Al Mustaqbal University College
Department of Pharmacy
4th stage
Toxicology

Lect. 5

Toxic Responses of The Kidney part2

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SPECIFIC NEPHROTOXICANTS

1. Heavy Metals

- Mercury
- Cadmium

2. Halogenated Hydrocarbons

- Chloroform
- Tetrafluoroethylene

3. Fungal Toxins

4. Therapeutic Agents

- Acetaminophen
- Nonsteroidal Anti-Inflammatory Drugs
- Aminoglycosides
- Amphotericin B
- Cyclosporine
- Cisplatin

Mercury

- The kidneys are the primary target organs for accumulation of Hg^{2+}, and the proximal tubule is the initial site of toxicity, depending on the dose or duration.
- The acute nephrotoxicity induced by $HgCl_2$ is characterized by proximal tubular necrosis and AKI within 24 to 48 hours after administration.

Mercury

- Early markers of $HgCl_2$-induced renal dysfunction include an increase in the urinary excretion of brush-border enzymes such as alkaline phosphatase and γ-glutamyl transpeptidase .
- chronic exposure to inorganic mercury results in an immunologically mediated membranous glomerular nephritis secondary to the production of antibodies against the GBM and the deposition of immune complexes

Cadmium

- Chronic exposure of humans and animals to cadmium is primarily through food and results in nephrotoxicity.
- In the workplace, inhalation of cadmium-containing dust and fumes is the major route of exposure.
- Approximately 50% of the body burden of cadmium can be found in the kidney and nephrotoxicity can be observed when Cd conc. exceed 50 µg/g kidney wet weight.

Cadmium

- Cadmium produces proximal tubule dysfunction (S1 and S2 segments) and injury characterized by increases in urinary excretion of glucose, amino acids, calcium, and cellular enzymes.
- This injury may progress to a chronic interstitial nephritis.

Chloroform

- The nephrotoxicity produced by chloroform is linked to its metabolism by renal cytochrome P450 and the formation of a reactive intermediate that binds covalently to nucleophilic groups on cellular macromolecules
- Cytochrome P450 biotransforms chloroform to trichloromethanol, which is unstable and releases HCl to form phosgene, which can initiate toxicity.

Chloroform

- The primary cellular target is the proximal tubule, with no primary damage to the glomerulus or the distal tubule.
- Proteinuria, glucosuria, and increased BUN levels are all characteristic of chloroform induced nephrotoxicity.

Tetrafluoroethylene

- Tetrafluoroethylene is metabolized in the liver by GSH-S-transferases to S-(1,1,2,2-tetrafluoroethyl)- glutathione.
- The GSH conjugate is secreted into the bile and small intestine where it is degraded to the cysteine S-conjugate (TFEC), reabsorbed, and transported to the kidney.

Tetrafluoroethylene

- The nephrotoxicity produced by haloalkenes is characterized

1. morphologically by proximal tubular necrosis, primarily affecting the S3 segment,
2. And functionally by increases in urinary glucose, protein, cellular enzymes, and BUN.

Fungal Toxins

- Mycotoxins are products of molds and fungi that produce nephrotoxicity and these include aflatoxin B1, citrinin, ochratoxins, fumonisins... etc
- Citrinin nephrotoxicity is characterized by decreased urine osmolality, GFR and RBF, glycosuria, and increased urinary enzyme excretion.

Fungal Toxins

- The location of citrinin-induced tubular vacuolization and necrosis include both proximal and distal tubules.
- Fumonisins B1 and B2 are commonly found on corn and corn products and produce nephrotoxicity in numerous species, some species are very sensitive (e.g., rabbits) whereas others are more resistant (e.g., mice)

Acetaminophen

- N-acetyl-p-aminophenol (APAP) nephrotoxicity is characterized by:

1. proximal tubular necrosis with increases in BUN and plasma creatinine;
2. decreases in GFR and clearance of para-aminohippurate; increases in the fractional excretion of water, sodium, and potassium;
3. increases in urinary glucose, protein, and brush-border enzymes.

Acetaminophen

- Renal cytochrome P450 2E1 has been associated with APAP biotransformation to a reactive intermediate, N-acetylp-amino-benzoquinoneimine (NAPQI) , that arylates proteins in the proximal tubule and initiates cell death.
- Two of the proteins that are targets of (NAPQI) are a selenium-binding protein and a glutamine synthetase

Nonsteroidal Anti-Inflammatory Drugs

- NSAIDs such as aspirin, ibuprofen, naproxen, indomethacin, and celecoxib are extensively used as analgesics produce their therapeutic effects through the inhibition of prostaglandin synthesis.
- AKI may occur within hours of a large dose of an NSAID, is usually reversible upon withdrawal of the drug, and is characterized by decreased RBF and GFR and by oliguria.

Nonsteroidal Anti-Inflammatory Drugs

- When the normal production of vasodilatory prostaglandins (e.g., PGE2 and PGI2) is inhibited by NSAIDs, vasoconstriction induced by circulating catecholamines and angiotensin II is unopposed, resulting in decreased RBF and ischemia.
- Chronic consumption of combinations of NSAIDs and/or APAP (more than 3 years) results in an often irreversible form of nephrotoxicity known as analgesic nephropathy.

Nonsteroidal Anti-Inflammatory Drugs

- The incidence of analgesic nephropathy varies widely, ranging from 2% and up to 20% of all end-stage renal disease.
- The primary lesion in this nephropathy is papillary necrosis with chronic interstitial nephritis.
- Initial changes are to the medullary interstitial cells and are followed by degenerative changes to the medullary loops of Henle and medullary capillaries.

Aminoglycosides

- The aminoglycoside antibiotics are so named because they consist of two or more amino sugars joined in a glycosidic linkage to a central hexose nucleus.
- Although they are drugs of choice for many gram-negative infections, their use is primarily limited by their nephrotoxicity.
- Renal dysfunction by aminoglycosides is characterized by reduced GFR and an increase in serum creatinine and BUN.

Aminoglycosides

- Polyuria is an early event following aminoglycoside administration and may be due to inhibition of chloride transport in the thick ascending limb.
- Within 24 hours, increases in urinary brush-border enzymes, glucosuria, aminoaciduria, and proteinuria are observed.

Amphotericin B

- Amphotericin B is a very effective antifungal drug whose clinical utility is limited by its nephrotoxicity.

- Renal dysfunction associated with amphotericin B treatment is dependent on cumulative dose and is due to both hemodynamic and tubular effects.

Amphotericin B

- With respect to hemodynamics, amphotericin B administration is associated with decreases in RBF and GFR secondary to renal arteriolar vasoconstriction or activation of TGF.
- Amphotericin B nephrotoxicity is characterized by ADH-resistant polyuria, renal tubular acidosis, hypokalemia, and either acute or chronic renal failure.

Cyclosporine

- Cyclosporine is an important immunosuppressive drug and is widely used to prevent graft rejection in organ transplantation.
- Nephrotoxicity is a critical side effect of cyclosporine, with nearly all patients who receive the drug exhibiting some form of nephrotoxicity.

Cyclosporine

- Clinically, calcineurin inhibitor (CNI)-induced nephrotoxicity may manifest as (1) acute reversible renal dysfunction, (2) acute vasculopathy, and (3) chronic CNI nephrotoxicity with interstitial fibrosis.
- Long-term treatment with cyclosporine can result in chronic nephropathy with interstitial fibrosis and tubular atrophy.

Cisplatin

- Cisplatin is a valuable drug in the treatment of solid tumors, with nephrotoxicity limiting its clinical use.
- The effects of cisplatin on the kidney including acute and chronic renal failure, renal magnesium wasting, and polyuria, and patients treated with cisplatin regimens permanently lose 10% to 30% of their renal function.

Cisplatin

- The nephrotoxicity of cisplatin can be grouped as (1) tubular toxicity, (2) vascular damage, (3) glomerular injury, and (4) interstitial injury.
- The antineoplastic and perhaps the nephrotoxic effects of cisplatin may be due to its intracellular hydrolysis to the reactive mono-chloro-mono-aquodiammine-platinum and the ability of these metabolites to alkylate purine and pyrimidine bases.

TANK YOU FOR YOUR ATTENTION