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Study of Renal Toxicity of Selective COX-2 Inhibitors in Comparison With Conventional NSAIDs

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Abstract:
Introduction: *Non-steroidal anti- inflammatory drugs presently are the most widely used drugs in medicine and the most frequent cause of adverse drug reactions, mainly affecting the renal system, which is a major public health concern. Previous studies report, that selective COX-2 inhibitors are safer when compared to non-selective cyclo-oxygenase inhibitors, regarding their adverse effects on renal system. But, recent studies reveal, that the renal safety of these selective COX-2 inhibitors is not much better than that of conventional NSAIDs. In view of the larger usage of selective COX-2 inhibitors, the study has been taken up to report, whether selective COX-2 inhibitors have got any advantages over conventional NSAIDs or not, regarding their renal adverse effects.*
Methodology: *Patients were divided into eight groups, fifteen patients of each. Each group was given one of the NSAIDs from the eight drugs those were selected for the study, for 15 days. In the selected group, both pre and post-treatment values of blood urea & serum creatinine are estimated, tabulated & subjected to statistical analysis. Pre & post treatment values of both systolic & diastolic blood pressure were also recorded & subjected to statistical analysis.*
Results: *Drugs like ibuprofen, diclofenac & meloxicam have shown significant change in the renal parameters; whereas, selective COX-2 inhibitor rofecoxib has shown a very high level of renal toxicity when assessed clinically.*
Conclusion: *In our short-term study, selective COX-2 inhibitors did not show any advantage over non-selective NSAIDs regarding their renal toxicity. But, long term studies are needed for further evaluation.*
Keywords: *Adverse drug reactions, Conventional NSAIDs, COX-2 inhibitors, Renal Toxicity*

I. Introduction

Non-steroidal anti- inflammatory drugs presently are the most widely used drugs in medicine. Presently, more than 100 NSAIDs have been tested clinically and more than 50 are there in the world market. Nearly 35 million people are taking them on daily basis and FDA has ranked them the most frequent cause of adverse drug reactions (1) .

The use of NSAIDs can also be expected to increase in the years ahead, partly because of the increasing age of the population and partly because of the newly developing indications, particularly in vascular disease and cancer prevention. It is therefore important to assess the safety and side effects of newer NSAIDs. In view of the larger usage of selective COX-2 inhibitors, the study has been taken up to report, whether selective COX-2 inhibitors have got any advantages over conventional NSAIDs or not, regarding their toxic effects on the renal system; by analyzing few non- selective NSAIDs and selective COX-2 inhibitors, in short- term treatment (2).

II. Aims and Objectives

To study the impact on the renal system, of both non- selective NSAIDs and selective COX-2 inhibitors

III. Materials and Methods

The study was an interventional, single blind & prospective and was taken up with the approval of institutional ethical committee. All patients included in our study gave informed consent for their participation and the study was done at Mahatma Gandhi Memorial Hospital, Warangal.

Subjects selected for the study:

Inclusion criteria:
Patients of above 30 years age; of either sex
Osteoarthritis patients
Rheumatoid arthritis patients

Patients with fractures and d i s l o c a t i o n s

Exclusion criteria:
History of acid peptic disease
History of bronchial asthma
History of bleeding disorders

Paracetamol	650 mg tid (About 2 gm per day)
Ibuprofen	400 mg tid (1200 mg per day)
Diclofenac	50 mg bd (100 mg per day)
Nimesulide	100 mg bd (200 mg per day)
Meloxicam	7.5 mg bd (15 mg per day)
Rofecoxib	25 mg bd (50 mg per day)
Celecoxib	100 mg bd (200 mg per day)
Valdecoxib	10 mg bd (20 mg per day)

Table 1. Drugs selected in the study and their doses

Methodology:

Patients were divided into eight groups, fifteen patients of each. Each group was given one of the NSAIDs from the eight drugs those were selected for the study (Table 1). In the selected group, prior to the administration of drug, the following tests are done in all the patients.

Blood Urea – by Phosphotungstate method
Serum Creatinine -by Alkaline picrate method
Blood Pressure readings were taken manually

The patient was advised to take the concerned NSAID, for a period of fifteen days, and they were not put on any antacid or H_2 blocker or proton pump inhibitor. All the out patients were briefed, of the common toxicity of the concerned NSAID and they were advised to inform us soon after the onset of symptoms like nausea, vomiting, diarrhea, epigastric pain, heartburn, dyspepsia, facial and pedal edema, headache and tinnitus. Whenever the patient reported an adverse effect, he or she was advised to stop the treatment and it was taken as the primary end point of our study, for that particular patient. After the completion of treatment, the bio-chemical parameters were repeated again, the values were recorded; and the results were subjected to statistical analysis, with the help of paired 't' test.

The following side effects were also noted down, if any, during the treatment period and tabulated, separately for each drug.

Renal toxicity parameters:
Edema
Decreased effectiveness of antihypertensive medications
Decreased effectiveness of diuretic medications

Name of the drug	**No of patients affected with renal toxicity**
Paracetamol	0
Ibuprofen	1
Diclofenac	1
Nimesulide	6*
Meloxicam	1
Rofecoxib	2*
Celecoxib	0
Valdecoxib	0

Table 2. Renal Toxicity values

IV. Results

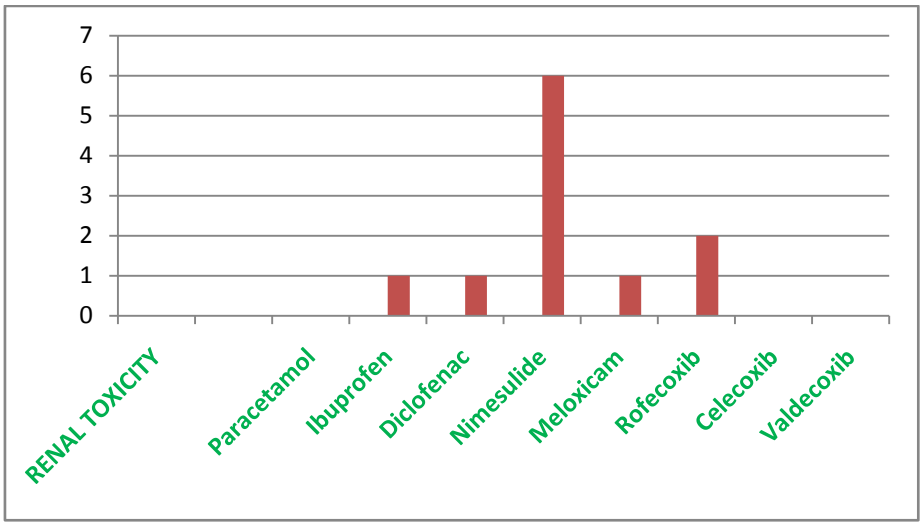

Fig 1.Renal toxicity

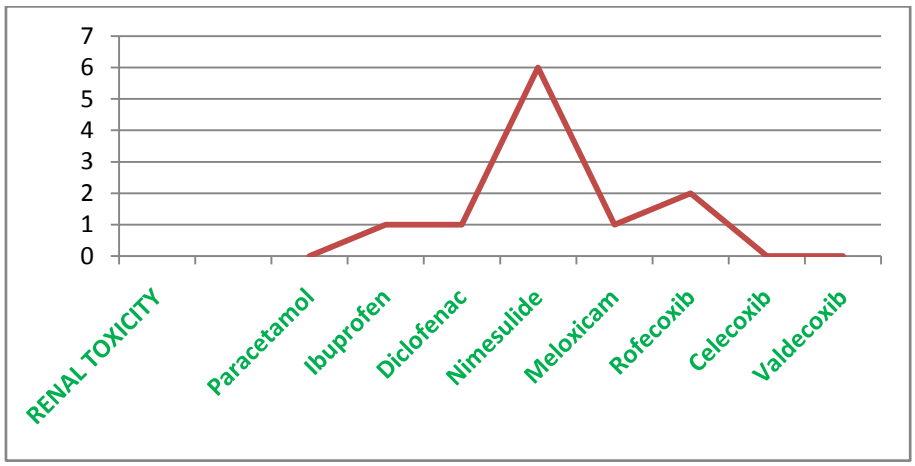

Fig 2.Renal toxicity

Name of the drug	'p' Value
Paracetamol	0.68
Ibuprofen	0.009*
Diclofenac	0.29
Nimesulide	0.62
Meloxicam	0.003*
Rofecoxib	0.62
Celecoxib	0.414
Valdecoxib	0.235

Table 3. 'p' values for Blood urea

Name of the drug	'p' Value
Paracetamol	0.70
Ibuprofen	0.39
Diclofenac	0.002*
Nimesulide	0.096
Meloxicam	0.647
Rofecoxib	0.39
Celecoxib	0.58
Valdecoxib	0.07

Table 4. 'p' values for Serum Creatinine

Name of the drug	'p' Value
Paracetamol	0.67
Ibuprofen	0.67
Diclofenac	1.0
Nimesulide	0.082
Meloxicam	0.04*
Rofecoxib	1.0
Celecoxib	0.33
Valdecoxib	0.33

Table 5. 'p' values for Systolic Blood Pressure

Name of the drug	'p' Value
Paracetamol	0.54
Ibuprofen	0.33
Diclofenac	0.75
Nimesulide	0.49
Meloxicam	0.67
Rofecoxib	0.43
Celecoxib	0.58
Valdecoxib	0.17

Table 6. 'p' values for Diastolic Blood Pressure

V. Discussion

Effect on the renal system:

NSAIDs are known to be nephrotoxic. In our present study, fluid retention & edema were reported less frequently with ibuprofen, diclofenac & meloxicam than with the other drugs & with paracetamol, it is not significant (Fig 1 & 2). Effects attributed to inhibition of PG production in the kidney- hypertension and edema - occur with nonselective COX inhibitors and much more with nimesulide & rofecoxib. Rofecoxib, a highly selective COX-2 inhibitor had also been shown to have an increased risk of salt and water retention (3, 4; Fig 1 & 2; Table 2). Clinically, both selective and non-selective NSAIDs are not free from renal toxicity (Fig 1 & 2).

But, in our short-term study, there were significant changes in blood urea values with the drugs ibuprofen & meloxicam (Table 3), and only diclofenac has shown significant changes in the serum creatinine values (Table 4). But, there is no much significant change in either systolic or diastolic blood pressure values with all the drugs, except meloxicam (Tables 5 & 6). But, NSAIDs may cause impairment of renal function, in patients suffering from hypovolemia, congestive heart failure or hepatic cirrhosis, since renal function in these patients may be dependent on the vascular effects of prostaglandins.

VI. Conclusion

In our short-term study, non-selective NSAIDs like ibuprofen and diclofenac were shown to be associated with risk of renal toxicity; whereas, among the selective COX-2 inhibitors, nimesulide and rofecoxib were shown to be associated with much higher renal toxicity, inferring that selective COX-2 inhibitors did not show any advantage over non-selective NSAIDs regarding their renal toxicity. Further long-term studies are required to assess the clinical safety of these selective COX-2 inhibitors.

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