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Abuse And Misuse Potential of Commonly Used Non Steroidal Anti Inflammatory Drugs (Nsaids) In Indian Scenario, A Pharmacovigilance Model Study

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ABSTRACT

Objectives:

1. To find out the incidences and study various aspects of Adverse Drug Reactions (ADR) in the patients receiving NSAIDs for more than 15 days
2. To test the impact of pharmcovigilance model study in reporting ADR.

Setting: 400 subjects on NSAID's who are on drug treatment for not less than fifteen days

Method: Study in patients on NSAID's therapy, the data was obtained from Physician records, Community Pharmacists and patients by individual interactions using structured format based on the guidelines of CDSCO.

Observations: Out of 400 patients 47 cases of ADRs were reported showing following demographic, 17% population consumed NSAID's for more than one year period, 36% for more than 6 months, 29% for over 3 months and 13% for more than one month and 6 % for more than 15 days. 49% patients did not follow up with the physician and continued the same therapy while 51 % visited their Physician for follow up check up. 20 % patients were given increased per day dosage while 10% got reduced per day dosage and remaining 70% continued on same dosage regimen. ADR cases in fixed dosage combination were 7% while on monotherapy 5%. ADR cases associated with Etoricoxib 1.9%, Diclofenac 2.1%, Aceclofenac 1.5%, Nimuselide 1.1%, Ibuprofen 1.4% and Paracetamol 0.4%. Commonly encountered ADR reported were of Drowsiness, Diarrhea, Gastro intestinal ulcer, Flatulence, elevated hepatic enzymes during LFT and bio chemical changes in KFT.

Conclusion: The evaluation of pharmacovigilance study demonstrated that NSAIDs are the most widely prescribed drugs in the management of pain. Monitoring of ADR is an important tool to prevent the damage to a organ system like Gastrointestinal, Renal system and hepatic functions. Fixed dose combinations of NSAIDs are less prescribed defining rationale use of NSAIDs in Indian scenario. Majority of the ADR reported were of mild to moderate in nature and no serious or severe reaction developed after prescribing NSAIDs which is a positive sign.

Key-words: ADR-Adverse Drug Reaction, CDSCO-Central Drugs Standard Control Organization NSAIDs, Pharmacovigilance.

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INTRODUCTION:

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. There are differences among countries (and even regions within countries) in the occurrence of ADRs and other drug-related problems. This may be due to differences in diseases and prescribing practices, genetics, diet, traditions of the people, drug manufacturing processes used which influence pharmaceutical quality and composition, drug distribution and use including indications, dose and availability.

Pain should be effectively controlled in all age groups because unrelieved pain has negative physical and psychological consequences. Active pain management may prevent negative consequences.[1]

The use of traditional and complementary drugs (e.g. herbal remedies) may also pose specific toxicological problems, when used alone or in combination with other drugs. Therefore, Pharmacovigilance is needed for detecting ADRs and specifically to combat counterfeit and substandard quality products. ADR monitoring ensures that patients obtain safe and efficacious products.

According to WHO'S definition an Adverse Drug Reaction (ADR) is a response to a drug that is noxious and unintended, and occurs at doses normally used in human for the prophylaxis, diagnosis, and treatment of disease, or for modification of physiological function.[2,3]

Lazarous et al.[4] estimated that ADRs were the fourth to sixth largest cause of death in the United States. There are few recent reports on epidemiology of ADRs.[5] In United Kingdom most of the studies were performed in the previous two decades and were restricted to specific areas such as monitoring of ADRs in geriatric patients.[6, 7]The largest UK study was based on retrospective review of case reports and gave poor documentation.[8]

The detection of adverse drug reactions (ADRs) has become increasingly significant because of introduction of a large number of potent toxic chemicals as drugs in the last two or three decades. WHO has intervened seriously in the matter and established an international adverse drug reactions monitoring centre at Uppsala, Sweden which is collaborating with national monitoring centers in around 70 countries.[9]

In India there are very few active ADRs monitoring centers and a lot of effort is required in order to collect ADR data which may generate from safety surveillance of billions of therapeutically active substances either alone or in combinations.

This study was a prospective analysis of ADRs caused by medicines prescribed to the patients in community practice for various painful inflammatory conditions, situated in east and south Delhi locality to define prevalence and to assess causality of these reactions.

METHODS

ADR monitoring was done from March 2012 to March 2014. Patients of varied age and sex visiting to retail pharmacies for refilling their medicines were included in the study. Patients of chronic painful inflammatory conditions were included while patients having concomitant ailments like diabetes, hypertension epilepsy etc. was excluded from this study. Patients taking more than five prescription drugs at a time were not included in the study. All mentally retarded, drug addicts, unconscious and patients unable to respond to verbal questions were also excluded from the study.

An informed consent was taken from the patients and pharmacists for participating in the study..

The adverse drug reactions experienced by the patients were documented on ADR monitoring form designed on the basis of WHO guidelines.[15] The form includes data like age, sex, demographic details, past medical history, present drug treatment, description of adverse drug reaction, its assessment and treatment for the drug reaction. Patients on concomitant therapies for chronic ailments like Diabetes, Hypertension, Pregnancy, Mental retardation, unable to comply, refusing the consent were excluded.

Monitoring was done by following two methods: Intensive ADR monitoring of patients by a registered pharmacist and voluntary reporting of ADRs by patient and consulting physician.

400 patients were interviewed using structured proforma later they were followed telephonically and refilling of their prescriptions at retail pharmacies. Data was evaluated on following parameters.

- Patient's details: Age, gender, NSAID consumed, frequency, duration, disorder for which the NSAID was prescribed / used, OTC usage etc.
- Medication used: NSAID alone or in fixed dose combination with Paracetamol (FDCs)
- Self medication without refilling of prescription
- Severity of ADR
- Usage of gastro protective agent
- ADR analysis-Causality assessment

RESULT:
Data of total 400 patients were collected from eight different retail pharmacy stores from East and South Delhi region. Data was analyzed for utilization pattern of NSAID's, patient details, and self consumption of NSAID's without consulting Physician, Analyses of ADR and outcome of ADR.

- During the study period, a total of 400 patients were interviewed (Table 1). A total of 47 ADRs were reported. The gender distribution among the patients who experienced ADRs was comparative with females having experienced more number of ADRs as compared to the males (33 versus 14). The frequency of ADRs was maximum (34%) in patients with age group of 50-70 years; next susceptible age group was that of patients (30-50 years) with 18% of ADRs. The number of ADRs in less than 30 years age was lowest (17%).(Table-1)
- The gastrointestinal side effects (e.g. gastritis, dysphasia, Belching, Epigastric pain etc.) were at the top with 37% followed by skin and subcutaneous disorders (19%). The findings revealed that 49% of the patients did not followed the regimen and continued consuming NSAID's of their own, 19% of the patients who did not followed drug regimen reported ADR's compared to 4% of the patients who used NSAID's after following drug regimen. (Table-2)
- Amongst dietary habits 7% of Non vegetarians (Male-11% and female-38%) shown symptoms of ADR, smokers and non smokers did not have any variations in ADR symptoms (both 6 %), 29% of the patients reporting ADR were Alcoholics amongst ADR group and 26% patients used fixed dose combinations.(Table-3)
- Out of a total number of 47 ADRs, Nimesulide and Paracetamol shown minimum % of ADRs, while highest 2.8 % observed with Diclofenac followed with 2.3% with Ibuprofen. Etoricoxib and Aceclofenac remained safer w r t ADR reporting with 1.3% and 1.5%. It is observed that Fixed Dose combinations with Paracetamol also shown 2% of ADR incidences.(Table 4).

DISCUSSION:
The study confirmed that most widely prescribed NSAIDs were Aceclofenac, Diclofenac, Etoricoxib, Nimesulide, Ibuprofen, and Paracetamol (Acetoaminophen). There is prevalence of fixed dose combinations also. Female population is more prone to suffering from kind illnesses, which requires NSAID's as compared to male population.

Elder age group (60 to 70 years) reported more ADR i.e 19% compared to average 12%. Female population had more prevalence of ADRs, with respect to male population (14% compared to 8%).

Previous studies report that the occurrence of ADRs is more common in women.[12-13] In our study the majority of ADRs were in 50-70 years age group. The reasons that could be attributed are that the patients of this age group suffered from low immunity and stressful life style. Increased stress in daily life make this age group more prone to hypertension and diabetes. So this age group used more number of medicines and frequently visited the medicine OPD for their regular check-up and complained for drug related adverse events, though most of these adverse events were mild and easily tolerated. 7% of the patients on poly therapy reported ADR in comparison to 5 % receiving Mono therapy.

Majority of the ADRs were associated with oral administration of medicines, whereas two topical reactions observed was erythema (localized skin redness) on application of diclofenac gel. Gastrointestinal ADRs were most commonly observed with oral medications; thereby the prescription was supplemented with gastro protective agents along with NSAID's.

This was observed from the present study that gastrointestinal side effects (e.g. gastritis, dysphagia Belching, epigastric pain etc.) at the top followed by skin and subcutaneous disorders.

CONCLUSION:

The present work provided base line information about the prevalence of ADRs and their distribution amongst different age groups, genders, and organ systems affected with use of NSAIDs. The data presented here will be useful in future, long term and more extensive ADR monitoring and framing policies towards rational use of drugs. Mono therapy with NSAIDs should be preferred, utmost care should be taken before prescribing NSAIDs to elderly patients preferably female patients. This study would help to improve Drug utilization in community practice particularly in avoidance of OTC dispensing of NSAIDs. The limitation of the present study is its small sample size.

Table-1: ADRs among various age groups in NSAID's users

ADRs amomg various age groups in NSAIDS users										
Age	**Male**		**Female**		**GROUP**		**TOTAL GROUP**			**% of Population**
(in years)	**Total**	**ADR**	**Total**	**ADR**	**Total**	**ADR**	**Total**	**ADR**	**%**	
10 to 20	8	0	4	1	12	1	400	**1**	**0.25**	**3**
20 to 30	17	1	18	2	35	3	400	**3**	**0.75**	**9**
30 to 40	27	1	43	4	70	5	400	**5**	**1.25**	**18**
40 to 50	54	5	79	9	133	14	400	**14**	**3.5**	**33**
50 to 60	38	4	65	11	103	15	400	**15**	**3.75**	**26**
60 to 70	24	3	23	6	47	9	400	**9**	**2.25**	**12**
	168	14	232	33	400	47	400	**47**	**11.75**	**100**
%	**42**		**58**		**100**	**0**				

Table-2: Follow up of therapy / Per day Dosage wise distribution

Follow up of therapy / Per day Dosage									
Period	**Male**			**Female**			**GROUP**		
(Month / Days)	**Total**	**ADR**	**%**	**Total**	**ADR**	**%**	**Total**	**ADR**	**%**
Followed (51%)	82	2	2	122	7	6	204	9	4
Not followed (49%)	86	12	14	110	26	24	196	38	19
	168	14	8	232	33	14	400	47	12

Table-3: Dietary habits wise and Therapy wise distribution

Category	Male		Female				
	Total	ADR	Total	ADR	Total	ADR	%
Alcoholic	32	8	16	6	48	14	4
Non Alcoholic	136	6	216	27	352	33	8
Smokers	72	11	24	12	96	23	6
Non Smokers	96	3	208	21	304	24	6
Vegetarians	96	6	180	13	276	19	5
Non Vegetarians	72	8	52	20	124	28	7
Mono Therapy	122	5	188	14	310	19	5
Poly therapy	46	9	44	19	90	28	7
Single generic	112	4	166	11	278	15	4
Fixed Dose Combination	56	10	66	22	122	32	8

Table-4: ADRs among various age groups in NSAIDs users

ADRs among various age groups in NSAIDS users													
Age	Male	Female	GROUP	Category of NSAIDs used							Total	Total	%
(in years)	Total	Total	Total	Etori coxib	Diclo fenac	Aceclo fenac	Nime silide	Ibupro fen	Parace tamol	FDC			
10 to 20	8	4	12	0	0	0	0	4	4	4	12	400	3
20 to 30	17	18	35	1	5	10	4	7	6	2	35	400	9
30 to 40	27	43	70	7	14	21	9	8	6	5	70	400	18
40 to 50	54	79	133	24	28	28	11	9	19	14	133	400	33
50 to 60	38	65	103	22	15	18	11	8	20	9	103	400	26
60 to 70	24	23	47	6	12	7	6	7	6	3	47	400	11
	168	232	400	60	74	84	41	43	61	37	400	400	100
%	**42**	**58**	**100**	**15**	**19**	**21**	**10**	**11**	**15**	**9**			

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