Drug-induced Kidney Disease

Introduction

- The kidney maintains the vital functions of clearing excess body fluid and removing metabolic and exogenous toxins from the blood
- The kidney is particularly vulnerable to drugs and other agents that cause renal damage
- The heart pumps approximately 25% of cardiac output into the kidneys
- Any drug in the blood will eventually reach the highly vascularized kidneys
- May potentially cause drug-induced renal failure
- If the drug is primarily cleared by the kidney, the drug will become increasingly concentrated as it is moves from the renal artery into the smaller vasculature of the kidney
- The drug may be filtered or secreted into the lumen of the renal tubules
- The concentrated drug exposes the kidney tissue to far greater drug concentration per surface area

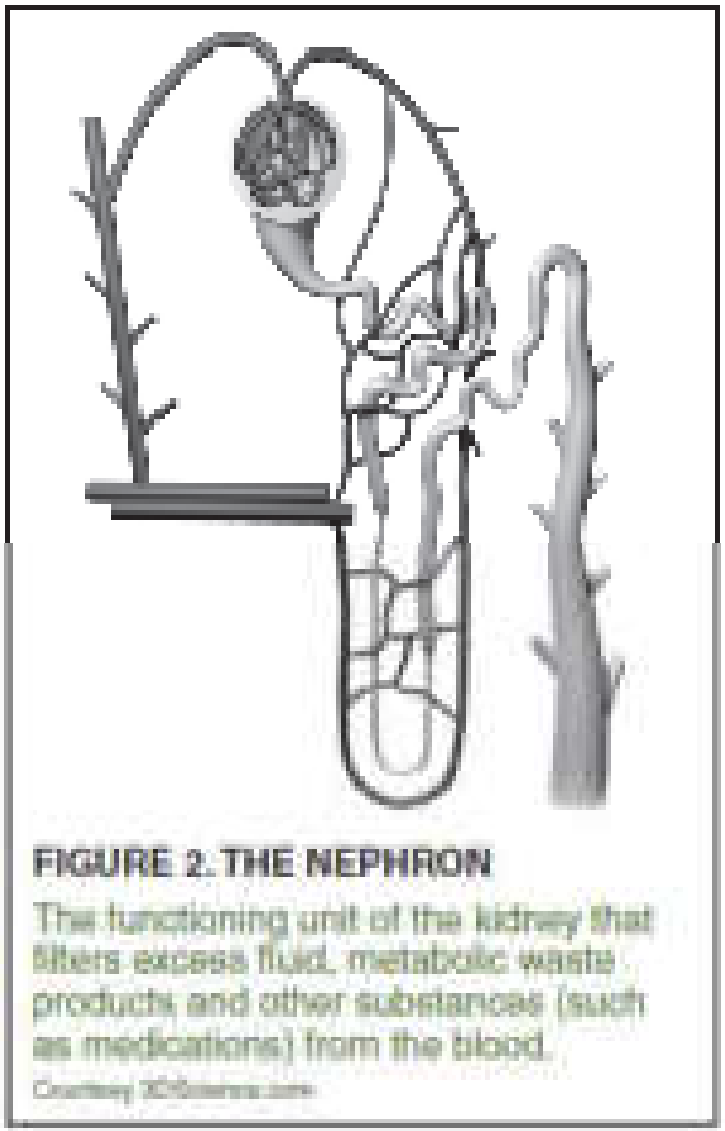

FIGURE 2. THE NEPHRON

The functioning unit of the kidney that filters excess fluid, metabolic waste products and other substances (such as medications) from the blood.

Courtesy 3DScience.com

Introduction

- Drug-induced kidney failure is a major adverse event associated with multiple medication classes
- Medications as diverse as OTC analgesics (ibuprofen, acetaminophen), antibiotics and chemotherapy agents can cause kidney damage
- Medication use accounts for 2% of hospital admissions for acute renal failure and up to 15% of admissions into intensive care

Causes of RF in H.patients

- Diagnostic procedures (IV contrast)
- Sudden decrease in blood pressure (gastrointestinal bleed, sepsis, variceal bleed)
- The addition of nephrotoxic medications (aminoglycosides, amphotericin, chemotherapy)
- Up to 16% of patients with baseline normal renal function who experience renal failure within the hospital setting have medication-induced renal failure

Clinical presentations

- Patients who experience acute-onset renal failure often complain of increased shortness of breath, ankle swelling and weight gain
- The reduced ability of the kidney to clear extra fluid from the body
- stopping the medication may allow the kidney to recover
- If the kidney has extensive damage, the kidney may reduce or even stop producing urine
- Hemodialysis may be necessary for a short-term bridge until the kidney can recover
- In some cases, the damage is irreversible and the patient will require life-long dialysis or a kidney transplant

Contd.

- Drug-induced renal disease can mimic renal disease from other causes, such as autoimmune disease and infection
- A thorough physical examination and medical history should be performed
- Increase in serum creatinine and BUN
- Additional urine tests: protein excretion, creatinine concentration, osmolality, or sodium excretion
- A thorough and accurate review of all medications, including all prescription, over-the-counter and herbal medications
- Importance of dose and duration of exposure
- rule out all other causes of kidney failure

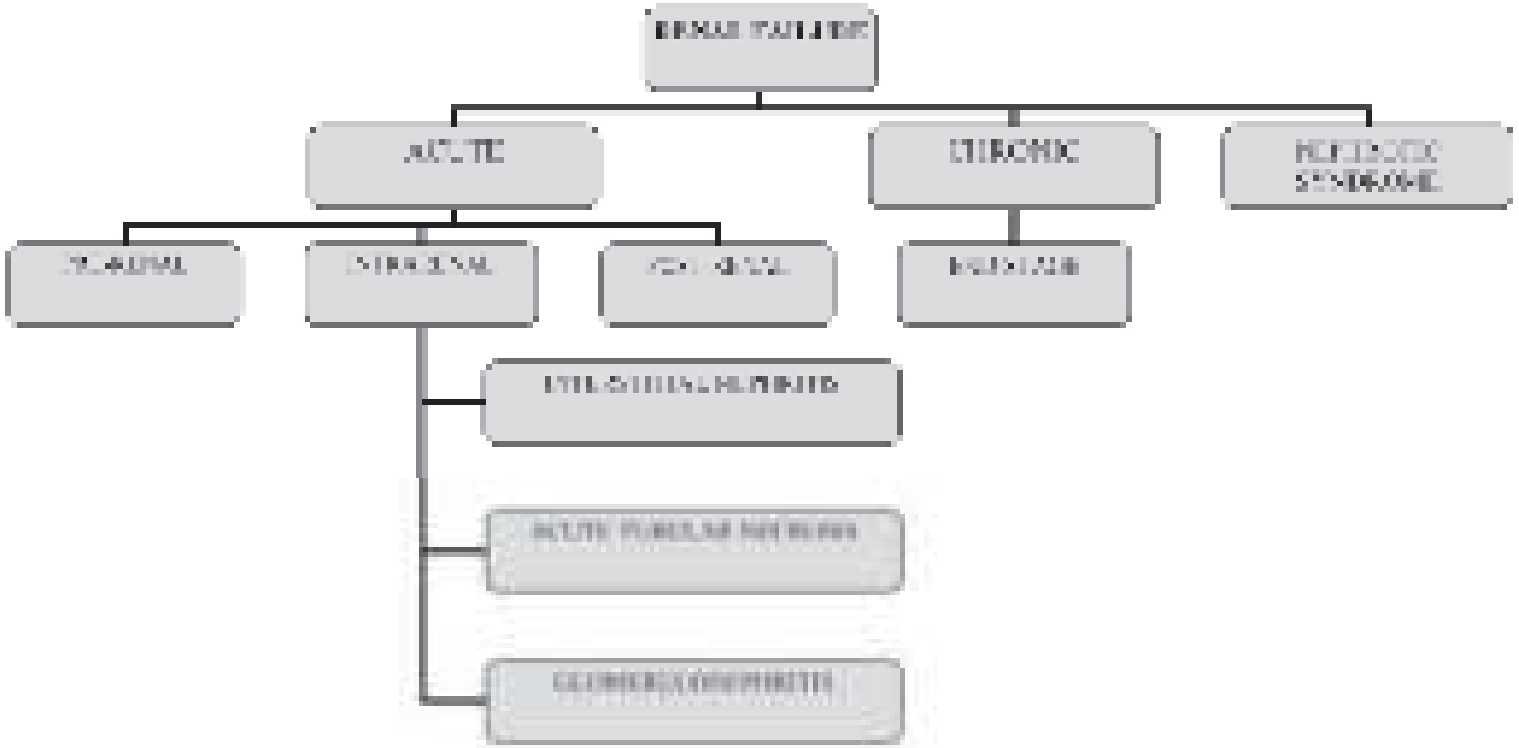

FIGURE 3. CLASSIFICATION OF DRUG-INDUCED RENAL FAILURE

Based on time frame (acute or chronic). Sub-classification of acute renal failure based on cause (pre-renal, intrarenal or post-renal). Nephrotic syndrome occurs with glomerular damage and the excessive loss of protein in the urine.

TABLE 1. DRUG CLASSES ASSOCIATED WITH RENAL FAILURE/DYSFUNCTION

Antibiotics
Analgesics
Anticonvulsants
Antivirals
Amphotericin B
Antineoplastics
Antihypertensives
Drugs of abuse
Diagnostic agents
Herbal supplements
HMG-CoA reductase inhibitors
Immune globulin
H_2-antagonists
Lithium
Proton pump inhibitors
Others

Pre-renal causes

- CHF
- Excessive dehydration due to fluid loss
- Diuretics
- Sepsis
- Combination of these causes

Pre-renal causes

- Vasoconstriction
- Amphotericin, noradrenaline and immunosuppressive agents such as tacrolimus and ciclosporin
- Contrast agents
- Iodinated contrast media, in particular, have been shown to inhibit the synthesis of nitric oxide in renal artery smooth muscle

Intrarenal failure

- Some medications, such as antibiotics, can cause a localized allergic reaction affecting the glomerulus (glomerulonephritis)
- penicillins, sulphonamides, rifampicin, cephalosporins and ciprofloxacin
- Phenytoin
- PPIs
- Affecting surrounding renal tissue (interstitial nephritis)
- More severe event occurs if the drug has a direct toxic effect on the tubules within the nephron (acute tubular necrosis or ATN)
- ATN can develop within hours to days from initial exposure
- severe cellular injury and cell death
- Simply stopping the medication causing the damage will not immediately restore kidney function

Osmotic nephrosis

- high doses of mannitol, immunoglobulins, dextrans and starches are nephrotoxic
- Direct effect on glomerular filtration
- or the uptake of these large molecules by pinocytosis into the proximal tubule
- sucrose-based IVIG: The renal failure began from 1 to 10 days after therapy

Nephrotic syndrome

- Abnormal amounts of protein in the urine
- Drugs : NSAIDs, penicillamine and gold
- damage the glomerulus and alter the ability of the glomerulus to prevent protein from being filtered
- Stopping the drug may resolve the damage to the glomerulus

Post-renal failure

- usually results from a mechanical barrier to moving urine from the collecting tubules into the bladder
- Mechanical obstruction :
  - enlargement of the prostate
  - kidney stones
  - Drugs that precipitate in the kidney (acyclovir, ganciclovir)
  - Co-trimoxazole

ANTIBIOTICS

- AIN is a hypersensitivity or allergic reaction to the drug
- Up to 71% of all cases of acute interstitial nephritis (AIN) are drug-induced
- The most common antibiotic classes associated with AIN are penicillins/cephalosporins and sulfonamides
- Ciprofl oxacin
- Rifampin
- acute renal failure, skin rash, increased eosinophils

Contd.

- Aminoglycosides (tobramycin, gentamicin, amikacin) and amphotericin B can cause ATN
- Risk of aminoglycoside toxicity is associated with increased dose, duration of therapy, dehydration and concurrent use of nephrotoxic drugs, such as NSAIDs
- Amphotericin B renal toxicity is related to cumulative dose, concurrent use of nephrotoxic drugs, baseline abnormal creatinine and concurrent use of diuretics
- 80% of patients receiving amphotericin B experiencing some decrease of renal function
- Saline hydration can decrease the toxicity

ANTIVIRALS

- Cidofovir, foscarnet, acyclovir and interferons can cause ATN
- Acyclovir can precipitate within the renal tubules

NSAIDs

- Long-term use can cause chronic renal insufficiency
- Patients who experience ARF with NSAIDs have underlying risk factors
- Prolonged NSAID use can cause chronic kidney disease, especially in the elderly
- 1-5 % of all end-stage renal disease (ESRD) patients have analgesic-associated nephropathy
- Risk factors for this nephropathy include gender (women>men), age (>50 years old) and prolonged use of the analgesic

NSAIDs

- Selective cyclooxygenase (COX-2) inhibitors cause similar renal dysfunction
- COX-2 exists as a constitutive enzyme in the thick part of the ascending loop of Henle and in the renal medulla
- COX-2 causes natriuresis and diuresis
- Inhibition of COX-2 by selective COX-2 inhibitors, such as celecoxib and rofecoxib causes renal dysfunction
- particularly in patients who are volume-depleted or haemodynamically unstable

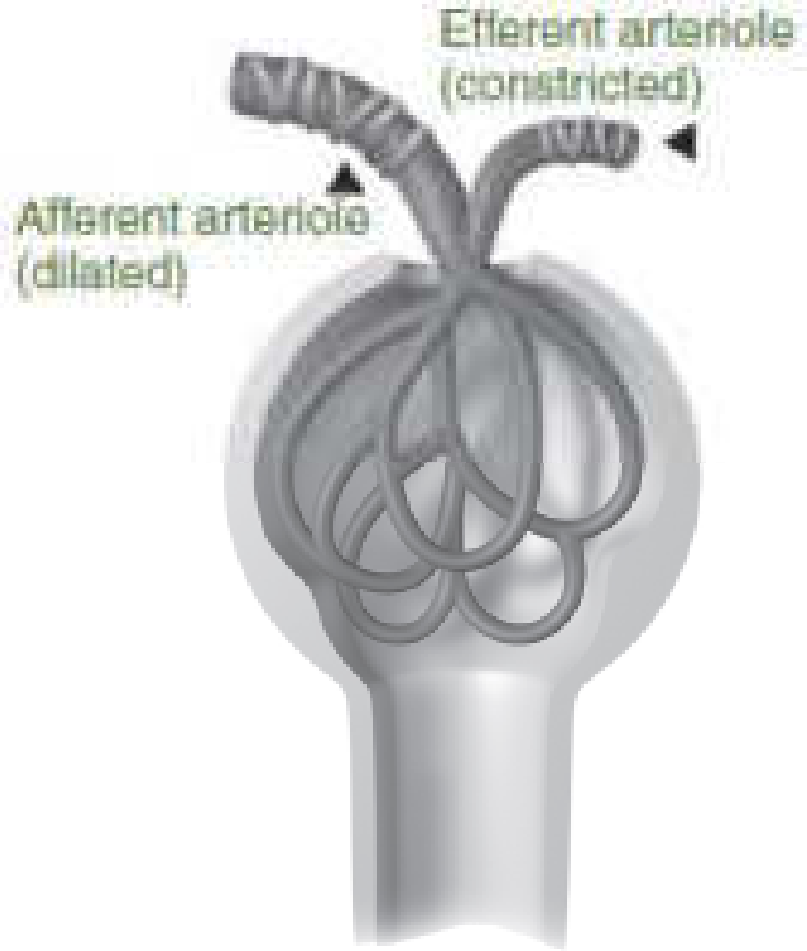
Efferent arteriole
(constricted)
Afferent arteriole
(dilated)

TABLE 2. FACTORS ASSOCIATED WITH NSAID-INDUCED RENAL FAILURE

Decreased EABV

Congestive heart failure, sepsis, cirrhosis, diuretics, hemorrhage, post-operative fluid changes, nephrotic syndrome, volume depletion/ hypotension

Normal to Increased EABV

Chronic renal failure, elderly, glomerulonephritis, contrast-induced nephropathy, obstructive nephropathy, cyclosporine

ACEIs & ARBs

- ARF
- stopping the medication should resolve the renal failure. Restarting the drug at a lower dose may be possible

CHEMOTHERAPY-INDUCED RENAL DAMAGE

- Nephrotoxicity is the major dose-limiting toxicity for cisplatin
- Both acute and late-onset toxicities occur
- aggressive replacement of magnesium (lost when the proximal tubule is damaged), saline hydration or mannitol infusion
- High dose methotrexate : postrenal obstruction by precipitating in the tubules of the nephron
- also direct toxicity

IMMUNOSUPPRESSANT

- Cyclosporine and tacrolimus
- acute, dose-dependent reduction in renal blood flow and chronic structural changes in the kidney

STATINS

- Rare but serious cases of rhabdomyolysis
- acute tubular necrosis
- Muscle pain, dark urine, electrolyte abnormalities and renal failure
- Recognizing the process as drug-induced renal failure and stopping the drug is essential

DRUGS OF ABUSE

- cocaine and heroin
- Cocaine use can cause renal artery thrombosis (clotting), severe hypertension and interstitial nephritis
- Long-term cocaine use can lead to chronic renal failure
- Long-term tobacco use also increases the risk of kidney cancer

Conclusion

- Many drugs cause AKI
- Age (particularly over 65 years), pre-existing renal impairment, comorbidities such as diabetes mellitus, heart failure, liver cirrhosis and hypovolaemia
- All increase the risk of drug-induced AKI
- Addressing potential risk factors
- understanding of the mechanisms of nephrotoxicity involved

THANKYOU