European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 04, 2022

ORIGINAL RESEARCH

Pharmacovigilance analysis of nonsteroidal anti-inflammatory drugs-induced chronic kidney disease

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ABSTRACT

Background: Chronic Renal Disease is a fast-growing disease worldwide achieving the endemic levels. The use of NSAIDs has been associated with renal function deterioration through variable mechanisms. Present study was aimed at pharmacovigilance analysis of nonsteroidal anti-inflammatory drugs-induced chronic kidney disease at a tertiary hospital. Material and Methods: Present study was retrospective, case record-based analysis conducted in case records of patients admitted & diagnosed as nonsteroidal anti-inflammatory drugs-(NSAID) induced chronic kidney disease. Results: In present study, 48 case records evaluated. Majority patients were from 51-60 years (37.5 %) & 41-50 years age group (27.08 %), were male (68.75 %) & labourer by occupation (52.08 %). Common co-morbidities noted were hypertension (77.08 %), bone and joint disease (33.33 %), diabetes (31.25 %), cardiovascular disease (29.17 %) & malignancy (4.17 %). Among 48 patients, common CKD stage was Stage 3a (39.58 %) followed by Stage 3b (29.17 %), Stage 2 (22.92 %) & Stage 4 (8.33 %). Treatment receiving were Hemodialysis (54.17 %), Only medicine (22.92 %), Peritoneal dialysis (10.42 %) & Kidney transplantation (12.5 %), Common NSAIDs used was Diclofenac/Aceclofenac (45.83 %), Paracetamol (39.58 %), Ibuprofen (27.08 %), Ketorolac (4.17 %) & Nimesulide (4.17 %). Oral Route of administration was common (77.08 %). Though majority of patients using 1 NSAID (47.92 %) followed by 2 NSAIDs use (35.42 %), ≥3 NSAIDs use (16.67 %). Common purpose of use was headache (60.42 %), generalized pain (45.83 %), joint pain (33.33 %), dental pain (14.58 %), menstrual pain (12.50 %) & renal colic (8.33 %). Conclusion: Non-steroidal anti-inflammatory drug induced nephrotoxicity should be considered as significant adverse effect. Physicians & general practitioners should discourage on the counter use of NSAIDs.

Keywords: Chronic kidney disease, nonsteroidal anti-inflammatory drugs, pharmacovigilance, paracetamol, diclofenac

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INTRODUCTION

Chronic Renal Disease is a fast-growing disease worldwide achieving the endemic levels.[1,2] This can be owned by the increasing incidence of systemic diseases such as ischemic heart diseases, hypertension, and diabetes as well as increasing awareness & diagnosis concerning chronic renal disease. DIN (drug-induced nephrotoxicity) incidence is rapidly increasing owing to easy access to the available drugs, increase in drug use, and availability of over-the-counter drugs including NSAIDs (non-steroidal anti-inflammatory drugs).[1]

NSAIDs are the cornerstone of pain management in patients who have inflammatory pain, acute pain (e.g. headache, postoperative pain, and orthopedic fractures) or chronic pain (e.g. rheumatoid arthritis, osteoarthritis, and gout).[3] The use of NSAIDs has been associated with renal function deterioration through variable mechanisms including alteration of the intraglomerular hemodynamic, nephrotic syndrome, glomerulonephritis, chronic interstitial nephritis, renal papillary necrosis, hyperkalemia, and podocyte injury.[4,5]

World Health Organization (WHO) defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problem, particularly long term and short-term adverse effects of medicines.[6,7] Present study was aimed at pharmacovigilance analysis of nonsteroidal anti-inflammatory drugs-induced chronic kidney disease at a tertiary hospital

MATERIAL AND METHODS

Present study was retrospective, case record-based analysis conducted at Tertiary Health Care Centre. Case records of patients admitted & diagnosed as nonsteroidal anti-inflammatory drugs-(NSAID) induced chronic kidney disease for duration of 3 years (January 2019 to December 2021). Study approval was obtained from institutional ethical committee.

Case records of patients admitted in medicine/ nephrology wards/ICU, diagnosed as nonsteroidal anti-inflammatory drugs-(NSAID) induced chronic kidney disease were evaluated. Age, gender, co-morbidities, type of NSAIDs, route of administration, indication, etc. necessary information was collected in case record proforma. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Statistical analysis was done using descriptive statistics.

RESULTS

In present study, 48 case records evaluated. Majority patients were from 51-60 years (37.5 %) & 41-50 years age group (27.08 %), were male (68.75 %) & labourer by occupation (52.08 %). Common co-morbidities noted were hypertension (77.08 %), bone and joint disease (33.33 %), diabetes (31.25 %), cardiovascular disease (29.17 %) & malignancy (4.17 %).

Table 1: Demographic characteristics

Characteristics	No. of patients	Percentage
Age groups (in years)		
30-40	6	12.50%
41-50	13	27.08%
51-60	18	37.50%
>61	11	22.92%
Gender		
Male	33	68.75%
Female	15	31.25%
Occupation		
Labour	25	52.08%
Professional	10	20.83%
Nonworking	13	27.08%

Co-morbidities		
Hypertension	37	77.08%
Bone and joint disease	16	33.33%
Diabetes	15	31.25%
Cardiovascular disease	14	29.17%
Malignancy	2	4.17%

Among 48 patients, common CKD stage was Stage 3a (39.58 %) followed by Stage 3b (29.17 %), Stage 2 (22.92 %) & Stage 4 (8.33 %). Treatment receiving were Hemodialysis (54.17 %), Only medicine (22.92 %), Peritoneal dialysis (10.42 %) & Kidney transplantation (12.5 %),

Table 2: CKD characteristics

Characteristics	**No. of patients**	**Percentage**
CKD stage		
Stage 2	11	22.92%
Stage 3a	19	39.58%
Stage 3b	14	29.17%
Stage 4	4	8.33%
Treatment		
Hemodialysis	26	54.17%
Only medicine	11	22.92%
Peritoneal dialysis	5	10.42%
Kidney transplantation	6	12.50%

Common NSAIDs used was Diclofenac/Aceclofenac (45.83 %), Paracetamol (39.58 %), Ibuprofen (27.08 %), Ketorolac (4.17 %) & Nimesulide (4.17 %). Oral Route of administration was common (77.08 %). Though majority of patients using 1 NSAID (47.92 %) followed by 2 NSAIDs use (35.42 %), ≥3 NSAIDs use (16.67 %). Common purpose of use was headache (60.42 %), generalized pain (45.83 %), joint pain (33.33 %), dental pain (14.58 %), menstrual pain (12.50 %) & renal colic (8.33 %).

Table 3: Pattern of NSAID use by CKD patients

Characteristics	**No. of patients**	**Percentage**
Types of NSAIDs used		
Paracetamol	19	39.58%
Diclofenac	22	45.83%
Ibuprofen	13	27.08%
Ketorolac	2	4.17%
Nimesulide	2	4.17%
Route of administration		
Oral	37	77.08%
Injection	7	14.58%
Both	4	8.33%
Number of NSAIDs use		
1	23	47.92%
2	17	35.42%
≥3	8	16.67%
Duration of NSAID use		
< 1 year	3	6.25%

1–3 years	7	14.58%
4-6 years	13	27.08%
>6 years	25	52.08%
Purpose of use		
Headache	29	60.42%
Generalized pain	22	45.83%
Joint pain	16	33.33%
Dental pain	7	14.58%
Menstrual pain	6	12.50%
Renal colic	4	8.33%

DISCUSSION

Pharmacovigilance has evolved from largely a record-keeping function, where the purpose was mainly to ensure the processing and submission of individual case reports, to the present, where it now focuses on proactively identifying safety issues and taking appropriate actions to minimize and mitigate risk to the patients.[8]

NSAIDS interact with some commonly prescribed medications, including loop diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blockers leading to reduced effectiveness along with increased risk of renal impairment.[9,10] Conditions causing NSAID-induced hemodynamic deterioration of renal function - Higher than usual dose, volume depletion due to flow loss diarrhea, congestive heart failure, nephrotic syndrome, cirrhosis particularly with ascites, preexisting renal disease, third space fluid sequestration, diuretic therapy, age > 65 years. [11,12]

The common risk factors associated with drug-induced nephrotoxicity and increasing risk and side-effects are co-existing use of other nephrotoxins, pre-existing renal dysfunction, volume-depleted state, and old age.[11,12] In general recurrent episodes of NSAIDs related Acute Kidney Injury(AKI) may lead to CKD or chronic exposure to NSAIDs may worsen unrecognized Acute Interstitial Nephritis (AIN) that can evolve into Chronic Nephritis with associated interstitial fibrosis or chronic papillary necrosis.

Zbigniew Heleniak et al.,[13] studied 972 individuals with CKD,, 16.9 % of patients used NSAIDs every day, or several times a week. The average number of tablets taken within a month was 21.8. Subgroup analysis revealed that NSAIDs were taken most often by patients on hemodialysis: 35 % of them used NSAIDs every day or several times a week (43.15 pills per month). The most common reason for using NSAIDs were bone-joint pain (29.3 %) and headache (26.2 %). Side effects of painkillers such as renal function deterioration and the possible promotion of stomach ulcers were experienced by 43.6 and 37.6 % of respondents, respectively.

In study by Ingrasciotta Y, wt al.,[14] 1,989 CKD cases and 7,906 matched controls were identified. A statistically significant increase in the risk of CKD was found for current users of oxicams (adjusted OR: 1.68; 95% CI: 1.15-2.44) and concerning individual compounds, for ketorolac (adj. OR: 2.54; 95% CI: 1.45-4.44), meloxicam (adj. OR: 1.98; 95% CI: 1.01-3.87) and piroxicam (adj. OR: 1.95; 95% CI: 1.19-3.21).

Sharma M et al.,[15] studied 97 patients, 60% were males and 40% were females. Mean age of patients was 45 ± 12.09 years. Herbal medication (29%) was the most common cause of drug-induced AKI, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (26%). Renal biopsy was done in 54 patients, 59.6% had acute tubulointerstitial nephritis (ATIN), 35% of patients had acute on the chronic TIN. Renal replacement therapy was required in 57.7% patients. Full renal recovery occurred in 38% patients while as, partial recovery occurred in 30% patients. Out of 29 patients with herbal medication intake,17% had full recovery compared to 56% in NSAID group.

In a systematic review and meta-analysis of 10 studies reporting NSAID risk of AKI in the general population, Zhang X et al.,[16] noted that the pooled odds ratio (OR) of AKI for current NSAID exposure was 1.73 (95%CI 1.44 to 2.07), with somewhat higher risk observed in older people (OR 2.51, 95%CI 1.52 to 2.68). In people with CKD, individual study OR of AKI due to current NSAID exposure ranged from 1.12 to 5.25, with pooled estimate OR 1.63 (95% CI 1.22 to 2.19).

Long term exposure to NSAIDs with the longest half-life, such as oxicams, is associated with an increased risk of CKD. Likewise, short-term use of ketorolac is also associated with an increased risk of CKD, probably acting as a trigger of renal function deterioration in patients with subclinical CKD.[14]

Present study limitations were smaller sample size, geographical area biases, retrospective nature of study and single-institution data. Hence, further longitudinal studies with a larger sample size, prospective studies with longer monitoring period are required to reach a definitive conclusion.

CONCLUSION

Non-steroidal anti-inflammatory drug induced nephrotoxicity should be considered as significant adverse effect. Physicians & general practitioners should discourage on the counter use of NSAIDs, while patients receiving NSAIDs for more than 1 month, monitoring of renal function and serum creatinine levels is mandatory during therapy, together with assessment of electrolytes and blood pressure.

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