Drug nephrotoxicity

Essay

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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
ورَسُولُهُ والْمُؤْمِنُونَ

صدق الله العظيم

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In the name of Allah, the Merciful, the Compassionate

Before all, praise is to Allah, the Almighty, on Whom ultimately I depend and to whom I relate any success in my life.

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Mohamed Ahmed Essa Zarka

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List of Abbreviations

4-OH-IF **:** 4-hydroxyifosfamide
5-ASA : 5-aminosalicylic acid
ABLC : Amphotericin B in lipid complex
ACE **:** Angiotensin-converting enzyme
ACEI **:** Angiotensin converting enzyme inhibitor
ADH **:** Antidiuretic hormone
ADP-ribose **:** Adenosine diphosphate ribose
AIDS : Acquired immune deficiency syndrome
AIN : Acute interstitial nephritis
AKI : Acute kidney injury
ALL : Acute lymphoblastic leukemia
AmB : Amphotericin B
ANP : Atrial natriuretic peptide
APAF-1 : Apoptotic peptidase activating factor 1
ARB **:** Angiotensin receptor block
ARBs **:** Angiotensin receptor blocker
ARF **:** Acute renal failure
ATN : Acute tubular necrosis
ATP **:** Adenosine triphosphate
AZT : Azidothymidine
BMI **:** Body Mass Index
BSP **:** Bromosulfophthalein
BUN **:** Urea nitrogen
CBDCA **:** Cis-diammine-1, 1-cyclobutane-dicarboxylato
CD **:** Colloidal dispersion
CDDP **:** Cis-diamine dichloro platinum
CF **:** Cyclophosphamide
CKD **:** Chronic kidney disease
CMV **:** Cytomegalovirus
COX-1 : Cyclooxygenase-1
COX-2 **:** Cyclooxygenase-1
Cr-EDTA **:** Chromium ethylenediaminetetra-acetic acid
CYP **:** Cytochrome

List of Abbreviations (Cont.)

DHEA-S : Dehydroepiandrosterone-sulfate
DMTU : Dimethylthiourea
DNA : Deoxyribonucleic acid
DNP-SG : Dinitropheny1-glutathione
DRI : Direct renin inhibitor,
E217 β G : Estradiol-17 β -D-glucuronide
EBV : Epstein–Barr virus
eCrCl : Estimated creatinine clearance
eGFR : Estimated glomerular filtration rate
ESRD : End-stage renal disease
estrone-S : Estrone sulfate
FasL : Fas ligand type-II transmembrane protein
FDA : Food and Drug Administration
GFR : Glomerular filtration rate
GSH : Glutathione
HDL : High density lipoproteins
HDMTX : High-dose methotrexate
HHV-6 : Human herpesvirus 6
HIV : Human immunodeficiency virus
HO-1 : Heme oxygenase-1
HSV-1 : Herpes simplex viruses type 1
HSV-2 : Herpes simplex viruses type 2
ICAM : Intercellular adhesion molecule
IDSA : Infectious Diseases Society of America
IDSA : Infectious Diseases Society of America
IFO : Ifosfamide
Kim1 : Kidney injury molecule-1
LDL : Low density proteins
LTC4 : Leukotriene C4
MATE : Multidrug and Toxic Compound Extrusion
MCP-1 : Monocyte chemoattractant protein
MDRD : Modification of Diet in Renal Disease
MRP-2 : Multidrug resistance proteins

List of Abbreviations (Cont.)

MRSA : Methicillin-resistant Staphylococcus aureus
MtDNA : Mitochondrial Deoxyribonucleic acid
MTX : Methotrexate
NAC : N-acetylcysteine
NAD : Nicotinamide adenine dinucleotide
NAG : N-acetylglucosamine
NAM : N-acetlymuramic acid
NAPQI : N-acetyl-p-benzoquinoneimine
NFkB : Nuclear factor kappa B
NO : Nitric oxide
NSAIDs : Non-steroidal anti-inflammatory drugs
NSAR : Non-steroidal antirheumatics
NtRTI : Nucleotide analogue reverse-transcriptase inhibitor
OAT : Organic anion transporter family
OATP : Organic Anion Transporting Polypeptide
OCTs : Organic Cation Transporters
p38MAPK : p38-mitogen activated protein kinase
PAH : p-aminohippurate
PAH : p-aminohippurate
PARP : Poly (ADP-ribose) polymerase
PARS : Poly (ADP-ribose) synthetase
PBPs : Penicillin-binding proteins
PEPT : Peptide transporters
PGE2, PGF2 : Prostaglandin E2, F2
P-gp : P-glycoprotein
PPAR-α : Peroxisome proliferator-activated receptor
RBF : Renal blood flow
RIFLE : Risk, injury, failure, loss and endstage kidney disease
RNS : Reactive nitrogen species
ROS : Reactive oxygen species
SCr : Serum creatinine

List of Abbreviations (Cont.)

SLE	**:** Systemic lupus erythematosus
TAL	**:** Thick ascending limb
TEA	**:** Tetraethylammonium.
TGF	**:** Transforming growth factor
TK	**:** Thymidine kinase
TNF-α	**:** Tumor necrosis factor alpha
UF	**:** Ultrafiltration.
URAT1	**:** Urate transporter
VEGF-A	**:** Vascular endothelial growth factor A
VSP	: VEGF signalling pathway
VZV	**:** Varicella zoster virus
α –KG	: Alpha-Ketoglutaric acid

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Introduction

The kidney is responsible for the elimination and metabolism of many foreign organic compounds including pharmacologic agents. Ultimately these agents reach the urinary space for excretion via glomerular filtration or tubular secretion. In some instances drugs must undergo transformation into metabolites, a reaction that may actually take place within tubular cells before secretion into the tubular lumen. Unfortunately, while performing its role as an excretory and metabolic organ, the kidney may undergo anatomic or functional changes as a result of drug-induced toxicity **(Chesney and Jones, 2009)**.

Certain nephrotoxins may preferentially damage specific nephron segments, depending on the area of maximal exposure, the location of specific uptake systems, and the nephronal location of specific intracellular sites that are susceptible to the toxin **(Jennings et al., 2004).**

Potential mechanisms for drug-induced renal dysfunction include alterations in renal perfusion and glomerular filtration, tubular cell damage, and tubular obstruction.Toxic nephropathy or drug-induced renal dysfunction is primarily a disorder of the renal tubule however, significant tubular damage eventually results in

alterations in glomerular function as well. In addition, drugs or their metabolites may alter glomerular blood flow through vasoconstriction of the glomerular capillaries. This may be a primary event through actions on the endothelial cell or a secondary event via activation of tubuloglomerular feedback after tubular damage allows increased distal delivery of solute and fluid **(Guo and Nzerue, 2002).**

Therefore, physicians must have vast knowledge in relation to the nephrotoxicities of therapeutic agents in order to avoid iatrogenic acute renal failure (ARF). In this essay, I would like to briefly review some of the drugs which possess such nephrotoxicity and occasionally induce ARF and the mechanisms of their nephrotoxicities (**Porter G A, 2008).**

Aim of The Work

In this work we will review focus on the clinical characteristics, mechanisms of injury, if known, and potential methods to reduce or prevent drug-associated renal damage and dysfunction. The most common offending agents have been chosen.

Chapter (1):

Anatomy and physiology of the Kidney

The kidney is responsible for the elimination and metabolism of many foreign organic compounds, including pharmacologic agents. Ultimately these agents reach the urinary space for excretion via glomerular filtration or tubular secretion. In some instances drugs must undergo transformation into metabolites, a reaction that may actually take place within tubular cells before secretion into the tubular lumen. While performing its role as an excretory and metabolic organ, the kidney may be at risk for drug-induced toxicity **(Chesney and Jones, 2009).**

Anatomy of the kidney:

Each kidney is a bean-shaped structure measuring approximately 11cm x 6 cm x 3 cm and weighing 120-170 grams in adult. The kidney is contained in a fibrous capsule. The hilum of the kidney which is present medially contains renal artery, vein, lymphatics and pelvis of the ureter. The kidney is contained in peri-renal fat. The kidney lies in the paravertebral gutter on the posterior abdominal wall retroperitoneally and opposite the twelfth thoracic down to the third lumbar vertebra. The right kidney is slightly lower than the left (liver effect), lower pole reaches one finger breadth above the iliac crest (Fig. 1) shows a longitudinal section of the kidney (**Gilliland, 2008).**

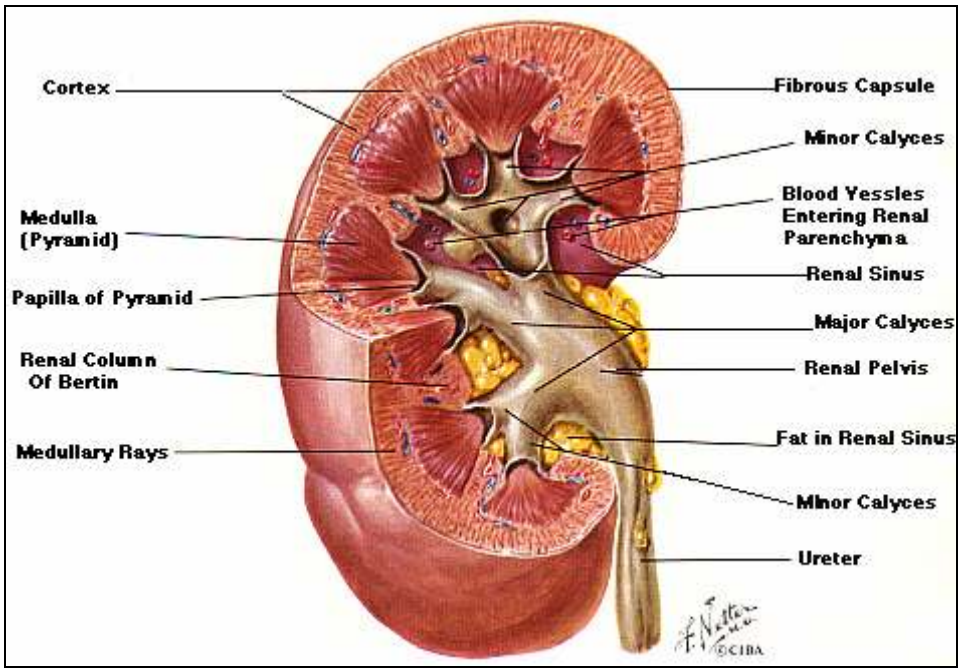

Fig. (1): *Right kidney sectioned in several planes exposing the parenchyma and renal sinus* **(Wood and Greenwell, 2013)**.

The Fig. shows the hilum containing the renal vessels and pelvis of the ureter which branches inside the kidney into 2-4 major calyces, each of which in turn branches into several minor calyces. The kidney parenchyma is divided into outer cortex (1cm thick) and inner medulla. The medulla is formed of 8-18 pyramids which are conical-shaped, with its base at cortico-medullary junction and its apex projects into minor calyces as papillae. The medullary pyramids are striated in shape. The cortex which is granular-looking may extend between pyramids forming columns of Bertini. Medullary rays are striated elements which radiates from the pyramids through the cortex **(Feher, 2012).**

Blood supply of the kidney:

The renal arteries arise from the aorta opposite the intervertebral disc L 1-2. In the hilum it gives anterior and