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Review Article

MANAGEMENT AND PREVENTION OF DRUGS INDUCED END STAGE RENAL DISEASE

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ABSTRACT

Under normal conditions each of the two million nephrons of the kidney works in an organized approach to filter, reabsorb, and excrete various solutes and water. The kidney is a primary regulator of sodium and water as well as acid-base homeostasis. The kidney also produces hormones necessary for red blood cell synthesis and calcium homeostasis. Impairment of normal kidney function is often referred to as renal insufficiency. Based on the time course of development, renal insufficiency has historically been divided into two broad categories. Acute renal failure (ARF) refers to the rapid loss of renal function over days to weeks. Chronic kidney disease (CKD), also called chronic renal insufficiency (CRI) by some, is defined as a progressive loss of function occurring over several months to years, and is characterized by the gradual replacement of normal kidney architecture with interstitial fibrosis. Progressive kidney disease or nephropathy is generally synonymous with CKD, and the two phrases are often used interchangeably. The working group of the National Kidney Foundation's Kidney Dialysis Outcomes and Quality Initiative (K/DOQI) has recently developed a new scheme to classify CKD based on the presence of kidney damage, structural or functional, for ≥3 months, with or without decreased glomerular filtration rate (GFR) from normal values of approx.120 mL/min. CKD is further categorized by the level of kidney function (as defined by GFR) into stages 1 through 5.1 Although these stages are defined later in this review, it is necessary to denote at this point that Stage 5 was previously referred to as End-Stage Renal Disease (ESRD) or End-Stage Kidney Disease (ESKD). The aim of this review article is to focus on the medical therapies which induce nephrotoxicity.

Keywords: *Chronic kidney disease, Glomerular filtration rate, End stage renal disease, Chronic renal insufficiency.*

1. INTRODUCTION

Drug-induced kidney disease or nephrotoxicity (DIN) is a relatively common complication of several diagnostic and therapeutic agents. It is seen in both inpatient and outpatient settings with variable presentations depending on the drug and clinical setting. Manifestations of DIN include acid-base abnormalities, electrolyte imbalances, urine sediment abnormalities, proteinuria, pyuria (pus in the urine), and/or hematuria. However, the most common manifestation of DIN is a decline in the glomerular filtration rate (GFR), which results in a rise in the serum creatinine (Scr) and blood urea nitrogen (BUN). Thus initial diagnosis of DIN typically involves detection of elevated Scr and BUN, for which there is a temporal relationship between the toxicity and use of a potentially nephrotoxic drug. This is consistent with the qualitative definition of acute renal failure (ARF) or an "abrupt and sustained decrease in glomerular filtration, urine output, or both. Unfortunately, numerous quantitative definitions of DIN and/or ARF based primarily on changes in the serum creatinine concentration have been published [1, 2]. Thus it is difficult to ascertain the true incidence of DIN for any drug. As a result, broad ranges of incidence have been reported in various studies of the same agent. DIN is often reversible on discontinuation of the offending agent, but may also lead to acute and/or end-stage renal failure. Many different mechanisms are involved in the pathogenesis of DIN. The development of drugs with novel mechanisms of action provides the potential for the presentation and identification of new unique nephropathies. This chapter reviews the epidemiology, pathophysiology, risk factors, and basic principles of prevention of drug-induced nephrotoxicity. Detailed discussions of these issues plus management strategies are presented for widely used agents that have been associated with a moderate to high likelihood of DIN.

2. EPIDEMIOLOGY

Drug-induced nephrotoxicity occurs in all settings in which drugs are ingested or administered. It is a significant source of morbidity and mortality in the acute care hospital setting. DIN accounts for nearly 7% of all drug toxicity and from 18% to 27% of all cases of acute renal failure in hospitals. Overall, in-hospital drug use may contribute to 35% of all cases of acute tubular necrosis (ATN), most cases of allergic interstitial nephritis (AIN), as well as nephropathy due to alterations in renal hemodynamics and post-renal obstruction. Aminoglycoside antibiotics, radio contrast media, nonsteroidal antiinflammatory drugs (NSAIDs), amphotericin B, and angiotensinconverting enzyme inhibitors (ACEIs) are frequently implicated. Computer-guided medication dosing for hospital in patients may improve the safety of potentially

harmful drugs and minimize the occurrence of DIN in this setting. The incidence and characteristics of outpatient or community acquired DIN are less well understood since mild toxicity is often unrecognized. However, the pharmacoepidemiology of these effects has become more important as care increasingly shifts to the outpatient setting. Although as many as 3% to 6% of hospital admissions have been attributed to adverse drug effects during outpatient therapy, 8 to 20% of hospital admissions due to acute renal failure have been attributed specifically to community-acquired DIN. NSAID nephrotoxicity is common and well defined, with between 1% and 5% of NSAID users developing nephrotoxicity. Prescribed and over-the-counter (OTC) NSAID therapy has been associated with a fourfold-increased risk of hospitalization for acute renal failure during the first month of therapy. Since more than 50 million people use NSAIDs in the United States, it is not surprising that 500,000 to 2.5 million people likely develop NSAID nephrotoxicity in this country annually [3].

3. ASSESSMENT OF KIDNEY TOXICITY

Since the most common manifestation of DIN is a decline in the GFR leading to a rise in the Scr and BUN, the onset of toxicity in hospitalized acutely ill patients is most often recognized by routine laboratory monitoring of the two chemistries. Decreased urine output may also be an early sign of toxicity, particularly with radiographic contrast media, NSAIDs, and ACEIs. In the outpatient setting, nephrotoxicity is often recognized by symptoms such as malaise, anorexia, vomiting, volume overload (shortness of breath or edema) or hypertension. Serum creatinine or BUN concentrations and urine collection for creatinine clearance may subsequently be measured to quantify the degree of loss of glomerular filtration. Marked intrasubject between-day variability of Scr values has been noted (±20% for values within the normal range. Furthermore, they may be altered as the result of dietary changes and initiation of drug therapy, which may interfere with the assay procedure. Thus a change in Scr of at least 0.5 mg/dL for subjects with a baseline Scr 2 mg/dL, when correlated temporally with the initiation of drug therapy is a common threshold for the identification of DIN. Nephrotoxicity may be evidenced by alterations in renal tubular function without loss of glomerular filtration. Indicators of proximal tubular injury include metabolic acidosis with bicarbonaturia; glycosuria in the absence of hyperglycemia; and reductions in serum phosphate, uric acid, potassium, and magnesium due to increased urinary losses. Indicators of distal tubular injury include polyuria from failure to maximally concentrate urine, metabolic acidosis from impaired urinary acidification, and hyperkalemia from impaired potassium excretion. Urinary enzymes and low-molecular-weight proteins are also used as early markers of nephrotoxicity. For example, urinary excretion of the enzymes N-acetyl-β-D-glucosaminidase, γ-glutamyl transpeptidase and glutathione S-transferase are markers of proximal tubular injury and have been used for the early detection of acute kidney damage in critically ill patients. The trans-membrane protein kidney injury molecule-1 (KIM-1) is expressed in the proximal tubule and is up-regulated in patients with ischemic acute tubular necrosis, appearing in the urine within 12 hours after the ischemic insult. High urinary excretion of KIM-1 is associated with a greater than 12-fold increase in the likelihood of ATN [4]. In the future, novel biomarkers such as KIM-1 may facilitate the earlier diagnosis of nephrotoxicity and minimize the long-term consequences of this common drug-induced disorder.

4. PATHOPHYSIOLOGIC MECHANISMS OF NEPHROTOXICITY

The kidneys are more sensitive than many other organs to drug toxicity. Immune-mediated, drug-induced nephrotoxicities include glomerulonephritis and allergic interstitial nephritis, either with or without nephrotic syndrome. The kidney is highly susceptible in part because of its large vascular surface area for exposure to circulating immune mediators and intrinsic immune function of glomerular mesangial cells and renal cytokine activation. Nonimmunologic mechanisms of DIN relate to several specialized characteristics of normal renal physiology, including regulation of blood flow, intra-renal drug metabolism, tubular transport processes, and urine concentration and acidification abilities.

5. PRINCIPLES FOR PREVENTION OF DRUG NEPHROPATHY

The primary principle for prevention of drug-induced nephrotoxicity is to avoid the use of potentially nephrotoxic agents in patients at increased risk for toxicity. However, when exposure to these drugs cannot be avoided, recognition of risk factors and specific techniques may be used to reduce potential nephrotoxicity. No generalizable risk factors are applicable to all drug classes and patient situations, since drug toxicity develops as a result of a wide range of mechanisms, from idiosyncratic hypersensitivity reactions to direct cellular toxicity. An exception is hemodynamically-mediated acute renal failure due to NSAIDs and ACEIs. Their toxicity is frequently preventable by recognizing pre-existing renal insufficiency and decreased effective renal blood flow due to volume depletion, heart failure, or liver disease. Elderly patients with hypertension or heart failure may be especially sensitive to the combined use of ACEIs and NSAIDs, particularly with concurrent diuretic use. Certain approaches to reduce drug toxicity are prudent and generally effective, for example, careful and adequate hydration to establish high renal tubular urine flow rates. However, other strategies to reduce drug toxicity are still theoretical and/or investigational and relate directly to the nephrotoxic mechanisms of the drug. For example, adefovir is a nucleotide antiviral that is actively

transported by OAT1. Inhibition of OAT1-mediated transport with NSAIDs minimizes accumulation of adefovir in renal proximal tubule cells and results in a reduction in toxicity. Diflunisal, ketoprofen, flurbiprofen, indomethacin, naproxen, and ibuprofen were at least as effective as probenecid, a known potent inhibitor of OAT1, at preventing cytotoxicity. Antioxidants have also been shown to be protective in gentamicin, cyclosporine, and cisplatin induced nephrotoxicity in experimental models [5]. Iron chelators are also protective against gentamicin toxicity. Specific drug-induced renal structural–functional alterations constitute the remainder of this discussion under the seven broad headings listed in Table 1. The general orientation of these topics is in order of decreasing clinical incidence. Pathophysiologic mechanisms of nephrotoxicity will be emphasized, in addition to clinical findings, prevention, and management.

Table 1: Examples of Drug-induced Renal Structural & Functional Alteration

Structural & Functional Alteration	Causative Drugs
Tubular epithelial cell damage	Aminoglycoside antibiotics, Radiographic contrast media, Cisplatin/carboplatin, Mannitol, Amphotericin B, Dextran, Osmotic nephrosis, Intravenous immunoglobulin,
Hemodynamically-mediated renal failure	Angiotensin-converting enzyme inhibitors Angiotensin II receptor antagonists, NSAIDs
Obstructive nephropathy	Acyclovir, Sulfadiazine, Indinavir, Foscarnet, Triamterene Methotrexate Extra-renal obstruction, Tricyclic antidepressants
Glomerular Disease	Gold, NSAIDs, Pamidronate
Tubulointerstitial disease (Acute allergic interstitial nephritis)	Penicillins, Ciprofloxacin NSAIDs, Omeprazole, Furosemide Chronic interstitial nephritis, Cyclosporine, Lithium, Aristolochic acid
Tubulointerstitial disease (Papillary necrosis)	Combined phenacetin, Aspirin, caffeine analgesics
Renal vasculitis, thrombosis, and cholesterol emboli (Vasculitis and thrombosis)	Hydralazine, Propylthiouracil, Allopurinol, Penicillamine, Gemcitabine, Mitomycin C, Methamphetamines, Cholesterol emboli, Thrombolytic agents, Warfarin
Pseudo-renal failure	Corticosteroids, Trimethoprim, Cimetidine

5.1. Acute Tubular Necrosis

5.1.1. Aminoglycosid leads to nephrotoxicity pathogenesis

The pathogenesis of reduced GFR in patients receiving aminoglycosides is predominantly the result of proximal tubular epithelial cell damage leading to obstruction of the tubular lumen and backleakage of the glomerular filtrate across the damaged tubular epithelium. The toxicity of various aminoglycosides is related to cationic charge, which facilitates binding of filtered aminoglycosides to renal tubular epithelial cell luminal membranes. For instance, neomycin has six cationic amino groups and is the most nephrotoxic aminoglycoside, whereas streptomycin, with three groups, is least toxic. Gentamicin and tobramycin, with five amino groups, have similar and intermediate toxicity, whereas amikacin and netilmicin, with four and three amino groups, respectively, may be less toxic. Binding to tubular epithelial cells is followed by intracellular transport and concentration in lysosomes. Subsequent binding to acidic phospholipids (phosphatidylinositol) causes their aggregation and inhibits phospholipase activity. This presents histopathologically as myeloid bodies within lysosomes of renal tubular epithelial cells. Cellular dysfunction and death may result from release of lysosomal enzymes into the cytosol, generation of reactive oxygen species, altered cellular metabolism, and alterations in cell membrane fluidity, leading to reduced activity of membrane-bound enzymes, including Na^+-K^+ATPase, dipeptidyl peptidase IV, and neutral aminopeptidase [6]. (Although binding of aminoglycosides to tubular epithelial cells is facilitated by the number of cationic groups present, inherent risks of toxicity are also a factor.

5.1.2. Management

Serum creatinine concentrations should be measured frequently (every 2 to 4 days) during therapy. Aminoglycoside use should be discontinued or the dosage regimen revised if the Scr increases by >0.5 mg/dL during a course of therapy. Other nephrotoxic drugs should be discontinued if possible, and the patient should be maintained adequately hydrated and hemodynamically stable. Dialysis may be necessary, but renal failure due to solely aminoglycoside toxicity is usually reversible.

5.2. Radiographic Contrast Media Nephrotoxicity

5.2.1. Pathogenesis

Contrast nephropathy appears to be due to direct tubular toxicity and renal ischemia. Direct tubular toxicity is suggested by renal tubular enzymuria and biopsy findings of proximal tubular epithelial cell vacuolization and acute tubular necrosis. In addition to the direct toxic effects of contrast media, the nonselective proteinuria induced by contrast media may indirectly damage tubular epithelial cells. In contrast to these findings, the low urine sodium concentration and low

fractional excretion of sodium frequently observed suggest preserved renal tubular function and participation of renal ischemia more than tubular toxicity. Renal ischemia may result from systemic hypotension associated with contrast injection, as well as renal vasoconstriction mediated by an imbalance of humoral agents, including prostaglandins, adenosine, atrial natriuretic peptide, nitric oxide, and endothelin [7-9]. Renal ischemia may also result from dehydration due to osmotic diuresis accompanying use of hyperosmolar agents (900 to 1780 mOsm/kg) and increased blood viscosity due to red blood cell crenation and aggregation.

5.2.2. Prevention

The importance of strategies aimed at preventing radiocontrastinduced nephrotoxicity cannot be overemphasized. All patients scheduled to receive radiocontrast media should be assessed for risk factors, and the risk:benefit ratio should be considered. Nephrotoxicity can be predicted in the majority of patients at risk, which justifies the use of preventative procedures with even minimal benefit. High-risk patients should be identified, primarily by medical history and indication for the contrast study, but also by prestudy serum creatinine concentrations. Nephrotoxicity is best prevented in high-risk patients by using alternative imaging procedures (e.g., ultrasound, magnetic resonance imaging, and nuclear medicine scans). However, if contrast media must be used, the smallest adequate dose should be administered. Dose reduction proportional to the level of renal insufficiency may be protective, but may limit the adequacy of imaging. Low-osmolality nonionic (iohexol and iopamidol) and ionic (ioxaglate) contrast agents may be used to prevent nephrotoxicity. Standard contrast media are not reabsorbed in the kidney and cause osmotic diuresis, which contributes to the renal toxicity observed with these agents. The second generation contrast agents have half the osmolality of standard agents, and have been associated with less toxicity, especially when used in patients with pre-existing kidney disease. The incidence of contrast nephropathy in non-diabetic patients with underlying kidney disease is more than twofold higher in those receiving standard contrast agents compared to those receiving low-osmolar agents [10]. However, use of low osmolar agents does not eliminate nephrotoxicity and the preventive measures outlined below should be utilized.

5.2.3. Management

Currently there is no specific therapy available for managing established contrast nephropathy. Care is supportive with dialysis as needed in selected patients. Careful attention must be given to preventing infection and bleeding and providing respiratory support in view of the high association of these complications with death.

5.3. Cisplatin and Carboplatin Nephrotoxicity

5.3.1. Pathogenesis

Proximal tubular damage appears acutely after administration of platin-containing compounds, as the result of impairment of cell energy production, possibly by binding to proximal tubular cellular proteins and sulfhydryl groups with disruption of cell enzyme activity and uncoupling of oxidative phosphorylation. The initial proximal tubular damage is followed by a progressive loss of glomerular filtration and impaired distal tubular function [11]. Renal biopsies generally show sparing of glomeruli with necrosis of proximal and distal tubules and collecting ducts.

5.3.2. Prevention

Toxicity is best prevented by dose reduction and decreased frequency of administration, which usually requires using the platin compounds in combination with other chemotherapeutic agents. Vigorous saline hydration is important and should be used in all patients; doses range from 1 to 4 L within 24 hours of cisplatin treatment to as high as 3 L/m2 within 24 hours for high-dose carboplatin.50 Although protective roles per se for furosemide or mannitol diuresis are less clear, their use is often necessary to maintain volume homeostasis. Amifostine, an organic thiophosphate that is converted to an active metabolite, chelates cisplatin in normal cells and has been shown to reduce the nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression associated with cisplatin and carboplatin therapy. The renoprotective effect of amifostine administration was recently demonstrated in patients receiving cisplatin/ifosfamide-based chemotherapy. Amifostine fully preserved GFR in patients with solid tumors after administration of two cycles of chemotherapy compared to a 30% reduction in GFR in controls. In addition, less severe hypomagnesemia and decreased tubular damage were observed in the amifostine group. Pretreatment with amifostine should be considered in patients at risk for renal dysfunction. Promising investigational techniques have included the use of hypertonic saline to reduce tubular cisplatin uptake; reduced renal exposure by use of localized intraperitoneal administration in conjunction with systemic administration of sodium thiosulfate for those with peritoneal tumors; use of N-acetylcysteine, a sulfhydryl donor, and disulfiram metabolite diethyldithiocarbamate. Recently the protective effect of melatonin, and the ability of cisplatin-incorporated polymeric micelles to maintain antitumor activity while reducing nephrotoxicity have been demonstrated [12].

5.3.3. Management

Acute renal failure due to cisplatin therapy is usually partially reversible with time and supportive care, including dialysis. Serum magnesium concentrations should be monitored frequently and hypomagnesemia corrected. Hypocalcemia and hypokalemia may be difficult to reverse until hypomagnesemia

is corrected. Progressive chronic kidney disease due to cumulative toxicity may not be reversible and in some cases may require chronic dialysis support.

5.4. Amphotericin B Nephrotoxicity

5.4.1. Pathogenesis

Renal pathologic findings include focal vacuolization of small arterial and arteriolar smooth muscle cells, as well as proximal and distal tubular epithelial cell damage. The mechanisms of renal dysfunction include direct tubular epithelial cell toxicity with increased tubular permeability and necrosis, as well as arterial vasoconstriction and ischemic injury. Tubular membrane permeability to solutes such as sodium and potassium increases when amphotericin binds to membranes and acts as an ionophore. Renal vasoconstriction occurs by unclear mechanisms, possibly including direct effects of amphotericin B on cellular calcium fluxes and activation of vasoconstrictor prostaglandins. Overall, the combined effects of increased cell energy and oxygen requirements due to greater cell membrane permeability, and reduced cellular oxygen delivery due to renal vasoconstriction, result in renal medullary tubular epithelial cell necrosis and renal failure.

5.4.2. Prevention

Nephrotoxicity is best minimized by limiting the cumulative dose and avoiding concomitant administration of other nephrotoxins, particularly cyclosporine. Additionally, providing hydration with a high sodium diet and 1 L intravenous 0.9% sodium chloride daily appears to reduce toxicity. Mannitol infusion to induce an osmotic diuresis has not been protective. Lastly, several liposomal amphotericin B formulations are now available and have been reported to reduce nephrotoxicity by enhancing drug delivery to sites of infection and thereby reducing exposure of mammalian cell membranes [13].

5.4.3. Management

Amphotericin nephrotoxicity is best treated by discontinuation of therapy and substitution of alternative antifungal therapy, if possible. Renal tubular dysfunction and glomerular filtration will improve gradually to some degree in most patients, but damage may be irreversible.

5.5. Pentamidine Nephrotoxicity

Pentamidine therapy for Pneumocystis carinii infections is also limited by nephrotoxicity. Prospective studies have shown azotemia in 60% to 90% of treated patients. Hyperkalemia, metabolic acidosis, hypomagnesemia, and hypocalcemia may also occur. Toxicity is more frequent in patients with the acquired immunodeficiency syndrome (AIDS) than in patients without this immune deficiency, and may be accentuated by concomitant amphotericin B therapy. The mechanism of toxicity is unknown, but tubular degeneration has been seen histopathologically. The primary alternative therapy for P. carinii, trimethoprim- sulfamethoxazole, may also cause renal dysfunction due to allergic interstitial nephritis and/or inhibition of tubular secretion of creatinine, but the incidence is lower than with pentamidine.

5.6. Foscarnet Nephrotoxicity

Foscarnet, an antiviral pyrophosphate analog used in AIDS and other immunosuppressed patients to treat cytomegalovirus (CMV) retinitis and life-threatening CMV infections, is a highly nephrotoxic agent. 66% of patients treated with foscarnet develop renal insufficiency. The mechanism appears to be complexation of foscarnet with ionized calcium and precipitation of calcium-foscarnet salt crystals in renal glomeruli causing a crystalline glomerulonephritis. The salt crystals may then secondarily precipitate in the renal tubules causing tubular necrosis. Foscarnet nephrotoxicity can be minimized by administering the appropriate dose after vigorously prehydrating the patient. Intravenous hydration provides better nephroprotection than oral hydration. In addition, cidofovir and adefovir, potent nucleotide analogs administered for CMV infection in AIDS patients, have been associated with renal proximal tubular cell injury and renal failure [14]. Probenecid blocks renal tubular epithelial cell uptake of cidofovir, and when combined with saline hydration can reduce the incidence of nephrotoxicity.

5.7. Osmotic Nephrosis

Several drugs, including mannitol, low-molecular-weight dextran, and radiographic contrast media, or drug vehicles, including sucrose and propylene glycol, have been associated with vacuolization, swelling, and ultimately necrosis of proximal tubular epithelial cells with a decline in renal function. The decline in renal function may be due to the hypertonic and osmotically active nature of these agents. Intravenous immunoglobulin solutions contain hyperosmolar sucrose and may cause osmotic nephrosis and acute renal failure, which is rapidly reversible on discontinuing therapy. Toxicity may be prevented by diluting the solution and reducing the rate of infusion. Hydroxyethylstarch, used as a plasma volume expander, has also been implicated in the development of osmotic nephrosis. Mannitol may rarely cause oligo-anuric renal failure with proximal tubular cell vacuolization on biopsy. Mechanisms include pinocytosis of mannitol into cells, causing swelling and tubular lumen obstruction. Mannitol can also cause direct renal vasoconstriction or induce an osmotic diuresis with increased solute delivery to the macula densa and subsequent tubuloglomerular feedback, leading to vasoconstriction of the glomerular afferent arteriole and decreased renal blood flow. Risk factors for mannitol DIN include excessive doses, pre-existent renal insufficiency, and concomitant diuretic or cyclosporine therapy. Nephrotoxicity may be prevented by limiting the dose and avoiding dehydration and concomitant

diuretic therapy. The serum mannitol concentration should be maintained.

5.8. Hemodynamically-Mediated Renal Failure

5.8.1. Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

5.8.1.1. Pathogenesis

The pathogenesis of ACEI- or ARB-mediated renal failure is a decrease in glomerular capillary hydrostatic pressure sufficient to reduce glomerular ultrafiltration. This often occurs in settings in which glomerular afferent arteriolar blood flow is reduced and the efferent arteriole is vasoconstricted to maintain sufficient glomerular capillary hydrostatic pressure for ultrafiltration. ACEI or ARB therapy reduces angiotensin II synthesis or activity, respectively, thereby dilating the efferent arteriole and reducing glomerular capillary hydrostatic pressure. This decreases glomerular ultrafiltration and GFR.

5.8.1.2. Prevention

A common strategy for at-risk patients is to initiate therapy with very low doses of a short-acting ACE inhibitors, the dose is gradually titrated upward and converted to a longer-acting agent after patient tolerance has been demonstrated. Outpatients may be started on low doses of long-acting ACEIs with gradual dose titration. Renal function and serum potassium concentrations must be monitored carefully, daily for hospitalized patients and every 2 to 3 days for outpatients. Monitoring may need to be more frequent during outpatient initiation of ACEI or ARB therapy for patients with pre-existing renal insufficiency, congestive heart failure, or suspected renovascular disease. Use of concurrent hypotensive agents and diuretics should be discouraged and dehydration avoided [15].

5.8.1.3. Management

Acute decreases in renal function and hyperkalemia usually resolve over several days after ACEI or ARB therapy is discontinued. Occasional patients will require management of severe hyperkalemia, usually with sodium polystyrene sulfate. ACEI or ARB therapy may frequently be reinitiated, particularly for patients with congestive heart failure, after intravascular volume depletion has been corrected or the diuretic doses reduced. The development of mild renal insufficiency (serum creatinine concentration of 2 to 3 mg/dL) may be an acceptable trade-off for hemodynamic improvement in certain patients with severe congestive heart failure or renovascular disease not amenable to invasive management. Congestive heart failure patients with greater renal insufficiency may be best treated by substitution of hydralazine and nitrates for afterload reduction.

5.9. Nonsteroidal Anti-Inflammatory Drugs

5.9.1. Pathogenesis

NSAIDs inhibit cyclooxygenase (COX)-catalyzed prostaglandin production and impair renal function by decreasing synthesis of vasodilatory prostaglandins from arachidonic acid.10 Renal prostaglandins are synthesized in the renal cortex and medulla by vascular endothelial and glomerular mesangial cells. Their effects are primarily local and result in renal vasodilation (particularly prostacyclin and prostaglandin E2 [PGE2]). They have limited activity in states of normal renal blood flow, but in states of decreased renal blood flow their synthesis is increased and they protect against renal ischemia and hypoxia by antagonizing renal vasoconstriction due to angiotensin II, norepinephrine, endothelin, and vasopressin. Administration of NSAIDs in the setting of renal ischemia and compensatory increased prostaglandin activity may thus alter the balance of activity between renal vasoconstrictors and vasodilators. This leaves the activity of renal vasoconstrictors unopposed and promotes renal ischemia with loss of glomerular filtration. This hemodynamically-mediated acute renal failure is the most common adverse renal effect of NSAIDs.

5.9.2. Prevention

NSAID-induced acute renal failure can be prevented by recognizing high-risk patients and using analgesics with less prostaglandin inhibition, such as acetaminophen, nonacetylated salicylates, aspirin, and possibly nabumetone. Non-narcotic analgesics (e.g., propoxyphene and tramadol) may also be useful but do not provide anti-inflammatory activity. When NSAID therapy is essential for high-risk patients, management of predisposing medical problems should be optimized and renal function monitored. Sulindac may be useful in high-risk patients since it is a potent NSAID that may have lesser effects on renal prostaglandin synthesis and function. The mechanism of renal prostaglandin sparing is unclear, but may involve intrarenal metabolism of the active drug, sulindac sulfide, by cytochrome P450–dependent mixed-function oxidases to an inactive metabolite, sulindac sulfoxide. However, this favorable effect of sulindac has not been consistently observed in patients with hepatic disease, especially at higher therapeutic doses or during prolonged therapy. Traditional, nonselective NSAIDs inhibit COX-1 and COX-2, while the selective drugs meloxicam, celecoxib, and valdecoxib preferentially inhibit COX-2. COX-2 inhibitors were anticipated to be beneficial in high-risk patients. However, recent data indicate they affect renal function similarly to nonselective NSAIDs and thus caution is warranted with their use, particularly in high-risk patients [16].

5.9.3. Management

NSAID-induced acute renal failure is treated by discontinuation of therapy and supportive care. Renal failure

may be severe, but recovery is usually rapid and dialysis is rarely necessary. Occasionally the hemodynamic insult is sufficiently severe to cause frank tubular necrosis, which can prolong recovery. The differential diagnosis of NSAID hemodynamically-mediated acute renal failure must include NSAID-induced acute interstitial nephritis, with or without the nephrotic syndrome, because steroid therapy may benefit this type of renal injury.

5.10. CYCLOSPORINE AND TACROLIMUS

5.10.1. Pathogenesis

A dose-related hemodynamic mechanism is likely during the initial months of therapy since renal function improves rapidly following dose reduction. Reversible vasoconstriction and injury to glomerular afferent arterioles occurs, possibly due to increased activity of vasoconstrictors, including thromboxane A2, endothelin, and the sympathetic nervous system, or diminished activity of vasodilators, nitric oxide, or prostacyclin. Vasoconstriction due to increased reninangiotensin system activity may also contribute. In contrast renal arteriolar hyalinization and chronic renal ischemia as well as increased extracellular matrix synthesis appear to contribute to cyclosporineinduced chronic kidney disease [17].

5.10.2. Prevention

Since acute DIN appears to be dose related, pharmacokinetic and pharmacodynamic monitoring is an important means of preventing toxicity. However, the persistent presence of therapeutic or low cyclosporine concentrations cannot preclude nephrotoxicity. Calcium channel blockers may antagonize the vasoconstrictor effect of cyclosporine by dilating glomerular afferent arterioles and preventing acute decreases in renal blood flow and glomerular filtration. Lastly, decreased doses of cyclosporine or tacrolimus, primarily when used in combination with other non-nephrotoxic immunosuppressants, may minimize the risk of toxicity, but this may increase the risk of chronic rejection.

5.10.3. Management

Acute renal insufficiency usually improves with dose reduction, and treatment of contributing illness or the discontinuation of interacting drugs. Chronic kidney disease is usually irreversible, but progressive toxicity may be limited by discontinuation of cyclosporine therapy or dose reduction, with the continuation of other immunosuppressants (e.g., prednisone or azathioprine).

5.11. Triamterene

Triamterene, a potassium-sparing diuretic, has been associated with transient decreases in creatinine clearance and abnormal urinary sediment in normal subjects and hypertensive patients [18]. In combination with hydrochlorothiazide, triamterene has caused reversible acute renal failure in elderly patients. In combination with indomethacin,triamterene has induced acute renal failure in normal subjects and patients at risk for NSAID nephropathy. A hemodynamic mechanism is most likely, as suggested by the apparent increased risk for nephrotoxicity during combined triamterene and indomethacin therapy. Presumably, triamterene causes renal vasoconstriction that is counterbalanced by increased renal synthesis of vasodilatory prostaglandins. Concomitant NSAID therapy may induce renal ischemia by preventing the compensatory increase in renal prostaglandin synthesis. The implications of these observations are unclear because triamterene and NSAIDs are frequently used together without apparent nephrotoxicity.

6. TUBLOINTERSTITIAL DISEASE

These diseases involve the renal tubules and their surrounding interstitial tissue. The presentation may be acute and reversible with interstitial inflammatory cell infiltrates, rapid loss of renal function, and systemic symptoms; or chronic and irreversible with interstitial fibrosis, slow loss of renal function, and no systemic symptoms. Papillary necrosis, a variant of chronic interstitial nephritis, originates deep in the renal medulla and papillae.

6.1. Acute allergic interstitial nephritis

Table 2: Examples of Drug-induced Renal Structural & Functional Alteration

Structural & Functional Alteration	Causative Drugs
Antimicrobial agents	Acyclovir, Aminoglycosides, Rifampin Amphotericin B, Aztreonam Cephalosporins, Ciprofloxacin Erythromycin, Trimethoprim, Indinavir, Penicillins, Vancomycin Sulfonamides, Tetracyclines Ethambutol, Sulfamethoxazole,
Diuretics	Acetazolamide, Amiloride, Thiazides Chlorthalidon, Furosemide, Triamterene,
Neuropsychiatric	Carbamazepine, Lithium, Phenytoin, Phenobarbital, Valproic acid
Nonsteroidal anti-inflammatory drugs	Indomethacin, Naproxen, Ibuprofen, Diflunisal,Piroxicam, Ketoprofen, Phenylbutazone, Diclofenac, Zomepirac
Miscellaneous	Acetaminophen, Allopurinol, Aspirin, Interferon-alfa, Gold, Azathioprine, Captopril, Ethambutol, Cimetidine, Clofibrate, Cyclosporine, Methyldopa, Omeprazole, P-aminosalicylic acid, Phenylpropanolamine, Propylthiouracil Radiographic contrast media Ranitidine, Sulfinpyrazone Warfarin sodium

6.2. Non-Steroidal Anti-Inflammatory Agents (NSAIDS)

6.2.1. Pathogenesis

The pathology of AIN is a diffuse or focal interstitial infiltrate of lymphocytes, plasma cells, eosinophils, and occasional polymorphonuclear neutrophils [19]. Granulomas and tubular epithelial cell necrosis are relatively common with drug-induced AIN. The pathogenesis is an allergic hypersensitivity response.90 Occasionally a humoral antibody-mediated mechanism is implicated by the presence of circulating antibody to a drug hapten–tubular basement membrane complex, low serum complement levels, and deposition of IgG and complement in the tubular basement membrane. More commonly, a cell-mediated immune mechanism is suggested by the absence of these findings and the presence of a predominantly T-lymphocyte infiltrate with an increased helper:suppressor cell ratio. In particular, NSAID interstitial nephritis involves T lymphocytes, possibly in response to altered prostaglandin synthesis.

6.2.2. Prevention

No specific preventive measures are known due to the idiosyncratic nature of these reactions. Patients must be monitored carefully to recognize the signs and symptoms and discontinue therapy promptly.

6.2.3. Management

No prospective treatment trials have been reported. However, prednisone therapy in a dose of 1 mg/kg daily for 4 weeks has been used and may improve the rate and extent of renal recovery.

6.3. Chronic Interstitial Nephritis

Lithium, cyclosporine, and only a few other drugs have been reported to cause chronic interstitial nephritis, which is usually a progressive and irreversible lesion. Streptozotocin and other antineoplastic nitrosoureas also cause dose-dependent chronic interstitial disease. In addition, mesalazine, 5-aminosalicylic acid, and ifosfamide may cause chronic interstitial nephritis, which usually resolves promptlywhen drug use is discontinued.

6.4. Lithium

Impaired ability to concentrate urine is due to a dose-related decrease in collecting duct response to antidiuretic hormone. This results from impaired formation of cellular cyclic adenosine monophosphate in response to antidiuretic hormone. Lithium-induced acute renal failure occurs predominantly during episodes of acute lithium intoxication [20]. The pathogenesis includes dehydration secondary to nephrogenic diabetes insipidus, as well as direct proximal and distal tubular cell toxicity. Chronic tubulointerstitial nephritis attributed to lithium is evidenced by biopsy findings of interstitial fibrosis, focal tubular atrophy, and glomerular sclerosis. The pathogenesis may involve cumulative damage from lithium-induced acute tubular necrosis. Alternatively, cumulative direct lithium toxicity may occur since duration. of therapy which has been correlated with the decline in the GFR. Finally, some patients may have increased susceptibility to lithium toxicity. Although the reason for this is unknown, this could explain the difficulty in characterizing the nephrotoxic effects of chronic lithium therapy.

6.4.1. Prevention

Prevention of acute and chronic toxicity includes maintaining lithium concentrations as low as therapeutically possible, avoiding dehydration, and monitoring renal function. It is unknown whether progression to severe renal failure can be prevented by stopping lithium use when mild renal insufficiency is first recognized. This poses a dilemma since lithium is highly effective for affective disorders and the risks and potential benefits of discontinuing such a beneficial drug need to be carefully considered. However, if lithium therapy is continued, renal function must be monitored and therapy discontinued if it continues to decline.

6.4.2. Management

Symptomatic polyuria and polydipsia can be reversed by discontinuation of lithium therapy or ameliorated with amiloride or NSAIDs during continued lithium therapy [21]. Acute renal failure is usually reversible with supportive care, including dialysis to reduce toxic blood lithium concentrations. Progressive chronic interstitial nephritis is treated by discontinuation of lithium therapy, adequate hydration, and avoidance of other nephro-toxic agents.

7. CONCLUSION

The pharmacoeconomics of drug-induced kidney disease have not been well defined. An analysis of aminoglycoside therapy in the acute care environment for 1984 to 1985 revealed 7.3% of patients experienced nephrotoxicity. The mean additional cost for each episode of toxicity (in 1984 dollars) was $2501. The average additional cost of toxicity for each individual treated with aminoglycosideswas $183.111 Individualized pharmacokinetic monitoring efforts were recently reported to decrease costs associated with aminoglycoside nephrotoxicity by more than $900 per patient.37 Outpatient care costs of NSAID toxicity have also been evaluated. Costs for hospital care for NSAID-induced acute hemodynamically-mediated renal failure and interstitial nephritis combined have been estimated at $990 million per year. The risk of ESKD stemming from immunosuppressant-induced nephrotoxicity contributes substantially to the cost of heart transplantation. The estimated cost per transplant patient was $6700 within 5 years, increasing to $14,200 within 8 years post-transplantation. Finally, patients who develop ESKD require dialysis, which typically costs more than $50,000 per year.

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