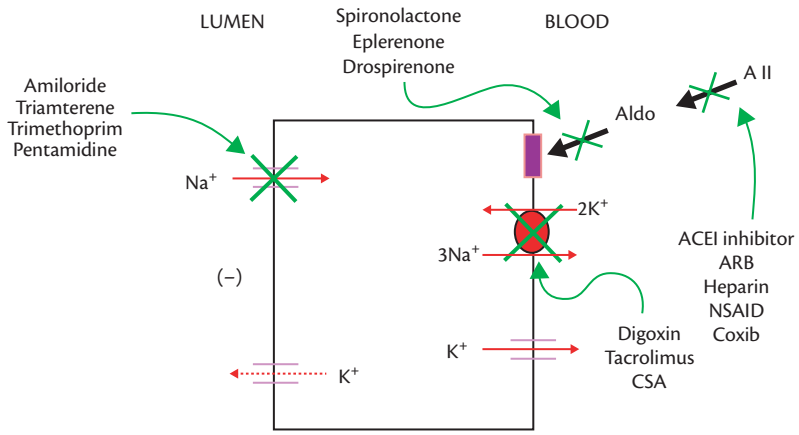

Fig. 362.21 Drugs can impair potassium secretion by the principal cell in the distal nephron (connecting tubule, cortical, and medullary collecting ducts) by competitively inhibiting the epithelial sodium channel (ENaC), reducing aldosterone receptor binding or aldosterone formation, or inhibiting sodium-potassium pump (Na-K ATPase) function.

Table 362.12 Drug-induced chronic kidney disease

Lithium	
Aristolochic acid	Balkan nephropathy
	Chinese herb nephropathy
Nitrosoureas	

that results in prolonged or repeated AKI theoretically puts a particular patient at risk for CKD and even dialysis dependence. Certain agents, however, result in CKD over time without causing acute disturbances in renal function (Table 362.12). Examples of these drugs include lithium, aristolochic acid, and the nitrosoureas.

Lithium

Lithium salts are common treatment for bipolar disorder, but have significant acute and chronic adverse effects. While the most concerning acute toxicity is the potentially fatal neurotoxicity associated with supratherapeutic serum levels, long-term lithium use has been linked to CKD (Bendz et al., 2010). The mechanism for chronic renal injury appears to be chronic interstitial nephritis (Grunfeld and Rossier, 2009). Renal biopsies have also demonstrated dilated tubules with microcyst formation (Walker et al., 1986). While most patients have relatively stable renal dysfunction, others can have progressive decline to ESRD. Risk factors for more severe CKD include total lifetime drug burden (Bendz et al., 2010). Withdrawal of lithium and use of alternate psychiatric agents may lead to improved GFR, but some patients may develop progressive CKD. Management of lithium-induced CKD can be challenging in patients whose psychiatric disease responds only to lithium. In such cases, communication with the patient's mental health providers is critical in maintaining the lowest tolerable serum lithium level. Such an approach seeks a balance between maintaining mental health and preventing progression of CKD.

Aristolochic acid

Renal failure attributed to aristolochic acid (AA) is also termed 'Chinese herb nephropathy' because initial case reports were linked to Chinese herbal weight loss products (Vanherweghem et al., 1993; Lord et al., 1999). The aetiologic agent appears to be AA, an alkaloid found in the *Aristolachiae* family of plants used commonly in Chinese herbal preparations (Vanherweghem et al., 1993). Patients with suspected AA nephropathy present with an elevated serum creatinine with minimal proteinuria and a history of exposure. In some cases, there has been rapid progression to ESRD. Renal biopsies have revealed widespread interstitial nephritis and tubular atrophy. Withdrawal of any preparations of AA is the only specific attempt to reverse or stabilize the renal dysfunction, but kidney disease may progress despite cessation of AA exposure.

The entity known as 'Balkan nephropathy', which has been of unclear aetiology, has been potentially linked to AA-related kidney injury (Lord et al., 1999). A plant native to the endemic region, *Aristolochia clematitis*, often grows in cultivated fields where its seeds, containing AA, mix with wheat grain during the annual harvest. Bread is prepared from flour made from locally grown wheat. As a result, residents of the endemic region who consume home-baked bread may be exposed to toxic amounts of AA and develop kidney disease.

Nitrosoureas

The chemotherapeutic agents known as the nitrosoureas are alkylating agents that can cause slow, progressive CKD over months to many years. The most nephrotoxic of this group are streptozotocin and semustine, while carmustine and lomustine are less nephrotoxic. High cumulative doses (>1.4 g/m^2) are associated with the development of CKD (Perazella and Moeckel, 2010). Kidney injury caused by these agents is characterized by tubulointerstitial fibrosis, tubular atrophy, and glomerulosclerosis (Perazella and Moeckel, 2010).

Conclusions

Drugs that are critical in both the diagnosis and treatment of a variety of diseases can cause renal injury. The potential for injury with a particular agent depends on the characteristics of that agent including absorption, metabolism, and excretion. Additionally, patient-specific risk factors such as age and pre-existing renal or liver disease can influence the toxic potential of therapeutic agents in a specific host. Drugs can cause renal injury in several ways, including prerenal, intrinsic, or postrenal/obstructive patterns of injury. While the nephrotoxicity of drugs is typically associated with AKI, CKD is increasingly being recognized as a long-term outcome of certain drug therapies. Prevention of toxic drug nephropathies begins with avoidance of certain agents in individuals at high risk for renal dysfunction. If that is not feasible, particular care must be taken to ensure that multiple nephrotoxic agents are not being used. Treatment of drug-induced renal disease includes cessation of suspected nephrotoxic agents, maintenance of urine flow with isotonic fluids, and if indicated, renal replacement therapy for uraemia. Lastly, with new therapeutic agents being introduced into clinical practice, physicians and other providers must be vigilant to detect emerging nephrotoxicities.

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CHAPTER 363

Drug dosing in chronic kidney disease

Ali J. Olyaei, Ted A. Foster, and Edgar V. Lerma

Introduction

Chronic kidney disease (CKD) affects approximately 26 million adults in the United States. With the incidence of CKD anticipated to increase in conjunction with growing chronic disease trends, early disease detection and aggressive management are necessary for improving this public health crisis. According to the National Kidney Foundation (2002), CKD is defined as the presence of kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for 3 or more months. The two main causes of CKD in adults are diabetes and hypertension, with heart failure the leading cause of death in the CKD population (Reilly and Berns, 2010). Renal impairment contributes to high susceptibility to adverse drug and disease interactions as the kidney is involved in all therapeutic drug absorption, distribution, metabolism, and excretion processes (Dowling et al., 2010). Subsequently, medication-related errors in patients living with CKD have led to increases in morbidity and mortality, as well as rising healthcare costs (Hudson and Nyman, 2011; Olyaei and Steffl, 2011; Stemer and Lemmens-Gruber, 2011a). Failure to properly adjust medications in patients diagnosed with varying stages of CKD may result in adverse drug reactions. Therefore, healthcare professionals must always review patient medications and assess kidney function prior to initiating or modifying pharmacological therapy to ensure patient safety and appropriately delay disease progression (Stemer and Lemmens-Gruber, 2011b).

Many pharmacologic agents have active metabolites that undergo renal excretion. The metabolism and elimination of these agents is dependent on normal renal function. Pharmacologic agents that do not undergo renal elimination may be altered, and therefore lead to adverse effects (Hassan et al., 2009). One study indicated that 40% of patients with CKD received excessive dose of medications (Bookstaver et al., 2008; Corsonello et al., 2011). Another study observed a positive association with the number of medications and higher mortality rate in patients with CKD. These findings highlight the importance of identifying patients with CKD, estimating renal function, and adjusting the drug dosage appropriately according to renal function.

The following is a systematic approach to dose adjustment in patients with renal insufficiency. Specific pharmacologic considerations in the setting of renal insufficiency along with drug removal by dialysis are also outlined (Verbeeck and Musuamba, 2009). This approach is the result of an extensive review of the medical literature, which is often conflicting and derived from varied patient populations. Information from prospective, controlled trials is limited. Therefore, recommendations and dosage tables should be employed as a starting reference for therapy in patients with altered renal function (Mueller and Smoyer, 2009; Janus et al., 2010; Wargo and English, 2010).

Principles of altered pharmacokinetics in renal failure

In patients with CKD, several pharmacokinetic factors may be altered. These include bioavailability, volume of distribution (Vd), protein binding, and biotransformation.

Bioavailability

Bioavailability refers to the percentage of a given dose that reaches the systemic circulation. Rate and route of administration are the primary factors which determine bioavailability. Drugs administered intravenously are deemed 100% bioavailable because the entire dosage reaches the systemic circulation. The bioavailability decreases when drugs are administered orally, subcutaneously, or intramuscularly. In most patients with CKD, bioavailability of most drugs are reduced and influenced by hepatic metabolism through increased release of uraemic factors like parathyroid hormone and inflammatory cytokines resulting in an alkaline gastric environment (Doogue and Polasek, 2011). Medications such as antacids, phosphate binders, proton pump inhibitors, and histamine-receptor blockers enhance an elevated pH thus limiting the absorption of drugs requiring an acidic environment like furosemide and ferrous sulphate. Physical symptoms of oedema, vomiting, and diarrhoea also limit drug transit time in the intestines resulting in decreased drug absorption (Naud et al., 2011, 2012).

Volume of distribution

The Vd of a pharmacologic agent is derived by dividing the total amount of drug in the body by the concentration of the drug in the blood. The Vd is useful for calculating the dose required to achieve a desired systemic drug level. An inverse correlation exists between the serum concentration and the Vd. Therefore, alterations in the extracellular fluid volume can affect the Vd. Volume contraction decreases the Vd while serum concentration rises. This is particularly true of hydrophilic compounds such as aminoglycosides. A rise in extracellular fluid volume due to oedema or ascites increases the Vd resulting in a lower serum concentration

(Olyaei and Bennett, 2009). The effects of CKD on drug distribution are related to hypoalbuminaemia exhibited by CKD patients experiencing malnutrition and increased albuminuria (Naud et al., 2011, 2012). Alterations to albumin binding sites reduce affinity for acidic drugs and promote competition for albumin binding with organic acids that accumulate because of reduced renal excretion. Subsequently, protein binding of acidic drugs may be reduced in CKD (Lam et al., 1997). Toxicity may result with higher levels of unbound drug exerting its pharmacologic effect, requiring frequent monitoring of blood levels. Maintaining lower levels of total drug or monitoring unbound drug is recommended for CKD. Drugs exhibiting decreased protein binding include theophylline, phenytoin, methotrexate, diazepam, prazosin, cephalosporins, penicillins, furosemide, and valproic acid (Naud et al., 2011, 2012).

Most drugs are circulated in both bound (to serum proteins) and unbound (free) forms. The unbound form is distributed throughout the body and is biologically active. The concentration of a given agent which is bound to plasma proteins may be considered as a storage pool for that agent. Renal failure tends to decrease protein binding for the majority of agents. This is, in part, because circulating organic wastes bind to carrier proteins displacing the pharmacologic agent. As a result, a larger concentration of the agent circulates in its free, active form. Most drug assays measure total drug concentration that contains both bound and free drug levels. In some cases (such as a patient receiving phenytoin) it may be prudent to specifically monitor unbound drug concentrations when a narrow therapeutic window exists (Table 363.1) (Diaz et al., 2012).

Biotransformation

Metabolism or biotransformation refers to the biochemical conversion of a drug from one chemical form to another. The majority of biotransformation occurs in the liver through hepatic metabolic pathways including oxidation, reduction, acetylation, or hydrolysis. The result is a more polar, hydrophilic metabolite which is more readily excreted. Many drug metabolites are pharmacologically active and depend on renal excretion for elimination from the body. Toxic metabolites dependent upon renal excretion may also form. Kidney impairment can have increased, decreased, and unchanged effects on drug metabolism. CKD can result in reduced activity of cytochrome P450 (CYP) enzymes due to the presence of uraemic toxins that inactivate enzymes leading to reduced metabolism (Momper et al., 2010; Nolin et al., 2011). Evidence also supports existence of induction enzymes that raise metabolism. Finally, drug and metabolite elimination is affected by CKD. Drugs eliminated unchanged by the kidney coupled with impaired renal function can lead to drug accumulation and prolongation of drug action. Hence, CKD patients are at risk of experiencing increased efficacy as well as toxicity. Nephrotoxic drugs such as aminoglycosides and vancomycin should be avoided or closely monitored to prevent harm. Ultimately, medications for patients with CKD must be carefully considered by healthcare professionals to prevent adverse outcomes and enhance disease management.

Approach to dose adjustment in patients with chronic kidney disease

A stepwise approach to dose adjustments in patients with CKD will allow clinicians to ensure that the proper medications are delivered at the appropriate dose with the best opportunity to avoid toxicity. This approach should be used as a starting point for dosage adjustments and must be closely monitored and modified on an individual basis.

Medical history and physical examination

The first step is to obtain a detailed patient history and perform a thorough physical exam. Focus should be paid to the aetiology of the patient's renal dysfunction, defining this as acute or chronic, and identifying complications from both any primary process and the renal dysfunction. An accurate active medication list, both prescription and non-prescription, along with allergies or intolerances should be documented. Clinicians should identify potential nephrotoxins and/or interacting medications. Ideally, for patients with CKD nephrotoxins should be avoided completely (Table 363.2). In addition, many medications may cause electrolyte derangements, which may be exaggerated in CKD patients.

Regarding the physical exam, particular attention should be given to the volume status and reassessment should be made frequently as shifts in extracellular fluid volume alter the Vd of many drugs. Identification of coexisting hepatic dysfunction will again allow for proper drug dosing.

An emphasis should be placed on calculating the correct patient weight given the role of Vd in appropriate drug dosing. Generally, the ideal body weight (IBW) should be calculated using the following formula:

$$\text{IBW}\ (\text{men}) : 50.0\ \text{kg} + 2.3\ \text{kg for every 2.5 cm over 152 cm}$$

$$\text{IBW}\ (\text{women}) : 45.5\ \text{kg} + 2.3\ \text{kg for every 2.5 cm over 152 cm}$$

For the obese patient, an adjusted body weight can be calculated using the following formula:

$$\text{ABW} = \text{IBW} + 0.4(\text{actual weight} - \text{IBW})$$

Renal function assessment

Renal impairment alters the pharmacokinetics of drugs and metabolites necessitating drug-dosing adjustments. Decreased clearance has been observed for drugs primarily eliminated by the kidney, but also by drugs eliminated by non-renal pathways demanding further research utilizing physiologically-based pharmacokinetic modelling to explore these changes in renal impairment (Zhao et al., 2012). Determination of clinical drug-dosing regimens should ultimately be individualized and based upon kidney function as measured by GFR (National Kidney Foundation, 2002). Since GFR cannot be measured directly, intrinsic markers such as inulin, iothalamate, or iohexol, are the desired standard, but unrealistic for use in clinical practice due to a complicated measurement process and expensive laboratory cost. Thus endogenous filtration markers, typically serum creatinine and urine measures, are used to estimate GFR (Hudson and Nyman, 2011; Olyaei and Steffl, 2011) It is important to note that serum creatinine alone is not an adequate representation of kidney function as the serum level is affected by multiple physiologic processes varying widely among individuals. For instance, older age, female sex, restriction of dietary protein, malnutrition, muscle wasting, and amputation decrease serum creatinine concentrations while African American

Table 363.1 Therapeutic drug monitoring

Drug name	When to draw sample	Therapeutic range	How often to draw levels
Aminoglycosides (conventional dosing) Gentamicin Tobramycin Amikacin	Trough: immediately prior to dose Peak: 30 min after a 30–45 min infusion	Gentamicin and tobramycin: Trough: 0.5–2 mg/L Peak: 5–8 mg/L Amikacin: Peak: 20–30 mg/L Trough: < 10 mg/L	Check peak and trough with 3rd dose For therapy < 72 hours, levels not necessary. Repeat drug levels weekly or if renal function changes
Aminoglycosides (24-hour dosing) Gentamicin Tobramycin Amikacin	Obtain random drug level 12 hours after dose	0.5–3 mg/L < 10 mg/L	After initial dose. Repeat drug level in 1 week or if renal function changes
Carbamazepine	Trough: immediately prior to dosing	4–12 mcg/mL	Check 2–4 days after first dose or change in dose
Ciclosporin	Trough: immediately prior to dosing	150–400 ng/mL	Daily for first week, then weekly
Digoxin	12 hours after maintenance dose	0.8–2.0 ng/mL	5–7 days after first dose for patients with normal renal and hepatic function; 15–20 days in anephric patients
Enoxaparin	4 hours after 2nd or 3rd dose	0.7–1.1	Weekly and as needed
Lidocaine	8 hours after IV infusion started or changed	1–5 mcg/mL	As needed
Lithium	Trough: before a.m. dose at least 12 hours since last dose	Acute: 0.8–1.2 mmol/L Chronic: 0.6–0.8 mmol/L	As needed
Phenobarbital	Trough: immediately prior to dosing	15–40 mcg/mL	Check 2 weeks after first dose or change in dose. Follow-up level in 1–2 months
Phenytoin Free Phenytoin	Trough: immediately prior to dosing	10–20 mcg/mL 1–2 mcg/mL	5–7 days after first dose or after change in dose
Procainamide NAPA (*N*-acetyl procainamide) a procainamide metabolite	Trough: immediately prior to next dose or 12–18 hours after starting or changing an infusion Draw with procainamide sample	4–10 mcg/mL Trough: 4 mcg/mL Peak: 8 mcg/mL 10–30 mcg/mL	As needed
Sirolimus	Trough: immediately prior to next dose	10–20 ng/dL	weekly for first month then as needed
Tacrolimus	Trough: immediately prior to next dose	5–10 ng/mL	Daily for first week, then weekly.
Valproic acid (divalproex sodium)	Trough: immediately prior to next dose	40–100 mcg/mL	Check 2–4 days after first dose or change in dose
Vancomycin	Trough: immediately prior to dose Peak: 60 min after a 60 min infusion	Trough: 10–20 mg/L Peak: 25–40 mg/L	With 3rd dose (when initially starting therapy, or after each dosage adjustment). For therapy less than 72 hours, levels not necessary. Repeat drug levels if renal function changes

race, ingesting cooked meats, and muscle mass increases levels. Estimates of GFR are achieved through recommended formulas that account for serum creatinine and other patient characteristics (age, sex, weight, or race) (Hudson and Nyman 2011; Olyaei and Steffl, 2011). The Cockcroft–Gault (CG) equation (Cockcroft and Gault 1976), the Modification of Diet in Renal Disease (MDRD) equation (Levey et al., 1999), and the most recent, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Stevens and Levey, 2009; Stevens et al., 2010) assist in identifying patients with CKD and screening for those at high risk of disease development. Variations in GFR estimates exist among these valid equations and it is uncertain which formula provides the most accurate medication dosing recommendations; therefore clinical judgement must be applied appropriately per patient application. The CG equation and MDRD are recommended for determining clinical drug-dosing regimens in CKD despite equation limitations. See Table 363.3 for a comparison of formulas for estimating kidney health that used creatinine clearance as estimated by the CG equation for a measure of kidney function (Jones, 2011). Today, MDRD is most commonly used in the clinic setting to assess kidney function and stage of kidney disease. However, healthcare professionals should proceed cautiously using these equations in

Table 363.2 Drug-induced kidney injury

Drug	Risk factor	Pathophysiology	Prevention	Management
NSAIDS	Chronic kidney disease, heart failure, dehydration, and diuretic	Haemodynamically-induced acute kidney injury due to vasoconstriction by decreased prostaglandin production, acute and chronic tubulointerstitial nephropathy Chronic interstitial nephritis and papillary necrosis, Na retention, hyperkalaemia, hypertension, and oedema	Avoid diuretic used at the same time. Avoid schedule NSAIDs therapy in patients with SCr > 1.5 mg/dL. Use NSAIDs with short half-life	Discontinue medication Consider opiate
Aminoglycoside (neomycin, gentamicin, tobramycin, amikacin, streptomycin)	Dose (levels >10 mg/dL for peak and > 2–3 mg/dL for trough), duration (> 7 days), concurrent nephrotoxins	AG accumulates within PCT and induces acute tubular necrosis, Non-oliguric kidney injury	Maintain therapeutic range Give once-daily dose if necessary	Reduce the dose, decrease frequency and duration of therapy Oral magnesium supplement in magnesium wasting
Aciclovir	High dose, IV bolus dose	Crystal nephropathy	Avoid rapid bolus infusion. Adjust for dosage for CKD, prior hydration (with the urine output maintained > 75 mL/hour) and slow drug infusion over 1–2 hours	Discontinue medication if possible, hydration and stop loop diuretic
Adefovir dipivoxil	≥ 30 mg/day renal impairment Pre-existing tubular dysfunction Duration of therapy	Depletion of mitochondrial DNA acute tubular degeneration	Dosage adjustment for CKD	Discontinue medication if possible
Cidofovir	Dose and duration, mild renal dysfunction,	Induced apoptosis in PCT, diabetes insipidus, renal failure, and Fanconi syndrome	Hydration and probenecid, In BK nephropathy, use only 0.25 mg/kg/week	Hydration and DC medication if possible
Tenofovir	Dose and duration, mild renal dysfunction, use of ACEI, ritonavir and low body weight, genetic polymorphisms	Renal toxicity is mediated by proximal tubule epithelial cells, Fanconi syndrome	Hydration and dosage adjustment	Hydration and DC medication if possible
Indinavir	Bolus dose	Crystal neuropathy, nephrolithiasis, obstructive ARF	Hydration, establish high urine flow, avoid bolus dose	DC medication. It takes 6–8 weeks before normalization of renal function
Foscarnet	Dose and duration, mild renal dysfunction,	Crystal neuropathy, direct tubular toxicity; acute tubular necrosis, nephrogenic diabetes insipidus	0.5–1 L NS infusion before each dose, adjust for stage of CKD	Dose reduction
Interferon		Prerenal acute kidney injury, tubulointerstitial nephritis, thrombotic microangiopathy, membranoproliferative glomerular sclerosis		Discontinuation
IVIG	Sucrose containing product, dehydration	Accumulation of sucrose in PCT forms vesicle, ↑ osmolarity and vacuolization,	Avoid radiocontrast concomitantly Avoid sucrose containing product	Hydration DC sucrose containing product
Lithium	Renal impairment, dehydration from fever, N/V, sun exposure, hyponatraemia, Diuretic, esp. thiazide used	Tubular dysfunction, chronic tubulointerstitial nephropathy (tubular atrophy and interstitial fibrosis) and progressive glomerulosclerosis	Therapeutic range (0.6–1.2 mEq/L), Prevent dehydration, Avoid low Na diet, Avoid thiazide and nephrotoxic drug	Amiloride for nephrogenic diabetes insipidus fluid restoration, haemodialysis (rebound can occur if stop too early)

CSA/tacrolimus	Dose, age, CKD	Calcineurin inhibitor nephrotoxicity (CIN); decrease prostaglandin, vasoconstriction, Reduced GFR, ischaemic collapse or scarring of the glomeruli, focal areas of tubular atrophy and interstitial fibrosis (striped fibrosis)	Maintain in therapeutic range Avoid drugs that raise levels (CYP3A4 inhibitor)	Dose reduction
Oral sodium phosphate	Dose, repeated dose, age, ARB and ACEI and CKD	Tubular and interstitial calcium phosphate deposits	Aggressive hydration, minimizing the dose of oral sodium phosphate	Discontinuation Hydration
ACEI		Vasoconstriction → prerenal ARF	Avoid in bilateral renal artery stenosis	Discontinuation
Methotrexate	Acidic urine High dose	Precipitate in the urine and induce tubular injury	Prior hydration, alkalize urine to pH > 7.0 (3 L of dextrose in water + 44–66 mEq of NaHCO3 per day)	Loop diuretic Leucovorin rescue
Ifosfamide	Use cisplatin at the same time	Direct tubular injury and mitochondrial damage, Fanconi syndrome, nephrogenic diabetes insipidus, hypokalaemia	Use of Mesna	Discontinuation
Cisplatin	Low chloride High dose used for bone marrow ablation	Acute tubular necrosis, nephrogenic diabetes insipidus, hypomagnesaemia	Vigorous hydration with forced diuresis: 2500 mL NS/hour prior and several hours after administration. Mannitol or furosemide used Amifostine (thiophosphate) Thiosulfate	Discontinue magnesium supplementation
Sulphonamide (sulfadiazine and sulfamethoxazole)	High dose during the treatment of toxoplasmosis in pts w/AIDS, urine pH < 5.5	Crystal neuropathy, nephrolithiasis,	Fluid intake > 3 L/day, monitor urine for crystal, if crystal are seen, alkalinization of urine to pH > 7.15	Hydration
Radiocontrast	Dose and frequency, osmolarity of contrast media	High osmolarity and medullary vasoconstriction	Hydration before and after the administration. Acetylcysteine or $NaHCO_3$ prior and after administration	Hydration
Aristolochia acid (Chinese herbal neuropathy and endemic Balkan nephropathy)	Use of vasoconstrictor such as fenfluramine/diethylpropion at the same time Batch-to-batch variability in toxin content Female gender Dose Genetically predisposition	Chronic tubulointerstitial nephritis		Discontinue Corticosteroid
Amphotericin B	Dose and duration, other nephrotoxic agent	Afferent vasoconstriction, decrease renal blood flow, distal tubular injury, hypokalaemia, hypomagnesaemia, metabolic acidosis due to tubular acidosis, polyuria due to nephrogenic diabetes insipidus	Use liposomal formulation (does not contain deoxycholate), Sodium loading (500–1000 mL of NS 30 min prior to admin Regularly monitor K, Mg, Na serum concentration	Hydration Dose reduction

- All of the above medications should be dosed based on renal function.
- Avoid concomitant use of nephrotoxic medications and diuretics.
- Patient-related risk factors for all above drugs are: age, previous renal insufficiency, *dehydration and volume depletion*, concurrent use of nephrotoxic drugs, CRF, diabetic neuropathy, severe CHF, etc.
- Adequate hydration prior to therapy and during the treatment of AKI because volume depletion is one of the most important risk factors.
- Obtain baseline BUN, SCr, and electrolytes and closely monitor renal function during the treatments.

Table 363.3 Comparison of formulas estimating GFR for drug dosing

Formula name	Equation	Clinical considerations
Cockcroft–Gault (CG)[a]	Creatinine clearance (mL/min) = (140 – age in years) × actual weight (kg) / serum creatinine (micromol/L); multiply the result by 1.2 for men	Estimates creatinine clearance not adjusting for body surface area (BSA) Standard for drug dosing despite limitations between pharmacokinetics and clinical practice.
Modification of Diet in Renal Disease (MDRD)[a]	Estimated GFR (mL/min/1.73 m^2) = $186 \times (S_{Cr})^{-1.154} \times (Age)^{\times 0.203} \times (0.742$ if female) × (1.210 if African American) = expanded $(5.228 - 1.154 \times \ln(S_{Cr}) - 0.203 \times \ln(Age) - (0.299$ if female) + (0.192 if African American)	Estimates GFR adjusting for BSA Used for drug dosing despite limitations between pharmacokinetics and clinical practice Valid for specified racial groups (African Americans, Europeans, Asians), patients with diabetes, kidney transplant recipients, and potential kidney donors Less accurate in those without CKD Invalid in children, pregnant women, elderly, some races, nutritional status and muscle mass variation
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)	$GFR = 141 \times \min(S_{Cr}/\kappa,1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]; where S_{Cr} is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.	Estimates GFR adjusting for BSA Not recommended for drug dosing Valid with higher levels of GFR, young patients with type 1 diabetes, and kidney donation evaluation Accurate as MDRD equation in CKD patients having lower GFR levels Invalid in children, pregnant women, some races, nutritional status, and muscle mass variation

[a]Indicates potential need of 24-hour urine collection for creatinine clearance when estimates based on serum creatinine may be inaccurate during the following clinical situations: extremes of age and body size, severe malnutrition or obesity, disease of skeletal muscle, paraplegia or quadriplegia, vegetarian diet, rapidly changing kidney function, and pregnancy.

In fact, the most common drug dosing recommendations are based on pharmacokinetic studies.

special populations like geriatrics where the use of a conservative estimate (CG equation) may be desired especially when prescribing drugs with a narrow therapeutic index in order to prevent toxicity and maximize efficacy (Hudson and Nyman, 2011).

Determining loading dose

In patients with normal renal function, steady-state drug concentration is achieved after approximately 3.3 half-lives. In patients with renal failure, the half-life may be significantly prolonged. Achievement of steady-state drug levels, which ensures therapeutic efficacy, may be greatly delayed if a loading dose is not given. In general, patients with renal failure should receive the same loading dose as patients with normal renal function in order to achieve a rapid therapeutic dose. Patients with renal failure receiving digoxin, however, should receive only 50–75% of the usual loading dose as its Vd is greatly reduced in renal failure.

The following formula can be used to calculate the loading dose with Vd in L/kg, IBW, and desired plasma concentration, Cp (mg/L):

$$LD = Vd \times IBW \times [Cp]$$

Determining maintenance dose

There are two ways to adjust the maintenance dosage in patients with renal failure: prolonging dosing interval and dosage reduction. Increasing the dosage interval can be directly correlated to the degree of renal impairment by the following formula:

$$\text{Dosing Interval} = \frac{\text{normal Clcr} \times \text{normal interval}}{\text{patient's Clcr}}$$

With the dosing interval remaining constant, dosage reduction corresponding to the degree of renal impairment can be determined by the following formula:

$$\text{Maintenance Dose} = \frac{\text{patient's Clcr} \times \text{normal dose}}{\text{normal Clcr}}$$

Dosage interval extension allows for adequate peak concentrations but may risk subtherapeutic trough levels. Dosing reduction may provide for more constant drug levels but increases the risk of toxicity from higher plasma trough concentrations.

Drug level monitoring

Despite appropriate dosage and interval modifications, patients with renal failure are at an increased risk of drug toxicity. Therefore, monitoring drug levels is of the utmost importance (Roberts, 2011). Multiple clinical aspects need to be accounted for including exact dose given, route of administration, time since last dose, and the particular drug's half-life in order to correctly interpret drug concentrations. Peak drug levels represent the highest drug concentration achieved after initial rapid distribution and predicts drug efficacy. Trough drug levels are obtained immediately prior to the next dose, represent the lowest serum concentration and predicts drug toxicity (O'Shea et al., 2009).

Drug level monitoring may be expensive and, unfortunately, not always available. Drug level monitoring does not guarantee a reduced incidence of toxicity. For example, aminoglycosides can concentrate in tissues such as the inner ear and renal cortex, which is not necessarily reflected as high serum concentrations (O'Shea et al., 2009). Ongoing clinical assessment is important even when drug levels are within the established therapeutic range. Most

assays do not distinguish between free and protein-bound drugs in the plasma. An increase in unbound drug is common in patients with renal failure. Table 363.1 summarizes therapeutic drug monitoring in renal insufficiency for drugs for which monitoring of drug levels is routinely recommended (Table 363.2).

Dialysis and drug clearance

Many drugs are substantially cleared by dialysis. The scheduling of drug administration and the possibility of dosage supplementation should be considered in patients receiving dialysis. Scheduled doses should be given upon completion of dialysis therapy. If this is not possible and dialytic treatment increases total body clearance of a given drug by > 30%, dosage supplementation may be necessary. Molecular weight (< 500 Da), water solubility of a drug, and the extent of protein binding are the primary factors as to whether a drug will be dialysed. Other factors influencing whether or not a drug is cleared by dialysis include Vd, non-renal excretion, ionic charge, and erythrocyte partitioning. Properties of the dialysate and dialyser membrane also affect drug clearance and include flow rate, temperature, pH, solute composition, volume (peritoneal dialysis), pore size, and surface area (Awdishu and Bouchard, 2011).

In terms of continuous renal replacement therapy (CRRT), creatinine clearance rates of up to 20–30 mL/min are currently being achieved. CRRT is in widespread use in both medical and surgical intensive care units. Limited data is available regarding drug removal with CRRT. Dosage adjustments can be determined through close monitoring of drug levels and clinical examination of the patient. During CRRT, solutes and drugs are removed by convective transport. Drugs may also be removed by membrane-drug binding. Drugs and solutes not bound to plasma proteins and dissolved in the plasma cross the dialysis membrane through plasma water ultrafiltration. The ultrafiltrate drug concentration is equal to the plasma concentration multiplied by the percentage of unbound drug.

Conclusions

Individual patient responses to drug therapy during renal insufficiency are variable, complex, and require a basic understanding of pharmacologic principles in order to maximize drug therapy and avoid toxicity. Dosage adjustment strategies should be based on several factors including not only reduction in GFR, drug level monitoring, and direct correlation with clinical picture, but clinicians must also take into account the many pharmacokinetic and pharmacodynamic parameters involved in drug therapy for patients with CKD. Every attempt has been made to provide the latest data on drug dosing in CKD in accordance with existing dosage recommendations. However, the clinical circumstances, co-morbid conditions, and drug–drug interactions should be considered to avoid drug toxicity and ensure the therapeutic benefits of each individual agent (Seyffart 2011).

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CHAPTER 364

Drug dosing in acute kidney injury

Thomas A. Golper, Andrew A. Udy, and Jeffrey Lipman

Give a man a fish and you feed him for a day. Teach a man to fish and you feed him for a lifetime.
Chinese Proverb

Introduction

Drug dosing in acute kidney injury (AKI) is one of the broadest topics in human medicine. It requires an understanding of markedly altered and constantly changing physiology under many disease situations, the use of the drugs to treat those variety of diseases, and the concept of drug removal during blood cleansing therapies. Early in AKI, kidney function may be supraphysiologic, while later in the course there may be no kidney function. As function deteriorates, other metabolic pathways are altered in unpredictable ways. Furthermore, the underlying disorders that lead to AKI alter metabolic pathways. Heart failure is accompanied by vasoconstriction in the muscle, skin, and splanchnic beds, while brain and cardiac blood flow proportionally increase. Third spacing occurs and lungs can become congested. As either kidney or liver function deteriorates, there may be increased or decreased drug sensitivity at the receptor level. Acidosis accompanies several failing organs. Protein synthesis is qualitatively and quantitatively altered. Sepsis affects tissue permeability. All these abnormalities influence drug pharmacokinetics and dynamics. AKI is accompanied by therapeutic interventions that alter intrinsic metabolism which is in turn complicated by kidney replacement therapy (KRT). So metabolism and removal are both altered and constantly changing. Drug management in AKI is exceedingly complex and is only beginning to be understood. Thus, we approach this discussion in a physiological manner. Critically ill patients pass through phases of illness, sometimes rapidly, other times slowly. The recognition of the phases and the need to adjust medication administration strategies is crucial to improving outcomes. An early phase involving supraphysiologic kidney function may be contributory to therapeutic failures that result in the complication of later AKI and kidney function failure.

Augmented renal clearance in the intensive care unit: mechanisms, risk factors, and implications for antimicrobial therapy

Pharmaceutical dosing regimens are largely developed from *in vivo* animal models, followed by safety and efficacy studies in healthy volunteers. These data are subsequently extrapolated without considering the unique characteristics of the target population. An increasingly recognized phenomenon in the critically ill is that of augmented renal clearance or ARC, which is broadly defined as the enhanced renal excretion of circulating solute (Udy et al., 2010c). Such changes in elimination are a direct consequence of the unique physiology and treatment provided and may promote subtherapeutic concentrations for many kidney-excreted antimicrobials. Thus, the application of 'standard' dosing regimens in the setting of ARC are likely to be suboptimal, risking treatment failure, or the selection of drug-resistant strains. There are risk factors and mechanisms promoting this phenomenon with important implications for antimicrobial therapy.

Physiological changes promoting ARC

The critically ill are a unique subset of hospitalized patients who typically manifest a systemic inflammatory response syndrome (SIRS), characterized by haemodynamic, respiratory, and haematological perturbations. Cellular hypoxia and damage (e.g. due to trauma or sepsis) activate an innate immune and inflammatory response via the release of cytokines and inflammatory mediators from the site of injury. A global feature of this response is the development of a hyperdynamic circulatory state, characterized by tachycardia, fever, high cardiac output and low systemic vascular resistance (Udy et al., 2010b). Such changes will result in an increase in major organ blood flow, leading to greater 'delivery' of solute to the kidney.

Preventing organ dysfunction is a major therapeutic focus in this setting, for which international guidelines recommend aggressive fluid loading and use of vasoactive medications to achieve specific haemodynamic targets (Dellinger et al., 2008). In this context, the use of both vasopressors and intravenous fluids will augment glomerular filtration, and may further enhance the elimination of renally eliminated antimicrobials. The 'renal reserve' represents an innate response to increased demand, typically demonstrated by an increase in glomerular filtration following protein loading (Thomas et al., 1994). The role of this 'reserve' remains uncertain in the setting of critical illness, although the excess catabolism that accompanies extreme biological stress could conceivably promote additional solute clearance (Fig. 364.1).

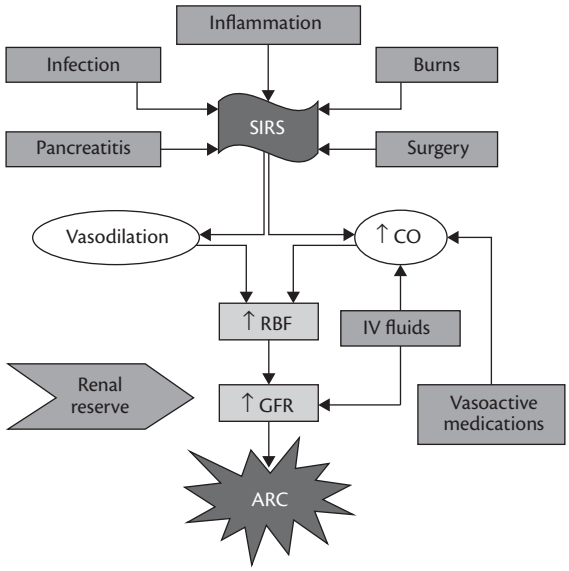

Fig. 364.1 Graphical representation of the mechanisms underlying augmented renal clearance in the critically ill. ARC = augmented renal clearance; CO = cardiac output; GFR = glomerular filtration rate; RBF = renal blood flow; SIRS = systemic inflammatory response syndrome.

Reproduced from Udy, A. A., Roberts, J. A., Boots, R. J., Paterson, D. L., and Lipman, J. (2010). Augmented renal clearance: implications for antibacterial dosing in the critically ill. *Clin Pharmacokinet*, 49(1), 1–16 with permission from Adis, a Wolters Kluwer business (© Adis Data Information BV 2010. All rights reserved.)

Recognizing ARC in the critically ill

Any assessment of kidney function in the intensive care unit (ICU) is primarily aimed at identifying injury, thereby allowing dose modification of renally eliminated drugs and providing a marker of injury progression. In this respect, serum creatinine concentrations are employed as a key biochemical marker for this purpose, despite some known limitations of this measure. Of note, although dose modification is well recognized in kidney injury, the converse, *increasing* doses in the setting of augmented clearances, is seldom considered in clinical practice. This largely stems from the poor sensitivity of creatinine concentrations to identify ARC, particularly when values are reported within the 'normal' reference range.

The most widely accepted index of kidney function to help guide drug dosing is the glomerular filtration rate (GFR). As such, defining ARC on the basis of an elevated GFR is attractive, as it represents a common, pragmatic, and repeatable measure of kidney function. However, this remains a complex task, as there is no consensus on an upper limit of 'normal' filtration, and any specific threshold would have to be closely linked with established drug concentration targets. Conservative values such as those recently reported in head injured patients (> 150 mL/min/1.73 m^2 in women, and > 160 mL/min/1.73 m^2 in men) are worthwhile starting points (Udy et al., 2010a), but require further refinement. It should also be recognized that any assessment of ARC on the basis of GFR alone fails to consider tubular function in renal drug handling, for which there is a well-described role. Currently there are limited data examining changes in these pathways in the critically ill.

Using measured or estimated GFR to identify ARC

Although gold standard measures of GFR (such as inulin clearance or radionucleotide studies) have been employed in a research setting, they are not routinely available, are expensive, and impractical in the ICU. In an attempt to improve the utility of serum creatinine concentrations in clinical practice, Levey and colleagues developed the Modification of Diet in Renal Disease (MDRD) equation from a population of primarily ambulatory patients with chronic kidney disease (CKD) (Levey et al., 1999). The estimated GFR (eGFR) has been widely adopted, although its role in modifying drug dosing remains uncertain. The Cockcroft–Gault formula, which calculates an estimated creatinine clearance (CL_{CR}), is a more traditional method of modifying drug dosing, although in a similar fashion to the MDRD equation, was never designed for application in the ICU. Significantly, such estimates fail to consider the marked physiological changes in this population, and not surprisingly, current data supports the assertion that these formulae are generally flawed in the critically ill, typically underestimating clearances in those manifesting ARC (Baptista et al., 2011).

As such, the most pragmatic, and cost-effective means of identifying ARC in the ICU remains a measured CL_{CR}. Although considered difficult to perform in ambulatory patients, the frequent requirement for urinary catheterization in the critically ill makes obtaining such measures relatively simple, while any errors associated with tubular creatinine secretion will tend to be mitigated by higher filtration rates. Time intervals can vary between 2 and 24 hours, although 8-hour collections appear to provide the best balance between accuracy and feasibility (Cherry et al., 2002). The utility of these measures is further underscored by the strong correlation between CL_{CR} values and antimicrobial drug elimination (Udy et al., 2010c).

Specific populations considered 'at risk' of ARC

Although there are limited current data exploring the epidemiology of this phenomenon, some information exists to help define those at greatest risk of manifesting ARC. A recent single-centre study examining the incidence of 'glomerular hyperfiltration' (defined on the basis of a measured 4-hour CL_{CR} > 120 mL/min/1.73 m^2) found that 17.9% of patients exhibited this phenomenon on the day of admission to ICU (Fuster-Lluch et al., 2008). Those manifesting higher filtration rates were generally postoperative or trauma admissions, younger, with lower illness severity scores, and higher diastolic blood pressures and urine outputs. Thus, surgery and major trauma appear to be important risk factors for ARC. Burn victims will also commonly manifest elevated filtration rates for prolonged periods of time, often associated with marked inflammation and protein catabolism (Loirat et al., 1978).

Patients suffering severe traumatic brain injury (TBI) routinely receive vasopressors and osmotherapy in an attempt to control intracranial hypertension and defend cerebral perfusion. Such interventions have been correlated with elevated CL_{CR}, although filtration rates continue to remain elevated even 'off' perfusion-based therapy, suggesting that TBI itself may promote ARC (Udy et al., 2010a). Subarachnoid haemorrhage represents another neurosurgical cohort where vasopressors and aggressive fluid loading are regularly employed to prevent delayed cerebral ischaemia associated with vasospasm. Although data is currently lacking, similar changes in glomerular filtration and drug elimination are likely.

Pregnancy manifests many similar cardiovascular changes to those encountered in SIRS, such that elevated glomerular filtration and enhanced kidney drug elimination have been well documented (Anderson, 2005). Despite some conflicting observations,

cystic fibrosis patients have also been noted to have augmented renal drug elimination. Patients with febrile neutropenia also often manifest enhanced renal antimicrobial elimination, although studies examining changes in CL_{CR} in this group are currently lacking. Recruitment of the 'renal reserve' may be a key driver of ARC in this setting.

Implications of ARC for antimicrobial therapy

Early, appropriate antimicrobial therapy is essential in improving outcomes from severe sepsis. However, application in the critically ill is not always straightforward, as these agents do not manifest easily titratable endpoints to guide therapy. ARC can significantly impact antimicrobial drug handling, promoting rapid kidney drug elimination and suboptimal drug exposure. For those agents that demonstrate time-dependant bacterial killing (see below), maintaining drug concentrations above the minimum inhibitory concentration (MIC) of the infecting organism for extended intervals, is essential in ensuring bacterial eradication (Roberts and Lipman, 2009). As such, ARC has perhaps the greatest clinical implications for these classes of agents, where a rapid decline in drug concentrations at the site of infection can predispose to treatment failure or the development of antimicrobial resistance (Roberts et al., 2008).

In this context, *personalizing* the application of antimicrobial therapy in the critically ill, through the use of therapeutic drug monitoring (TDM) or where unavailable, CL_{CR} measures, should be considered a clinical imperative. Where ARC can be demonstrated, or in high-risk groups, application of alternative dosing regimens (such as more frequent dosing, extended or continuous infusions), can then be considered. Although outcome data is currently scarce concerning the use of such regimens (largely due to the heterogeneity of the populations under study), pharmacokinetic data supports such an approach in achieving optimal drug exposure (Roberts and Lipman, 2009).

ARC: conclusion

As a consequence of the underlying inflammatory response, and interventions provided, ARC represents a new challenge for accurate antimicrobial dosing in the critically ill. There is significant potential for suboptimal drug exposure, and treatment failure. One consequence of treatment failure is sustained illness, leading to AKI and a subsequent complete reversal in drug management strategies. Clinicians must be cognizant of such changes in kidney function and constantly adjust dosing regimens where appropriate.

The pharmacokinetic effects of the acute kidney injury condition

AKI is a dynamic process. Even a solitary-kidney patient with nephrectomy for malignancy will experience changing metabolism as the body adapts to the anephric state. Compound that physiology with the other conditions that often lead to AKI, and a one-size-fits-all approach to drug management will not succeed.

Absorption

Gastrointestinal drug absorption may be altered by oedematous bowel (Sica, 2003), altered bowel perfusion, the use of acid-suppressant agents (antacids, proton pump inhibitors, or histamine blockers), the presence or absence of enteral nutrition, bowel motility, or fistulous losses. Therefore, drug administration by the oral route leads to unreliable absorption. Rectal administration is probably also unreliable but there is limited experience. For these reasons, parenteral administration is preferred.

Distribution

Drug distribution may reflect true dispersion and/or tissue binding. Both are affected by altered kidney function and its frequently associated disorders. Fluid overload often accompanies AKI, increasing the volume of distribution for water-soluble drugs and those that especially distribute in the extracellular space, such as aminoglycosides. The capillary leak seen in sepsis can increase the extracellular water space by clinically significant amounts (Finn et al., 1996), and bedside techniques are now available to assess the magnitude (Schwenk et al., 1998; Marx et al., 2000). For ascites, effusions, or oedema, additional aminoglycoside must be administered to achieve the target drug level (Etzel et al., 1992). Since aminoglycosides do not distribute into fat, an opposite approach must be taken in the obese. But fat is weighed and weight-based dosing including fat will lead to higher than expected levels, and may explain the increased aminoglycosides nephrotoxicity in the obese (Corcoran et al., 1988). Alternatively, an unappreciated increase in extracellular water may lead to under-dosing, contributing to the poorer prognosis in those with capillary leak (Schwenk et al., 1998). A consistent strategy to utilize actual versus ideal body weight is important, with operational emphasis on 'consistent'.

Uraemia and other organ dysfunction may affect tissue binding, manifesting as a change in the volume or distribution (Vd) and unexpected drug effect (enhanced or reduced). This may be a consequence of altered binding to membranes, receptors, or carrier proteins. There is decreased drug binding to albumin in AKI (Campion, 1973) as well as decreased albumin concentrations. Displacing substances could include retained solutes in uraemia or liver failure, as well as accumulated drugs that compete for albumin binding sites. The free (unbound) fraction is the active agent and is that which is metabolized, excreted and removed by kidney replacement (dialysis-like) therapies (KRTs) (Golper et al., 1985).

Metabolism

AKI alters drug handling by the kidneys as well as other organs, and vice versa. Liver disease also affects kidney tolerance to injury (Lietman, 1988). Drug metabolism is predominantly by the kidney and liver, but the bowel and lungs participate and are vulnerable to impairment in AKI. The non-renal clearance of drugs differs in AKI versus CKD, probably related to the gradual adaptations of non-renal metabolic pathways. This may be secondary to induced enzymatic metabolism by the drug itself or retained solutes. The non-renal clearance of drugs could be increased or decreased in CKD depending on its unique metabolism. Some cytochrome P450 pathways are actually downregulated in CKD, possibly also caused by the accumulation of endogenous inhibitors (Guevin et al., 2002). The change in the non-renal clearance seen in CKD may not be the same as that seen in AKI. Empiric assumptions/predictions are not prudent. Additionally, one must be aware that the duration of and speed of the loss of kidney function influences this effect (Macias et al., 1991).

Elimination

Secretion is usually preserved better than filtration in progressive CKD, but in AKI the comparative role of renal drug elimination

processes is not known. Both the nature of the injury and the pace of its development are contributory. Within a 24-hour period, kidney function might change completely. Under anephric conditions there is no renal drug elimination. The lack of a reliable, rapidly determined measure of filtration or secretion hampers precise dosing recommendations based on kidney function (Steven et al., 2009). Furthermore, as AKI progresses, the kidney elimination of drugs is changing. The elimination by KRT may be quantitatively large or small, constant or intermittent.

Goals of therapy

When a drug therapy has a specific goal that can be assessed clinically, dosing adjustments may be titrated more easily (e.g. anticonvulsants, vasopressors, vasodilators, inotropes, or anti-arrhythmics). When the goals are less defined, clinical judgement must be augmented by other support systems such as TDM. In treating infections some antibiotics are more effective if time above the MIC is sustained (time-dependent killing, e.g. penicillins, cephalosporins, carbapenems, lincosamides, macrolides) versus other antibiotics where an achieved peak concentration is the desired goal (concentration-dependent killing, e.g. aminoglycosides, metronidazole, daptomycin) (Amsden et al., 2005) versus drugs whose benefit is a combination of both effects (e.g. glycopeptides, fluoroquinolones, and linezolid). So for each drug administered in AKI, where standard dosing is unclear, key management principles are to determine what is the clinical goal, and considering how a drug acts, how to achieve that goal.

Since it takes three to five half-lives ($t_{½}$) to achieve a steady-state concentration, drugs with longer $t_{½}$ in renal insufficiency may require a loading dose, such as vancomycin or aminoglycosides. This is also the case if AKI increases the drug's Vd. Removal by KRT often mandates supplemental dosing or modifying an otherwise scheduled dose (Golper and Marx, 1998). TDM is clearly of value in this setting but the conditions around the sampling must be understood. Random sampling is acceptable if the sampling time is known relative to the last dose or intervention that might alter clearance, such as KRT. Plasma levels for some drugs rebound after dialysis (Fig. 364.2). A peak level must be drawn after the immediate distribution phase, typically an hour after administration. TDM requires specific and reliable assays delivered in a timely manner, and awareness of the level needed for efficacy and associated with toxicity. While this discussion emphasizes post-KRT dosing, an argument can be made for dosing aminoglycosides prior to intermittent KRT (Mohamed et al., 2007; Sowinski et al., 2008).

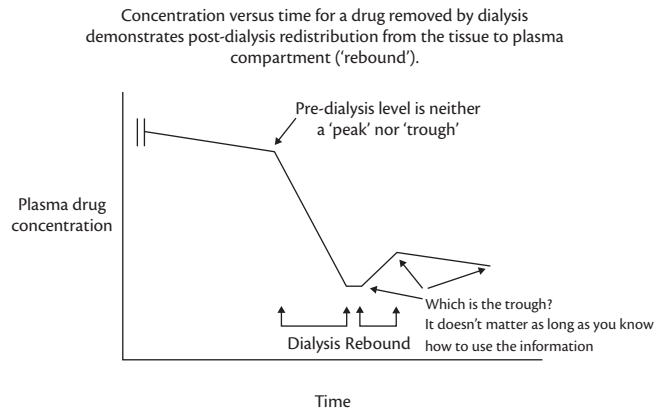

Fig. 364.2 Therapeutic drug monitoring utilization with kidney replacement therapy drug removal requires knowledge of the timing and condition of the sampling. Shown here are post-haemodialysis samples at various times post dialysis, all of which could represent a trough level.

Adjustment of drug management for kidney replacement therapy

We have mentioned the confounders affecting drug handling during changing kidney function. That dynamic situation precludes straightforward and precise guidelines on drug management (Vilay et al., 2008). Once kidney function deteriorates to the point of requiring KRT, there is at least the possibility that one has achieved a new steady state, albeit without kidney function. Unfortunately, even this is not so. Not only are these patients ill with kidney failure, but other organ systems are also still in dynamic (non-steady-state) conditions. Furthermore, at the point where KRT is mandated, drug management has to be adjusted for the KRT.

Operational differences in kidney replacement therapy and their influence on drug management

Continuous versus intermittent KRT

KRTs can be most simply categorized as continuous or intermittent. Seldom is continuous KRT truly 24 hours per day and has actually been defined by the Acute Dialysis Quality Initiative (ADQI) as the intent to be continuous (Kellum et al., 2002). This is a reasonable definition. Intermittent KRT could vary from several hours daily to several hours over many days. Metabolism differs while under KRT beyond the KRT removal of drugs. The operating conditions of the KRT have major effects on drug removal during the KRT, but also on total body metabolism. So drug management must be conducted with an awareness of these many cofounders.

Frequency and duration

For the KRTs that are intermittent, the major determinant of either frequency or duration is tolerance of fluid removal, rather than solute removal. However, that is where the impact on drug management becomes most complex, because KRT may be applied or not, depending on factors independent of the drugs. KRTs may be applied for 2–12 hours per day or every few days. That is why in Fig. 364.2 we emphasize that knowing the conditions of the sampling for TDM is crucial to understanding drug management in this dynamic situation.

Solute transport process

Another method to categorize KRT is by transport process, convection versus diffusion. Most therapies are a combination of the two processes. This is highly relevant to drug removal since convective therapies are associated with a higher clearance of larger-molecular-weight species compared to diffusive therapies. Furthermore, this difference in size of removed molecules may affect intrinsic metabolism differently because of the selective removal of endogenous inhibitors or inducers of drug metabolism. Convection treatments are more likely to be conducted under hypothermic conditions compared to diffusive KRTs. So these two

polar transport processes could result in considerable variation in drug handling (Golper and Marx, 1998).

Blood flow rate

A further categorization of KRTs relates to blood flow rate (Qb) through the extracorporeal circuit. Clearance through the circuit can never exceed Qb and equals Qb with 100% extraction. Qb depends on the nature of the access to the circulation which is almost always through dual-lumen catheters in central veins. Not all catheters are equal in delivering Qb due to location, vein pathologies, catheter luminal size, or catheter damage during placement. Blood is actively pumped from the vein in veno-venous access and if the vessel and catheter are functioning normally, the blood pump speed is the major controllable factor in Qb. A common phenomenon, rarely justified because there is little evidence to support its utility, is for the KRT nurse to decrease the Qb if blood pressure drops. During this period of hypotension intrinsic drug metabolism is altered and drug removal by the KRT is decreased, further impacting on any perceived 'steady state'. This may be quite transient or sustained. Thus, attention to Qb is mandatory to understand drug management during KRT.

Dialysate flow rate or ultrafiltration rate

In diffusion the transport driver is the concentration gradient between blood and dialysate. Dialysate can become saturated with solute under conditions of high Qb and low dialysate flow rate (Qd). This is often the case when dialysate needs to be sterile, since sterile dialysate is needed in peritoneal dialysis and some forms of haemodialysis (e.g. open membranes that allow back passage of inflammatory mediators from dialysate to blood, see below). So situations exist where Qd may be limited. Clearance by the circuit can never exceed Qd. If dialysate is 100% saturated, clearance equals Qd.

In convection the transport driver is the ultrafiltration rate (UFR) determined by the intrinsic hydraulic permeability property of the membrane and the transmembrane pressure (TMP). The latter is usually determined by the machine after a particular membrane is selected and UFR ordered. The UFR can be viewed similarly to Qd. The circuit clearance in convection can never exceed the UFR. If the solute's sieving coefficient (concentration ratio of filtrate to circuit blood) is unity, clearance is equal to the UFR. In convective KRTs the fluid substituting for the filtrate is sterile and thus expensive. So this substitution fluid replacement rate can be the limiting variable. Enough substitution fluid must be administered to keep fluid balance in the specified range for that patient at that time.

Membranes

For simplicity, KRT membranes can be categorized as tight (low flux) versus open (high flux). Tight membranes are generally less permeable to water, that is, require higher TMPs to move water across the membrane, and have smaller pores for solutes to diffuse through. Thus, solute removal is limited by molecular size. This is advantageous because dialysate does not need to be sterile with these membranes. The more open membranes, and the degree of openness is quite variable, allow water passage with less TMP and since the pore size is larger, enhanced passage by diffusion of larger molecules. These membranes mandate ultraclean or sterile dialysate to prevent the back transport of noxious agents from dialysate into blood (Golper and Leone, 1989). Solute clearance is directly proportional to the surface area of the membrane. Other mentioned operational manoeuvres easily compensate for surface area, for example, increased Qb, Qd, UFR, duration, and frequency.

The operating characteristics of the KRT have a major impact on the rate and quantity of drug removal, as well as the uraemic condition and its effect on non-renal drug clearance. The more intense is the KRT, the greater the drug removal effect and the possibility that under-dosing might occur. Knowledge of a drug's pharmacokinetics, pharmacodynamics, and the nature of the KRT are all necessary for optimal drug management.

The many variables involved are the reason this discussion has centred on physiology and operational characteristics. Specific agents (Heintz et al., 2009), specific KRTs (Golper, 1992), and step-by-step principles (Vilay and Mueller, 2010; Matzke et al., 2011) are discussed in several invaluable reviews.

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