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A Comparison between the Acute Effects of Coxis on renal function with that of diclofenac Sodium in patients with rheumatological disorders

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Abstract :
The aim of this study was identify the effect of (coxibs) on renal function in comparison to the traditional (NSAIDs) to provide more insight on this issue. Particular emphasis has been paid to the possible acute renal toxicities such as acute decline in renal function, hyperkalaemia, hypertension and sodium and water retension, the study was conducted during the period from (February –August) 2018 , Rheumatological out-patient clinic in Ibn-Sina Teaching Hospital in Mosul**.** patients and methods **:** Eighty patients with different rheumatological disorders who have no history of pre-existing renal disease. They were divided into 2 groups: Group A (40 patients): Treated with diclofenac sodium and Group B (40 patients): Who were treated with celeecoxib. Twenty healthy subjects, group C were taken as a control group. They have all undergone clinical examination including measurement of their body weights and blood pressure at the start of the study and repeated a month later. Certain Biochemical markers including urea, creatinine, serum sodium and potassium have been measured at the start and repeated a month later following the commencement of treatment. Results: Patients in group B had decrease in renal function manifested as arise in blood urea, (P <0.001), and both group had increase in serum creatinine group A (P<0.05) group B (P<0.001), and decline in creatinine clearance group A (P <0.001), group B (P <0.001), compared with the control group. There was also significant sodium and potassium retention in both groups. Group A (sodium P<0.05 potassium P <0.001), group B (sodium P<0.001 potassium P <0.001). Conclusion:_ The effects celecoxib (COX-2 inhibitors) on renal function are similar to those observed with diclofenac (non-selective NSAID's) and, consequently, standard precautions to avoid renal toxicity with the use of non-selective NSAID's apply to coxibs.

Keywords : **Celecoxib (COX-2 inhibitors) ; Renal Function ; Diclofenac Sodium ; Rheumatological disorders.**

Introduction :

Non-steroidal anti inflammatory drugs (NSAIDs) represent one of the most commonly used classes of drugs in the world [(1)]. They are anti inflammatory, analgesic and antipyretic agents used to reduce pain, decrease swelling and improve function in people with many different forms of arthritis[(2)].These drugs act by inhibition of cyclooxygenase-1 and cyclo oxygenase-2 (COX-2), preventing the formation of prostaglandins. [(3),(4)] The major adverse effects of these drugs are gastro-intestinal, consisting primarily of gastric erosions and ulceration [(5)]. Nephrotoxicity is

less common, but it's too potentially devastating. The decline in renal function is specially pronounced in the elderly and in patients with pre-existing renal disease. (6)

Selective cyclooxygenase-2 (COX-2) inhibitors which include celecoxib, , and valdecoxibe offer the analgesic and suppression of inflammation provided by traditional NSAIDs . The introduction of these drugs (COX-2 inhibitiors) has produced an impressive reduction in gastric problems (7), creating optimism that renal function might be similarly spared. This assumption was based on the basic idea that these selective agents spare COX-1 isoenzyme which is constitutive maintaining normal cell function within the mucosa of many organs, in contrast to COX-2 which is inhibited by these agents, is undetectable in most tissues. It is an inducible enzyme and becomes abundant in activated macrophages and other cells at the site of inflammation. (8) Based on these hypothesis, selective COX-2 inhibitors (coxibs) would primarily target inflammation with minimal disturbance of homeostatic, COX-1 function.

Unfortunately, COX-2 has recently been shown to be constitutively expressed in many organs including the kidney, where its presence may reflect important homeostatic function (9). Inhibitors of COX-2 thus might compromise renal function, raising the question of whether selective COX-2 inhibitors offer any improvement in renal safety over non-selective COX inhibitors and might similarly adversely affect renal function.

A few studies have already been conducted on the renal effect of COX-2 inhibitors providing at least preliminary insight on to this potential problem .

Patients and methods :

Eighty patients were studied, all with different rheumatological disorders, they were predominantly female with 73% and male 27%, their age range between (40-80) years with a mean age of (58.5± 7.49 SD). Those patients were collected among attendants to the rheumatological outpatient clinic of Ibn-Sina Teaching Hospital in Mosul from February to August 2018. Twenty healthy sex and age matched subjects were taken as a control group.

Exclusion criteria were renal disease, hepatic disease, diabetes mellitus, cardiovascular disease, hypertension, patients taking immunosuppressant drugs, concomitant use of drugs which can affect kidney function and peptic ulcer.

Patients were not treated with any drug for their rheumatological disorder for at least 4 weeks before the start of the study. Initial evaluation of all participitants include detailed history, complete clinical examination including blood pressure measurement, body weight and presence or absence of peripheral oedema.

Blood sample was taken from the patients and the control group for measuring the blood urea, serum creatinine, serum sodium, and serum potassium. Following the initial evaluation, patients were randomly divided into 2 groups (A and B). The number of patients in both groups with their age and sex distribution were well matched. Group C included (20) healthy subjects who were taken as a control with their age and sex matched with group A and B, Group A were given diclofenac sodium (25 mg T.I.D) a non-selective NSAIDs. Group B were given celecoxib 200 mg B.I.D. as a selective COX-2 inhibitor.

The clinical examination was repeated on day 8. Each patient was examined by the same doctor who was unaware of the type of medication taken by the patients. Blood sample was taken on day 28 of the study from each patient and control subject

and sent to the lab, requesting the same biochemical tests which were measured at the start of the study.

Statistical analysis :

The entire variables were presented for as number and frequency, mean ±SD is calculated every quantitative variable. Chi-square test used for comparison between all variable (control and study groups). t- test used to calculate mean difference between study and control before and after giving the drug. [10]

Results :

The results of the clinical and biochemical variables which were studied in the two groups, before the start of the treatment and one month after, were as follows:

1. Body weight : (Table 1,2,3) , increase in body weight was only noted in group A, however, this increase reach a statistical significance when compared with the control group .
2. Blood pressure: No significant increase in blood pressure was noted in both groups.
3. Peripheral oedema: No clinically detectable edema was noted in both groups.
4. Blood urea: There was no significant rise of blood urea in group (A). A very highly significant rise was noted in group (B), however, this rise did not reach a statistical significance when compared with the control group.
5. Serum creatinine: A very highly significant rise was found in both groups A and B (Table 1 & 2), the rise of serum creatinine in the treated groups (A and B) achieved statistically significant difference when compared with the control group (Table - 4).
6. Serum sodium: A very highly significant increase was noted in both group A and group B (Table 1&2). The statistical difference between group A and the control group was significant , while in the group B it did not reach statistically significant difference, comparism between group A and group B there is no any difference (Table - 4)
7. Serum potassium: A very highly significant increase was noted in the treated groups after taking the drugs (Table 1& 2), but this increase was not statistically significant when compared with the control group (Table 4).

Table (1) show the results in group A before and one month after treatment

Parameters	Before taking the drug			One month later		P-value
Body weight	72.45± 13.22 kg			72.60± 13.17kg		P≤0.05 *
Mean arterial blood pressure	91.16±11.87 mm/Hg			92.04±11.07 mm/Hg		P≥0.05 -
Peripheral oedema		No	%	No	%	P≥0.05 -
	0	35	87.5	35	87.5	
	1	5	12.5	5	12.5	
Blood urea	4.77±0.85 m mol/L			4.86±0.82 m mol/L		P≥0.05 -
Serum creatinine	100.25±23.05 µ mol/L			106.875±22.14 µ mol/L		P≤0.05 *
Serum sodium	136.10±3.45 m mol/L			136.62±3.42 m mol/L		P≥0.05 -
Serum potassium	4.28±0.482 m mol/L			4.33±0.493 m mol/L		P≤0.05 *

In peripheral oedema ; 0= (-ve) for oedema ; 1= (+ve) for oedema

* S = significant ≤ 0.05 ; NS = not significant ≥ 0.05.

Table (2) show the results in group B patients before and one month after treatment

Parameters	Before taking the drug			One month later		P-value
Body weight	78.02± 6.60 kg			78.10± 6.61kg		P≥0.05 -
Mean arterial blood pressure	92.91±8.10 mm/Hg			93.58±7.74 mm/Hg		P≥0.05 -
Peripheral oedema		No	%	No	%	P≥0.05 -
	0	33	82.5	34	85.0	
	1	7	17.5	6	15	
Blood urea	4.77±1.03 M mol/L			4.98±1.033 m mol/L		P≤ 0.05 *
Serum creatinine	100.82±20.96 M mol/L			110.02±22.98 µ mol/L		P≤ 0.05 *
Serum sodium	137.28±3.22 M mol/L			137.98±3.27 m mol/L		P≤ 0.05 *
Serum potassium	4.33±0.533 M mol/L			4.39±0.521 m mol/L		P≤ 0.05 *

Table (3) show the mean value of the clinical & Biochemical variables studied in control group

Parameters	Mean value ± SD	
Body weight	77.300± 8.67 kg	
Blood pressure	94.00±10.95 mm/Hg	
Peripheral oedema	No	%
	18	90
	2	10
Blood urea	4.98±0.650 m mol/L	
Serum creatinine	96.10±2.65 µ mol/L	
Serum sodium	139.75±4.24 m mol/L	
Serum potassium	4.215±0.491 m mol/L	

Table (4) show the results of comparison between the control and both treated groups, then between both group A and B

Parameters	group A X Control	group B X Control	group A x group B
Body weight	72.60±13.17X77.300±8.67 *	78.10±6.61 X 77.300±8.67 -	P= 0.021 *x
Blood pressure	92.04±11.07 X94.00±10.95 -	93.58±7.74 X94.00±10.95 -	P=0.473 -
Peripheral oedema	P=0.778 -	P=0.594 -	P=0.747 -
Blood urea	4.86±0.82 X6.89±0.650 -	4.98±1.033X4.89±0.650 -	P=0.568 -
Serum creatinine	106.875±22.14X96.10±2.65 *	110.02±22.98X96.10±2.65 *	P=0.534 -
Serum sodium	136.62±3.42X139.75±4.24 *	137.98±3.27X139.75±4.24 -	P=0.73 -
Serum potassium	4.33±0.493X4.15±0.491 -	4.39±0.521X4.15±0.491 -	P=0.995 -

(*x) : Only there is significant change in body weight in those patient with group A in comparism with group B

Discussion :

The renal toxicity of traditional NSAIDs , which include acute decline in renal function , fluid and electrolyte disorders , oedema, has been studied extensively and well known to all physicians [11] . On the other hand, many physicians believe that the selective COX-2 inhibitors, the relatively newly introduced drugs are devoid of renal toxic effects.

This study showed that coxibs can cause acute decline in renal function as manifested by the small but very highly significant rise in blood urea, serum creatinine. These change were also noted in the group of patients treated with diclofenac (traditional NSAIDs), this is due to the inhibition of prostaglandins synthesis that are important in maintaining renal blood flow and glomerular filtration rate by both group of drugs, although this decline was slight among the healthy people included in this study , it can be particularly important in people who depend on the counterbalancing vasodilating properties of prostaglandins to support renal blood flow and glomerular filtration , such as congestive cardiac failure, cirrhosis , underlying renal disease [12] ,[13]

The study has also shown a very highly significant rise in serum sodium in both groups at treatment and the rise was even higher among patients treated with coxibs. A number of factors may contribute including decrease renal blood flow and increase sodium chloride resroption in the loop of Henele [14] [15] [16] despite the lack of significant rise in blood pressure among our previously normotensive patients, this sodium retension can be clinically relevant in patients with heart failure , renal failure and hypertensive patients which are at risk of exacerbation of their previously controlled blood pressure.

A small but very highly significant rise in serum potassium are explained by the reduction in the synthesis of rennin and aldosteron by both group of drugs [17] [18] [19] . Although the rise in potassium was not sever in this study , it can very well be so and might even be life- threatening when these drugs are taken by patients with underlying renal insufficiency, diabetes mellitus , or in combination with potassium retaining drugs such as angiotensin converting enzyme inhibitors [20][22] .

This study offers evidence that coxibs even for a short period can adversely affect renal function, and this added more support that COX-2 isoenzyme is important in renal hemodynamic and play a role in salt and water balance and that inhibition of COX-2 can compromise renal function in away similar to COX-1 inhibition by the traditional NSAIDs . The likely explanation of this similarity in the side effect in both group of drugs in that both COX-1 and COX-2 isoform are membrane –associated and are 65% identical in amino acid sequence. More significant, they are almost identical at their catalytic site, resemblance that allow them to carry similar enzymatic function[21].

Such conservation of structure allows both of the COX- isofrom to synthesize the same group of prostaglandins. Of the various prostaglandins (PGI2) produced most abundantly in the renal cortex and (PGE2) (synthesized in the juxtamedullary glomeruli , medullary interstitial cells) are physiologically predominant .Both prostaglandins (PGI2 and PGE2) increase renal perfusion and sodium and water excretion.

Conclusion :

celecoxib, a selective COX-2 inhibitors appears to be similar to diclofenac sodium (traditional NSAIDs) in term of their effect on renal function. The standard renal precaution that apply to the use of non-selective NSAIDs to avoid renal toxicity, also apply to coxibs. They should be used carefully in patient with congestive heart

failure, hypertension particularly in patients taking angiotensin converting enzyme inhibitors and or potassium sparing diuretics or taking salt substitutes , and in patients with diabetes and renal insufficiency, who are volume depleted or have cirrhosis such patients should have base line renal function performed prior to initiation of therapy , should given a lower doses and most have their renal function monitored closely throughout their treatment .

Recommendation :

We recommend to study how long do these acute effects persist after with drawl of the drug .

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