Urinary System

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INTRODUCTION

This chapter focuses on the basic anatomy and physiology of the urinary system, the mechanisms and patterns of toxicological injury including common toxic substances that affect the urinary system, and the healing and repair after toxicological damage.

ANATOMY AND PHYSIOLOGY

The urinary system of dogs and cats consists of the kidneys, ureters, bladder, and the urethra. The function of the urinary system is to filter blood, reabsorb important nutrients, and eliminate wastes in the form of urine. The kidneys regulate the amount of water reabsorbed and excreted, maintain the pH of the blood, and control the concentration of electrolytes (Na, K, Ca, and Cl), proteins, and hormones in the blood. Additionally, the kidneys secrete hormones that regulate blood pressure, water balance, red blood cell production, and calcium homeostasis (Haschek et al. 2007).

The kidneys receive approximately 25% of the cardiac output and can be divided into three main parts: the outer cortex, which receives 90% of the renal blood flow; the medulla, which receives 6%–10% of blood flow; and the renal papilla, which receives 1%–2% of the total renal blood flow.

The functional unit of the kidney is the nephron, which is composed of a glomerulus, proximal convoluted tubule, loop of Henle, distal tubule, and collecting duct. The glomerulus is composed of an anastomosing tuft of fenestrated endothelial cells that form a filter for the blood, with the initial filtrate flowing into Bowman's space surrounding the glomerulus and progressing into the proximal tubule. The renal tubules reabsorb 60%–80% of the filtered solute, including water, electrolytes, glucose, amino acids, small peptides, and organic acids. In the medulla, the loops of Henle play a major role in the concentration of urine and maintenance of the blood's electrolyte balance. The filtrate then passes into collecting ducts, which control the excretion rates of electrolytes and urea as well as further maintain acid/ base and water balances. The renal papilla empties the urine through the renal pelvis into the ureters. From the ureters the urine passes into the bladder where it is stored until it is excreted through the urethra.

Renal function is largely measured clinically by the serum renal markers blood urea nitrogen (BUN) and creatinine; due to reserve capacity of the kidney, approximately 50%–75% of nephrons must be damaged before these values become significantly elevated. *Azotemia*, the term for elevations of serum BUN and creatinine, can occur due to prerenal, renal, and postrenal causes. Prerenal azotemia is most commonly the result of dehydration and occurs without renal insufficiency. Renal azotemia is caused by kidney dysfunction, generally due to injury by infectious, metabolic, toxic, or neoplastic processes. Postrenal azotemia is usually associated with obstruction of urine outflow (e.g., bladder "stones"), resulting in a back pressure of urine within the kidney that decreases glomerular filtration. Determination of whether azotemia is prerenal, renal, or postrenal is essential to aid in diagnosis and therapeutic management of the patient. When

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azotemia is present along with the clinical signs associated with renal failure (vomiting, gastrointestinal bleeding, gastritis, oliguria/anuria/polyuria), the condition is termed *uremia*.

MECHANISMS OF TOXICOLOGICAL INJURY

Renal tubular injury is the most common form of nephrotoxic insult in animals (Haschek et al. 2007). Tubular damage may result from direct injury to the epithelial cells by the toxicant or its metabolites, from mechanical obstruction of the tubules, from mineralization of the basement membrane, or from ischemia due to vasoconstriction of renal blood vessels. Toxicants such as lead, arsenic, aminoglycoside antibiotics, and many anticancer drugs cause direct injury to the tubular epithelium. Renal epithelium, particularly in the proximal tubules, contains high levels of metabolic enzymes that can detoxify some compounds present in the filtrate. However, other compounds (e.g., diquat, acetaminophen) can be bioactivated into toxic metabolites by these same enzymes and result in injury to the epithelial cells. Pigments such as hemoglobin (e.g., due to intravascular hemolysis from zinc toxicosis) or myoglobin (e.g., due to muscle damage from monensin toxicosis in dogs) are also directly injurious to renal tubular epithelium.

Some toxicants will result in the precipitation of crystals into the urine as the tubular filtrate becomes more concentrated. Overdoses of drugs such as penicillins, cephalosporins, and acyclovir may result in transient crystalluria, and the crystals can cause mild epithelial damage, which is usually reversible. Tubular obstruction by calcium oxalate crystals is a major cause of renal injury in ethylene glycol intoxication; however, direct tubular epithelial injury due to acidosis also contributes to lesions seen in ethylene glycol toxicosis. Mineralization (deposition of calcium) of renal tubules can result from hypercalcemia associated with some toxicoses (e.g., cholecalciferol rodenticide toxicosis) and can also occur as a sequel of uremia. Mineralization along the tubular basement membrane, within epithelial cells, and within renal blood vessels (impeding blood flow) results in degeneration and necrosis of tubular epithelial cells, cell sloughing, and decreased tubular regenerative ability.

Agents that cause vasoconstriction can impede glomerular filtration as well as cause ischemic damage to the renal tubules. The renal papilla is especially susceptible to ischemic injury because it normally receives only 1% of total renal blood flow, but any portion of the nephron may be affected. Nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen, aspirin, phenylbutazone) decrease prostaglandin levels within the kidney, decreasing prostaglandin-mediated vasodilation and resulting in vessel constriction (Sebastian et al. 2007). Other agents (e.g., the antifungal amphotericin B) induce vasoconstriction by direct interaction with renal arterioles (Sawaya et al. 1995).

Injury to renal tubules impairs water and solute reabsorption, resulting in dilute urine (isosthenuria) due to loss of concentrating ability, as well as spillage of amino acids, glucose, small peptides, and other solutes into the urine. Polyuria will occur unless the tubules become obstructed by swollen tubular epithelium, crystals, sloughed epithelial cells, pigments, or other debris; in these instances oliguria or anuria can occur. When blockages occur, increased tubular pressure counteracts the capillary hydrostatic pressure in the glomerulus, resulting in further decrease in glomerular filtration. A nephron that has damaged tubules can leak filtrate into the systemic circulation, contributing to azotemia as BUN and creatinine are reintroduced into the bloodstream from the damaged tubules.

PATTERNS OF TOXICOLOGICAL INJURY

Nephrotoxic agents can cause renal insufficiency that may progress to acute renal failure (ARF) or chronic renal failure (CRF) depending on the toxicant involved, dose, and duration of exposure. ARF often results from exposure to a relatively high dose of a nephrotoxic agent, causing sudden loss of kidney function, whereas CRF tends to occur more insidiously and may be the result of repeated insults to the kidney (e.g., from repeated exposures to nephrotoxins over time) or it may reflect progression of acute disease. An individual may be more or less susceptible to toxic renal damage due to genetic factors, age, prior renal disease, general overall health, or concurrent medication administration. Patients with CRF oftentimes adapt to their renal disease and may maintain a relatively normal clinical appearance for quite some time in spite of fairly high elevations of serum BUN and creatinine (compensated CRF). Generally, these patients display polyuric renal failure and are able to maintain themselves, provided they have access to adequate fresh water in order to compensate for the increased fluid losses. However, with progression of the renal disease or sudden change in hydration status, these patients may suddenly decompensate and present with clinical signs similar to an ARF patient.

Because of its high blood flow, high metabolic activity and concentration of wastes, the kidney is especially susceptible to toxic injury. While the glomeruli and proximal tubules are exposed to large amounts of bloodborne toxicants, the more distal aspects of the nephron and lower

urinary tract are exposed to higher concentrations of toxicants for a greater period of time as a result of accumulation of toxicants within tubular lumens.

Renal toxicants may cause glomerular damage, resulting in a decrease in glomerular filtration and resulting in azotemia, or increasing the "pore" size of the glomerular filter resulting in the leakage of proteins into the urine. Renal toxicants affecting glomeruli are rare in animals, although some rattlesnake venoms have been associated with glomerular injury (Fitzgerald and Rumbeiha 2004).

Their relatively high metabolic activity, high content of metabolic enzymes, and closer proximity to glomerular filtrate make the proximal tubules more susceptible to a wider range of toxicants than the rest of the nephron (Sebastian et al. 2007). In domestic animals, the proximal renal tubules are most commonly affected by nephrotoxicants, although the distribution of tubular lesions can vary depending on the toxicant involved. For example, tubular injury from melamine:cyanuric acid crystals, the lesion seen in kidneys of animals affected by melamine-contaminated pet foods in the U.S. in 2007, tends to occur in the distal tubules and collecting ducts, whereas calcium oxalate crystals from ethylene glycol metabolism tend to affect primarily the proximal tubules (Puschner et al. 2007). In nephrons undergoing degeneration necrosis, affected tubular cells will swell (degeneration) and then shrink and slough. Cellular debris from damaged tubules manifests as granular casts in the urine sediment.

Damage to the renal papilla can disrupt loops of Henle, resulting in loss of urine-concentrating ability as well as electrolyte imbalances.

Toxic damage to the distal areas of the urinary tract—renal pelvis, ureters, urethra, and bladder—is relatively uncommon. The rapid flushing of urine through the pelvis, ureters, and urethra may explain their relative resistance to toxicologic injury. The urinary bladder, because it stores urine, has occasionally been associated with syndromes arising from toxicants (e.g., cyclophosphamide-induced cystitis).

HEALING AND REPAIR OF THE URINARY SYSTEM

Because much of the nephron is comprised of epithelial cells there is potential for cellular regeneration following toxic injury, provided the tubular basement membrane has remained intact and adequate residual epithelial cells are present. Regeneration of tubular epithelium is usually visible microscopically within 3 days of insult, but it can take up to 3 weeks for the tubules to return to normal structure (Haschek et al. 2007) and up to several more weeks for return to full renal function. The glomerulus tends to be less forgiving, and glomeruli damaged by toxic insults may be permanently dysfunctional (Table 15.1).

Table 15.1. Nephrotoxicants

Lesion	Toxicant	Species
Nephrosis (renal tubular degeneration and necrosis)	Metals (lead, mercury, arsenic, cadmium)	Dogs, cats
	Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, aspirin, phenylbutazone, carprofen, deracoxib)	Dogs, cats
	Lilies (*Lilium* or *Hemerocallis*)	Cats only
	Grapes/raisins/Zante currants/Sultanas (*Vitis* spp.)	Dogs, (cats anecdotal only)
	Antineoplastics (e.g., cisplatin)	Dogs, cats
	Diquat/paraquat	Dogs, cats
	Ethylene glycol	Dogs, cats
	Zinc phosphide	Dogs, cats
	Melamine	Dogs, cats
	Amphotericin B	Dogs, cats
Mineralization	Cholecalciferol and analogues (vitamin D_3, cholecalciferol rodenticides, calcitriol, calcipotriene)	Dogs, cats
Glomerular injury	Rattlesnake venom	Dogs, cats
Bladder injury	Cyclophosphamide	Dogs, cats

CHAPTER 15 STUDY QUESTIONS

1. The most common form of renal injury in animals is
   a. Glomerular injury
   b. Renal tubular injury
   c. Interstitial injury
   d. Tubulointerstitial injury
   e. Papillary necrosis
2. In renal tubular injury, the most common manifestation is _____ except when massive necrosis of tubular epithelial cells results in occlusion of the lumens of renal tubules, in which case _____ or _____ may occur.
   a. Anuria, polyuria, oliguria
   b. Oliguria, polyuria, anuria
   c. Oliguria, anuria, polyuria
   d. Polyuria, oliguria, anuria
   e. Anuria, oliguria, polyuria
3. Cellular debris from damaged renal tubules can be seen in the urinary sediment in the form of
   a. Hyaline casts
   b. Oxalate crystals
   c. Granular casts
   d. Struvites
   e. Dhole bodies
4. The ability of renal tubular epithelium to regenerate depends on the presence of sufficient residual cells and on the integrity of the
   a. Renal papilla
   b. Interstitium
   c. Glomerular mesangium
   d. Renal tubular basement membrane
   e. Vascular endothelium

ANSWERS

1.b. Tubular injury is the most common form of renal injury in animals.
2.d. Polyuric renal insufficiency is the most common manifestation of renal tubular injury.
3.c. Granular casts.
4.d. The integrity of the tubular basement membrane is considered an essential factor in whether tubular epithelium can regenerate following an injury.

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