DRUG-INDUCED NEPHROPATHY

Essay

Submitted for partial fulfillment of Master Degree in
Nephrology

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2011

أمراض الكلي نتيجة تأثير الدواء

رسالة

مقدمة توطئة للحصول على درجة الماجستير فى

أمرض الكلي

مقدمة من

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الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة الآية

Acknowledgment

First and above all thanks to **Allah**.

I would like to express my endless gratitude and appreciation to my eminent professor, *Prof. Dr. Hany Aly Refaat*, *Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, for giving me the honor to work under his supervision and from whom I did learn a lot. He encouraged me, removed all the obstacles from my way and pushed me to achieve success.*

My sincere thanks to *Prof. Dr. Magdy El-Sharkawy*, *Professor of Internal Medicine, Faculty of Medicine, Ain Shams University for his continuous guidance, honest help and endurance that made this thesis come to light.*

Last but not least, I would like to thank, my Professors and colleagues for their endless support and my patients for their co-operations.

INTRODUCTION

Anatomical, physiological, and biochemical features of the kidney make it particularly sensitive to many environmental compounds. Factors contributing to the sensitivity of the kidney include: large blood flow, the presence of a variety of xenobiotic transporters (organic cations and anions transporters) metabolizing enzymes, and concentration of solutes during urine production ***(Terry et al.,* 2003).**

Acute interstitial nephritis is a frequent cause of acute renal failure, representing about 10% of all biopsied cases. Early recognition of drug-induced acute immunoallergic interstitial nephritis prevents the development of severe chronic renal injury ***(Beauchamp et al., 2008).***

Analgesic nephropathy had been one of the more common causes of chronic renal failure, particularly in Australia and parts of Europe and the United States ***(Pinter et al., 2004).***

Renal vasoconstriction is a common finding in contrast nephropathy; it is mediated in part by contrast-induced release of endothelin and adenosine and by the high osmolality of the contrast agent ***(Pflueger et al., 2000).***

Vascular disease can develop following exposure to varios medications through direct and indirect effects. A number of

glomerular lesions have been described with therapeutic agents and illicit drugs. Acute interstitial nephritis occurs from drug-induced allergic reaction which promotes interstitial inflammation and tubular damage. Acute tubular necrosis is a dose dependant process that occurs from direct drug toxicity on tubular epithelia ***(Mark, 2005).***

Less common pattern of drug induced tubular injury includes osmotic nephropathy, crystal nephropathy and nephrocalcinosis ***(Mark, 2005).***

Thus one can arbitrarily classify drug induced kidney disease into pre-renal, intrarenal and postrenal. The majority of the drug-induced renal injury involves the tubules and the interstitium. Less commonly therapeutic agents may injury the vasculature produce various type of glomerular disease or obstruct urine flow and cause obstructive nephropathy ***(Mark, 2005).***

Therapeutic agents have long been associated with the development of iatrogenic renal failure. The mechanisms of drug toxicity can vary a great deal based on the pharmacological action, metabolism and ultimate pathway of excretion of the agent administered. Many medications are filtered, secreted, reabsorbed and ultimately excreted by the renal parenchyma. As

a result, the kidney is a common site of drug toxicity. Therapeutic agents adversely impact kidney function through various pathways. These include induction of prerenal azotemia by afferent arteriolar vasoconstriction and/or efferent arteriolar vasodilatation in patients with underlying risk factors. There are four histological components of the kidney; the blood vessels, glomerulus, interstitium and tubules. Patterns of drug induced renal injury can be subdivided based on which of the four components of the renal parenchyma is primarily affected. The renal collecting system ultimately moves urine from the kidney into the bladder. From here, urine is excreted out of the body. Interruption of urine flow anywhere along the urogenital system can cause postrenal azotemia ***(Mark, 2005).***

Thus, one can arbitrarily classify drug induced kidney disease into prerenal, intrarenal and postrenal processes. The majority of drug-induced renal injury involves the tubules and interstitium. Less commonly, therapeutic agents may injure the vasculature, produce various types of glomerular disease, or obstruct urine flow and cause obstructive nephropathy ***(Mark, 2005)***.

AIM OF THE ESSAY

Aim of the essay is to discus the role of drugs in producing different types of nephropathies, their possible pathophysiologic changes and putting a strategy to minimize or prevent such complications in our community.

PRERENAL AZOTEMIA

Haemodynamic acute renal failure (ARF) may result from drugs that reduce renal blood flow (RBF) and glomerular filtration rate (GFR). Clinical presentation in these patients reflects exacerbation of the underlying disease by the drug and is characterised by renal hypoperfusion with bland urine sediment, urine sodium (Na^+) concentration <10-20mEq/1, fractional excretion (FE) of Na" <1%, and in those on diuretic, FE urea <35%. A number of medications are employed in clinical practice that have this potential when used in patients who have underlying factors that incur risk of drug-induced prerenal azotemia. Factors associated with risk include:

- True intravascular volume depletion (nausea with vomiting, diarrhoea, diuretics).
- Effective intravascular volume depletion (congestive heart failure [CHF], cirrhosis, nephrotic syndrome).
- Acute and chronic kidney disease, and older age.

Such medications include those that diminish RBF by promoting afferent arteriolar vasoconstriction (NSAIDs, selective COX-2 inhibitors, calcineurin inhibitors, vasopressors) or induce efferent arteriolar vasodilatation (angiotensin-convert-ing enzyme [ACE] inhibitors,

angiotensin receptor blockers [ARBs]) at a time when the kidney is marginally perfused and susceptible to further reductions in GFR (Box 1**) *(Mark, 2005)*.**

Box 1. Drugs associated with prerenal azotemia.
1-Afferent arteriolar vasoconstriction :
1- NSAIDs and Selective COX-2 inhibitors
2- Calcineurin inhibitors
3- Amphotericin B
4- Radiocontrast agents
5- Vasopressor agents
6-IL-2
2-Efferent arteriolar vasodilatation:
1-ACE inhibitors
2- ARBs
Il-2: Recombinant interleukin-2; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; COX: Cyclooxygenase;NSAID: Nonsteroidal anti-inflammatory drug.

1.1 Afferent arteriolar vasoconstrictors:

1.1.1 NSAID and selective COX-2 inhibitor nephrotoxicity:

Box 2. Clinical renal syndromes associated with NSAIDs.
Acute toxicity
• Haemodynamic acute renal failure
• Hypertension, oedema, congestive heart failure
• Hyponatremia
• Hyperkalemia and metabolic acidosis (type 4 RTA)
• Acute interstitial nephritis
• Acute papillary necrosis
Subacute/chronic toxicity
• Nephrotic syndrome (minimal change, membranous)
• Analgesic nephropathy (papillary sclerosis)
• Renal and uroepithelial cancer
NSAID: Nonsteroidal anti-inflammatory drug; RTA: Renal tubular acidosis.

NSAIDs are widely used agents in the treatment of pain and inflammation. NSAIDs act by inhibiting cyclooxygenase (COX). Prostaglandins (PGs) are the major products of COX enzyme metabolism ***(Clive et al., 1984; Smith et al., 1994)***. The synthesis of PGs from arachidonic acid is catalyzed by two different isomers of cyclooxygenase, COX-1 or COX-2. These isozymes are ~ 65% identical in their amino acid sequence and nearly identical at their catalytic site ***(Smith et***

al., 1994; Crofford, 1997). Structure conservation at the catalytic site allows them to carry out similar enzymatic functions and produce similar PGs. The COX-2 DNA sequence identifies it as an 'inducible gene that has a number of sites that links its transcription to the presence of appropriate protein triggers ***(Smith et al., 1994; Crofford, 1997)***. In contrast, the gene sequence of COX-1 lacks the sites that are required to facilitate rapid protein transcription in response to stimuli, consistent with a gene that expresses its constitutive product protein without any prerequisite signal. The differences in gene regulation between the COX isomers provide a molecular basis for their purported roles as 'constitutive' (COX-1) and 'inducible' (COX-2) enzymes. The COX-2 isoform, however, is also constitutively expressed and upregulated in the kidney and may reflect important homeostatic functions of this isoform ***(Smith et al., 1994; Komhoff et al., 1997; Fitzpatrick et al., 2001)***.

NSAID use has been associated with multiple patterns of renal toxicity (Box 2) ***(Clive et al., 1984)***. PGs mediate vasodilatation, which is an important autoregulatory role in the maintenance of renal perfusion in certain situations. For example, true or effective intravascular volume depletion and acute and chronic kidney disease place patients at risk for hemodynamically-mediated ARF when NSAIDs attenuate the counter-regulatory effect of prostaglandin-mediated renal

vasodilatation. Profound reductions in RBF and GFR can be associated with ischemic acute tubular necrosis (ATN). Prerenal azotemia is the most common renal injury noted following NSAID therapy.

The major limitation of NSAID use is gastrointestinal (GI) and renal toxicity. COX-1 is constitutively expressed in GI tissue and plays a critical role in PG production and gastric cytoprotection. COX-2 is expressed at lower levels, but is upregulated in the setting of inflammation. In an effort to decrease GI toxicity, a new class of drugs that selectively inhibit COX-2 was developed. The COX-2 inhibitors celecoxib, rofecoxib and valdecoxib have a lower incidence of adverse GI effects, but clearly offer no advantage with respect to haemodynamically-mediated ARF **(**Upregulation of COX-2 enzyme, rather than COX-1 in states of renal stress underlies this observation. The COX-2 isoform produces vasodilatory PGs that are required to maintain RBF and GFR in clinical disease states such as true or effective volume contraction and acute or chronic kidney disease. Thus, as pointed out by Perazella and Tray, haemodynamic ARF from the selective COX-2 inhibitors develops mainly in patients with these underlying risk factors and is identical to that observed with traditional NSAIDs ***(Perazella, 2001; Perazella et al., 2001)*****.**

Approximately 1% to 5% of patients exposed to NSAIDs develop diverse nephrotoxic syndromes warranting