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RESEARCH ARTICLE

BIOPSY PROVEN ACUTE INTERSTITIAL NEPHRITIS SECONDARY TO NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ABUSE IN A SIXTY TWO YEAR OLD MAN

Uduagbamen P.K, Shitu A.O, Ano-edward GH, Idris S.O, Kasali O.E and Dairo I.O

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Abstract

Acute interstitial nephritis (AIN) can be caused by non-steroidal anti-inflammatory drugs (NSAIDs) particularly in prolonged therapy and large doses. We present the management and reviewed the literature. Sixty-two year old man with, vomiting and hiccups of one week after seven weeks of daily Diclofenac sodium100mg and Meloxicam 15 mg, for body pains.

Results: He had asterixis. Laboratories showed pyuria, haematuria, anemia (28%), creatinine (714 µmol/L) and potassium (6.9 mmol/L). Histology showed acute interstitial nephritis. He had cardio-protective-treatment and haemodialysis, with kidney function restoration.

Conclusion: NSAIDs should be taken in low, single doses and, for short period to avoid AIN. Haemodialysis is beneficial in restoring kidney function.

Introduction:-

Non-steroidal anti-inflammatory drugs (NSAIDs) are readily available, cheap, over-the-counter (OTC) drugs used in treating painful and stressful conditions.[1] NSAIDs are often abused, their use is commoner in females (dysmenorrhoea), the elderly (arthritis) and, artisans (aches) hence the higher prevalence in resource poor settings..[2]NSAIDs are mostly safe when prescribed, and for short period, but with background kidney disease, or stressful states (hepatic disease, heart failure, dehydration, heat and exercises) requiring compensatory prostaglandins (PGs) to upgrade kidney function, their use could precipitate kidney injury.[3] Their use is associated with poor blood pressure (BP) control in hypertensives receiving anti-hypertensives.[3] While acute TIN can be self-limiting particularly with cessation of offending agents, severe forms could be seen, often requiring dialysis treatment. [4] We report a case of biopsy proven severe acute AIN secondary to NSAIDs abuse, in a 62 year old Nigeria man.

Case Report:

A 62 year old clergy man, non-hypertensive, non-diabetic, presented at our facility with a 7 week history of generalised body pain and weakness, a week history of progressive reduction in urine volume and a 3 day history of vomiting and hiccups. His urine was frothy but hadno urinary symptom suggestive of infection, irritation, or obstruction. He had been on treatment for cervical spondylosis of which he had a flare 7 weeks prior to presentation that made him add oral Diclofenac 100mg and Miloxicam 15mg daily to his routine Acetaminophen therapy. He neither took alcohol nor smoked cigarette, nor use herbal remedies.

He was feverish (T=37.6^{O}C), pale, had pedal oedema, and his blood pressure (BP) was 162/94mmHg. Crepitations were heard at the lung bases.The epigastrium was tender and he had flapping tremor.

Corresponding Author:-Uduagbamen P.K (Associate Professor).
Department of Internal Medicine
Bowen University Teaching Hospital, Ogbomosho, Nigeria
Email: petr.uduagbamen@gmail.com

A provisional diagnosis of acute kidney injury (AKI) secondary to NSAIDs abuse was made, to keep in view acute interstitial nephritis.

Urinalysis showed protein 3+, microscopy showed crystals, pyuria and haematuria, and urine albumin creatinine ratio (ACR) was 23mg/g. Arterial blood gases (ABG) showed potassium 6.9 mmol/L and metabolic acidosis while electrocardiogram (ECG) showed tall-tented T waves. While being worked up for urgent haemodialysis (HD), he was commenced on:

Intravenous (IV) Calcium gluconate 10%, 10ml 2-hourly till commencement of HD;
IV soluble Insulin 5 IU in 500ml of 5% Dextrose water 6-hourly;
IV Frusemide 60mg twice daily;
Tab Nifedipine 30mg twice daily.

High potassium containing food were stopped.Liver function test showed hypoalbuminemia (3.0mg/dL), haematocrit was 28%, platelets (214), leucocytes (5600/mm^3) with neutrophilia (72%), and erythrocyte sedimentation rate (ESR) was 22mm/hr. Urine microscopy showed few crystals, pyuria and haematuria and 24 hour urine protein was 2.6g/day. Random blood glucose (RBG) was 92mg/dL. Clotting profile parameters were not deranged (INR=1.1). Renal scan showed normal-size, grade 2 echogenic kidneys. He made 900 ml of urine in the first 24 hours.He had dialysis via a non-tunnelled (direct) internal jugular venous catheter (IJVC) and he was commenced on Irbesatan 150 mg daily after normalization of serum potassium.

He had three haemodialysis sessions over 5 days but without significant interdialytic kidney function stabilization, for which he was worked up for a kidney biopsy. He had a pre-procedure fourth dialysis session with intradialytic blood transfusion. The blood pressure was well controlled and urine output was improved with daily range between 2.2 and 2.9 litres prior to the biopsy. He initially requested for discharge and to continue other treatment at home, and with follow up visitations, but after counselling, he consented to a kidney biopsy which was uneventful. Immunofluorescence and special staining were unavailable for more detailed characterization of the histologic tissue. The post-biopsy urinalysis showed no blood nor protein and the urine volume at 15, 30, 60, 90 and 120 minutes were 0, 5ml, 14ml, 25ml and 40ml respectively. Sample for renal biochemistry taken 6 hours post biopsy on account of low urine output showed moderately deranged parameters (Table 1). He had the fifth dialysis session a day after biopsy and was discharged home the following day after been counselled on access site and post biopsy care, and his disease condition. He was reviewed a week, and 3 weeks post biopsy and his clinical, renal biochemical and hematologic parameters progressively normalized. He is on monthly clinic visits and his clinical and laboratory parameters have been stable.

On account of the grade 2 renal echogenicity result, the possibility of a background chronic kidney disease (CKD) was entertained. He had no repeat kidney biopsy. Though his clinical and laboratory findings showed full recovering from AKI, he is being followed up with regular monitoring of his serum renal biochemistry, urine and ultrasound results.

Based on the histology result, the definitive diagnosis was reviewed.

Definitive diagnosis:
Acute interstitial nephritis (AIN) secondary to NSAIDs abuse.

Prednisolone 10mg daily and Omeprazole 20mg twice daily were added for a month. His prednisolone was reduced to 5mg daily after 2 weeks. Both prednisolone and omeprazole were discontinued after a month.When reviewed a week later, he was clinically stable, the pulse rate was 76/min, BP was 138/80 mmHg and his lung fields were clear.

Discussion:-

Acute interstitial nephritis is a form of acute kidney injury (AKI) with a sudden reduction in kidney function as evident by a reduction in urine output and an increased in serum levels of nitrogenous waste, with reduction in creatinine-based glomerular filtration rate (GFR).[5] Exogenous causes of AKI such as NSAIDs and herbal remedies induces acute interstitial nephritis via inhibition of the formation and, effects of renal prostaglandins [prostacyclin (PGH_2), PGE_2 and PGD_2] mediated renal vasodilatation, a mechanism that becomes necessary in stressed kidneys

states like heart failure, liver disease, background kidney disease, old age, moderate-severe dehydration and connective tissue diseases like systemic lupus erythematosus (SLE).[6]

Pathophysiologic changes in NSAIDs-induced acute interstitial nephritis

NSAIDs-induced kidney disease is mediated via induction of various patho-physiologic mechanisms like pre renal ischemia, direct toxicity to nephrons, altered medullary vasculature and the establishment of a concentration gradient along the papillary tip of the inner medullary cells. This results from the "up-to-ten-fold" increase concentration of drug metabolites in the vasa recta.[7] The resulting inflammatory responses lead to papillary ischemia, necrosis and interstitial oedema, and in chronic injurious states, progress to tubular atrophy,tubular wall dilatation and interstitial fibrosis.[8]

The induction of a hyporeninemic, hypoaldosteronism-like state leads to hyperkalaemia as was seen in the index patient. Concurrent hyponatremia could also been seen due to tubular injury that causes release of cytokines with alteration of the Na^+K^+ATPase causing fluid retention.[9] This causes imbalance in tubular absorptive/secretory capacity, inner medulla damage with defective concentrating ability and loss of polarity between the apical and basolateral membranes. This feature, that typifies many exogenous nephrotoxins, causes a non-oliguric AKI as was seen in the index patient.[10]

NSAIDs metabolism involves the depletion of Sulphydryl (SH) enzymatic systems, glutathione reductase and calcium transporting ATPases (Calmodulin). This increases cytoplasmic calcium concentration, which when sustained,inactivates the protective enzymes systems while degrading enzymes like proteases, phospholipases, endonucleases and protein kinases are activated, leading to mitochondrial damage, cytoskeletal alterations, altered cell signalling and apoptosis.[11]

About 50 percent of Blacks and Caucasians are slow acetylators, majority of Eskimos, Asians and most other races are rapid acetylators**.** Slow acetylation may lead to higher serum drug concentrations, with increased nephrotoxicity and hepatic damage.[11,12] Though, we didn't assess the acetylation status of index patient, being an African most likely increased the risk of NSAIDs nephrotoxicity in him.

Interstitial nephritis can result from all classes of NSAIDs.[13] Two renal-stressing conditions in the index patient were dehydration and exercise as he fasted for at least 18 hours daily, engaged in exercise–associated prayers while using the maximum doses of Diclofenac and Miloxicam. It is reported that exercise in heat with dehydration decreases the GFR by 51%.[14] Differential diagnoses of acute interstitial nephritis such as renal atheroembolic disease, obstructive uropathy and connective tissue diseases were rule out in him from history, absence of previous endovascular procedure or skin changes, urinalysis with microscopy, full blood count (FBC) and ESR, and imaging results.

Treatment modality for AIN depends on the degree of affectation, some are self-limiting particularly with discontinuation of the offending agent(s). Steroid use in treating NSAIDs induced AIN is more common than the use of other cytotoxic agents.[15] Prednisolone 1mg/kg is commonly used in this regard and response to treatment is good,particularly with early treatment. Maintaining fluid balance is essential in restoring kidney function. Dialysis treatment that was given to the index patient is usually needed in the context of severe kidney damage associated with acidosis, markedly deranged renal biochemical parameters and fluid retention.[4] Blood pressure control is not commonly a major challenge in AIN as was the case with index patient.[10] However, blood transfusion is often needed in severe disease as the case with index patient.

Utmost Care is always needed during the recovering phase as there could be marked derangement in renal biochemistry secondary to excessive water, salts and electrolytes loss resulting from a lag in tubular recovery compared to the glomerulus.[5,9] Considering the higher risk of CKD following an AKI, compared to the general population, follow up is needed for the monitoring of kidney function to ensure complete recovery and its sustenance. Prognosis depends on age, presence of comorbidities, severity of kidney damage, promptness and adequacy of the management modalities and, background kidney function prior to the insults. Prevention is essentially based on avoidance and/or optimal management of risk factors.[2]

Conclusion:-

NSAIDs are cheap, commonly abused drugs that can cause AKI particularly in stressed kidney. AIN from NSAIDs use, though could be self-limiting, can be severe enough to warrant dialysis treatment.Histological diagnosis is very essential for effective treatment and recovering of kidney function. These drugs are best avoided in kidney-stressedstates, and if not possible, these drugs should be taken in prescribed doses and for short period.

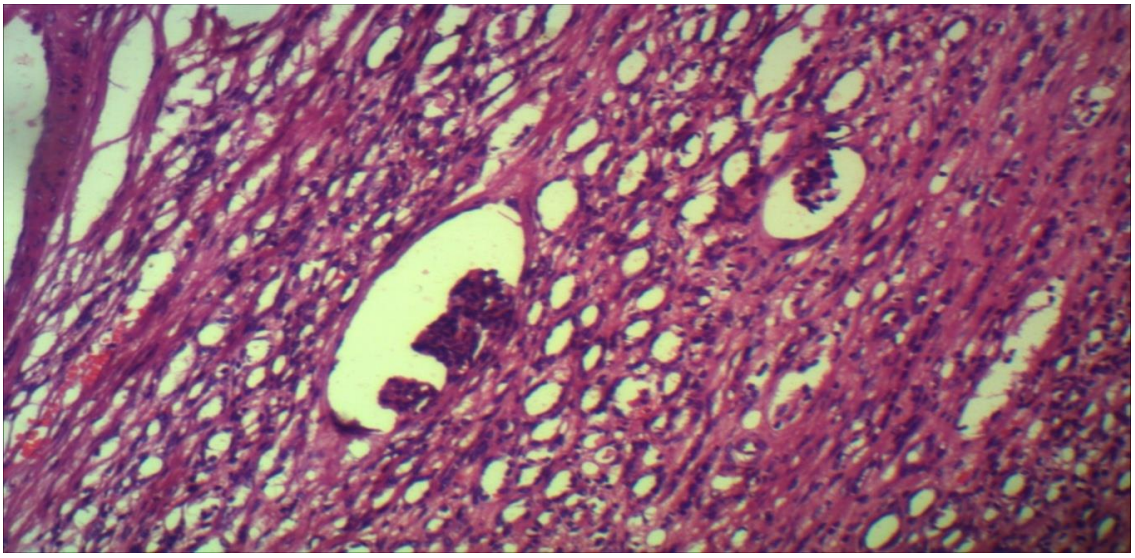

Figure 1:- Photomicrograph showing the renal histologic features in a 62 year old man who took Diclofenac100mg and Meloxicam 15mg daily for 7 weeks. H/E (x60).

Table 1:- Renal biochemistry findings.

Variables	Sodium	Potassium	Chloride	Bicarbonate	Creatinine	Urea	URR
	mmol/L	mmol/L	mmol/L	mmol/L	µmol/L	mmol/L	%
	135-145	3.5-5.5	97-107	22-30	50-110	3-7	>65
Predialysis	131	6.9	96	15	556	17.9	
Postdialysis	133	4.7	98	19	356	11.1	37.9
Predialysis	134	6.3	97	17	514	17.2	
Postdialysis	133	5.1	100	19	297	10.8	37.2
Predialysis	132	5.7	96	18	312	10.8	
Postdialysis	136	4.2	100	21	194	3.2	70.3
Predialysis	132	6.1	94	19	253	10.7	
Postdialysis	139	4.4	99	21	152	4.9	54.2
Predialysis	135	5.5	95	19	161	9.2	
Postdialysis	138	3.8	102	22	105	5.4	41.3
Predialysis	130	5.5	95	19	161	9.2	
Postdialysis	139	3.8	102	22	105	5.4	
1 wk post discharge	141	4.8	101	22	114	5.2	
3 wks post discharge	140	4.6	100	24	101	4.9	
6 mths post discharge	138	4.2	102	24	104	5.2	

HCO3-bicarbonate, URR-urea reduction ratio

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