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NEPHROTOXICITY

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Abstract : Nephrotoxicity is characterized by any adverse functional or structural change in the kidney due to the effect of chemical or biological product, that is inhaled, ingested or absorbed or which yields metabolite with an identifiable toxic effect on the kidney. Mechanism of nephrotoxicant-induced cell death-3types of cell death occur in renal cells these are apoptosis, autophagy and necrosis. Major pathophysiological factors involved in the nephrotoxicity are: Production of Free Radicals involved in Oxidative stress , Proinflammatory Mediators involved in Inflammation, Mitochondrial dysfunction

I. INTRODUCTION

NEPHROTOXICITY

Nephrotoxicity is characterized by any adverse functional or structural change in the kidney due to the effect of chemical or biological product, that is inhaled, ingested or absorbed or which yields metabolite with an identifiable toxic effect on the kidney(Aslam et al., 2013) A number of therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome. The usage of certain drugs in the long run may lead to nephrotoxicity as these drugs tend to get accumulated in the form of by-products which lead to renal failure.(Aslam et al., 2013) Nephrotoxic drugs include antiretrovirals (example, tenofovir), antimicrobials (example, aminoglycosides) and chemotherapeutic agents (example, cisplatin) (Perazella, 2009). These drugs induce their nephrotoxicity on the tubular, glomerular, interstitial or vascular components of the kidneys. Toxicity of drugs on renal tubular cells is enhanced by the impairment of mitochondrial function, tubular transport interference, increase in oxidative stress and formation of free radicals (Zager, 1997).

Mechanism of nephrotoxicant-induced cell death-

3types of cell death occur in renal cells these are apoptosis, autophagy and necrosis

Apoptosis include both intrinsic and extrinsic. Apoptosis occurs in both human and animal kidneys during AKI. Apoptosis can be detected in the kidneys after toxin exposure, inflammation and ischemia.(Andrea Havasi) In the healthy human adult, nearly 50–70 billion cells die an apoptotic death every day.(Andreeff M, Goodrich DW) Although this 'programmed cell death' is necessary to maintain the health of the organism but the dysregulation of cell death by excessive or defective apoptosis results many disease in heathy adult.(Mao H, Li Z, Zhou Y et al.)

Major pathophysiological factors involved in the nephrotoxicity are:

- Production of Free Radicals involved in Oxidative stress
- Proinflammatory Mediators involved in Inflammation
- Mitochondrial dysfunction

Major pathophysiological factors involved in Gentamicin induced Nephrotoxicity:

Oxidant Mechanism:

Nephrotoxicity is a major complication of Aminoglycoside antibiotic which is widely used in the treatment of gram-negative bacteria infections. Reduction of oxygen along with univalent pathway leads to the generation of superoxide anion, hydrogen peroxide, hydroxyl radical, and water. A large body of in-vitro and in vivo evidence indicates that they reduced oxygen metabolites are important mediators of Gentamicin Nephrotoxicity. Gentamicin enhance the generation of superoxide anion and hydrogen peroxide by renal cortical mitochondria. The interaction between the superoxide anion and hydrogen peroxide in the presence of metal catalyst can leads to the generation of hydroxyl radical. Gentamicin release iron from renal cortical mitochondria and enhance generation of hydroxyl radical. These in vitro observations have been supported by in-vivo studies in which reactive oxygen species have been shown in protective effects of Gentamicin induced acute renal failure. These studies may have broader implication in being relevant to other aminoglycosides including streptomycin and being applicable to other major toxicity of aminoglycoside such as ototoxicity.

Inflammation:

Nephrotoxic drugs often induce inflammation in glomerulus, proximal tubules, and surrounding cellular matrix. Inflammation that disturb normal kidney functions and induce toxicity includes glomerulonephritis, acute and chronic interstitial nephritis. Glomerulonephritis has been shown to be closely related to proteinuria. Acute interstitial nephritis, a type of drug-induced immune

response, is induced by NSAIDs and antibiotic drugs such as Rifampicin. Chronic interstitial nephritis occurs frequently by long-term use of calcineurin inhibitors, lithium, some anticancer drugs or analgesics.
In case of chronic interstitial nephritis, early detection is especially important because it is difficult to diagnose most of the functionality of the kidney is destroyed.

Mitochondrial dysfunction:

Mitochondrial dysfunction by Gentamicin activates the intrinsic pathway of apoptosis, interrupts the respiratory chain, impairs ATP production, and produces oxidative stress by increasing superoxide anions and hydroxyl radicals, which further contributes to cell death. Indirect mitochondrial effect is mediated by increasing Bax level through the inhibition of its proteosomal degradation. It acts by inhibition of mitochondrial oxidative phosphorylation.

Clinical Aspects:

Nephrotoxicity induced by aminoglycosides is clinically non-oliguric renal failure with slow rise in serum creatinine , BUN, and decrease in glomerular filtration rate. (amin Hasanvand) after several days of treatment aminoglycosides causes enzymuria, proteinuria, glycosouria, fanconi's and barter like syndrome.(oooo). The use of aminoglycosides in single dose diminish its nephrotoxicity

High dose in animals and its effect :

High doses are given to animals for immediate development of cortical necrosis and renal dysfunction. Large number of structural, metabolic, and functional changes, is observed in tubular cells responsible for renal dysfunction. Changes observed in the apical membrane mediated by the drug during uptake of proximal tubular cells. Inhibition of protein synthesis and alteration of gene expression and mitochondria involve uptake and intracellular distribution of drug to the corresponding receptors

AGENTS WHICH CAUSES NEPHROTOXICITY

Drugs, diagnostic agents, and chemical are well known to be nephrotoxic. The following are some of the important nephrotoxic agents.

1. Heavy metals:
▪ Mercury, arsenic, lead bismuth
2. Antineoplastic agents
▪ Alkalating agents: Cisplastin, cyclophosphamide
▪ Nitrosoureas: Streptozotocin, Carmustine, Lomustine and Semutine
▪ Antimetabolites: High dose Methotrexate, Cytosine, Arabinose, high dose 6-thioguanine, flurouracil
▪ Antitumor antibiotics: Mitomycin, Mithramycin, Doxorubicin
▪ Biologic agents: Recombinant leukocyte and interferon.
3. Antimicrobial agents:
▪ Tetryacycline, Acyclovir, Pentamidine, Sulphadiazine, Trimethoprin, Rifampicin, Amphotericin B
4. Aminoglycosides:
▪ Gentamicin, Amikacin, Kanamycin, Streptomycin
5. Miscellaneous:
▪ Radiocontrast agents: Non- steroidal anti-inflammatory agents (NSAID's), Ibuprofen, Indomethacin, Aspirin etc.[4]

Biomarkers of drug induced kidney damage:

The most prominent marker of kidney damage is proteinuria (Makris and Spanou, 2016).
Serum creatinine and blood urea nitrogen increase 7 to 10 days after initiation of aminoglycoside therapy.
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