INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

DRUG UTILIZATION AND ADVERSE DRUG REACTION MONITORING IN NSAID USERS IN A SOUTH DELHI HOSPITAL

Mujahid M[1], Sharma M[2], Aqil M[2], Iqbal D[1] and Prem Kapur[3]

[1]Faculty of Pharmacy, Hamdard University, New Delhi, INDIA
[2]Faculty of Pharmacy, Integral University, Lucknow, Uttar Pradesh, India.
[3]Majeedia Hospital, Hamdard University Campus, Hamdard Nagar, New Delhi.

ABSTRACT

The objective of the present work was to study the drug utilization and adverse drug reactions associated with non steroidal and anti-inflammatory drugs prescribed in Majeedia Hospital, a university teaching hospital in South Delhi. About 300 patients using NSAIDs were randomly selected. Patients were interviewed after informed consent was obtained. Interviews were conducted by using structured questionnaire (Open Question method). Patients' prescriptions were also reviewed for analyzing the drug utilization pattern and adverse drug events. Morisky Medication adherence score was to used determine patient compliance.

A total of 505 NSAIDs were prescribed to 300 patients in the 4 month study. The average no. of non-steroidal anti-inflammatory drugs per prescription was optimum (n=1.68) with aceclofenac (31%) being the most frequently prescribed drug followed by diclofenac (15.64%) and nimesulide (13%). Oral route (n=433, 87.74%) was predominantly preferred mode of administration of NSAIDs followed by topical therapy (n=60, 11.88%), whereas only 12 (2.38%) medicines were administered by parenteral route.

Twently four 24 (8%) cases of ADRs were reported in a pool of 300 patients in the 4 month study period. The incidence of ADRs on long term use of NSAIDs has been reported to be high in previous studies and hence long term pharmacovigilance studies are needed in order to formulate strategies to minimize prevent incidence of ADRs. Patient compliance was found to be poor in the study subjects which could be improved with proper patient counseling by clinical pharmacists.

INTRODUCTION

Drug utilization study is a powerful tool to ascertain the role of drugs in society. They create sound socio medical and economic basis for health decision-making. With the developing burden of acute gout and arthritis, drug utilization studies are performed to promote rational use of analgesics. Drug utilization studies identify treatment adherence problems and thus design interventions to improve drug use.

ADR monitoring is needed because there is a large variation in genetic factors, dietary factors, disease patterns, environmental factors and drugs used. In India the nutritional status of patients are also different. Due to increased prevalence of certain diseases like tuberculosis, diabetes, hypertension results in the use of so many drugs concurrently and it may cause drug-drug interaction and leads to adverse effects. So the ADR monitoring may provide an actual data about the adverse effects and its relationship with the drugs, which are being used by the patients.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) plays a fundamental role in controlling inflammation and pain. NSAIDs are generally indicated for the symptomatic relief of the following conditions namely, rheumatoid arthritis, osteoarthritis, acute gout, dysmenorrhoea, metastatic bone pain, headache and migraine post-operative pain, mild to moderate pain due to inflammation, pyrexia, renal colic. NSAIDs are commonly used class of over the counter and prescription medications, and therefore, isolating an NSAIDs as the causative factor of a drug eruption can be a clinical challenge[1]. NSAIDs have been found to be the causative agent in 27% of all adverse drug eruptions.

The most common side-effects of NSAIDs are related to the gastrointestinal tract, peptic ulcer and its complications being the most serious. Many studies, of various designs and in many countries, of patients with peptic ulceration, haematemesis and melena, perforation, or death related to these outcomes have documented an increased risk in patients taking these drugs. Although most NSAIDs share the same basic mechanism of action, the inhibition of prostaglandin synthetase, there is little information to indicate whether different NSAIDs are associated with comparable risks of serious upper gastrointestinal toxicity[2,3]. Differences in the response to NSAIDs could be due to not only the different types of NSAIDs but also to intersubject variation[4] and varying drug utilization patterns among different NSAIDs[5]. Determining the comparative gastrointestinal toxicity of the different NSAIDs has proved to be difficult due to the large sample size required. Only five [6,7,8,9,10] out of 34 epidemiologic studies recently reviewed by the authors in a meta-analysis on NSAIDs and upper gastrointestinal toxicity presented any NSAID-specific risk ratio data on these complications, but these had little precision [11]. Two subsequent studies, a community based case-control study using billing data from Medicaid patients in the U.S.[12], and a hospital based case-control study in Spain[13], reported separate risk ratios for each individual NSAIDs. The thalidomide tragedy at the beginning of the 1960s led to greater focus on drug safety. Statutory requirements on documenting the efficacy and safety of new drugs were reinforced, and systems were established for reporting spontaneous adverse drug reactions (ADRs) after drugs had been marketed [14]. Despite rigid requirements for documenting the ADR profiles of new drugs, reporting of unexpected ADRs does occur after marketing of the drugs, resulting in drug recalls.

There are numerous examples of this: mibefradil was recalled in 1998 due to new information about potentially harmful interactions with other drugs [15], and sertindole was temporarily suspended from the market in December 1998 due to concerns over the risk of cardiac arrhythmia and sudden death[16]. Recently, the recall of rofecoxib from the market in 2004 due to new data about increased risk of cardiovascular problems attracted worldwide attention[17].

A review of the literature[18] has documented that spontaneous reports of ADRs are often the only form of evidence used as a basis for recalling drugs when serious ADR cases emerge after licensing of the drugs. Often, serious ADRs are reported anecdotally or as small case series, and this amount of evidence is often considered to provide convincing evidence of a causal association that does not need further verification[19]. Elderly patients may have many reasons to require NSAID therapy, such as osteoarthritis, but are also at an increased risk for heart failure as they age. Aspirin usage is not a factor in new onset heart failure. COX-2 inhibitors have also been studied, and rofecoxib, which has been withdrawn from the market, appears to have a higher incidence of heart failure than celecoxib, possibly indicating that the risk is not a class effect. Topical NSAIDs account for two-thirds of the most frequently prescribed NSAIDs in Germany[20]. Post marketing data could be a useful tool for understanding the ADR profile of drugs if reporting can be adequately monitored and verified. It is hoped that early evaluation of the clinically meaningful factors such as metabolism, pharmacogenetics, and effect of physiologic and patho-physiologic states on the clinical effect of a drug during drug development would significantly reduce the incidence and severity of post-marketing ADRs[21].

NSAIDs are associated with a number of adverse effects. These include effects on the kidney and exacerbating asthma in some people, but the most important adverse effect of NSAIDs and aspirin is that on gastrointestinal tract. The objective of the present study was to evaluate the drug utilization of the non-steroidal anti-inflammatory drugs in Outpatient Departments of Mjeedia Hospital and to ascertain the incidence and pattern of adverse drugs reactions (ADR) due to NSAIDs.

Materials and Methods

Study design
It was a prospective drug utilization study to assess the use of non-steroidal anti-inflammatory drugs (NSAIDs). The study was approved by Jamia Hamdard Institutional Review Board on 15th Feb. 2007.

Study Setting
The study was carried out in the In Patients Department (IPD) and orthopedic OPD, Majeedia Hospital, Jamia Hamdard, New Delhi.

Duration of the study
It was a short study for 4 months (February to May, 2007)

Study population
About 300 OPD and IPD patients using NSAIDs were randomly selected

Inclusion criteria
All the patients irrespective of the age and sex including pregnant and lactating women attending OPD and IPD were included in the study. All the patients who were prescribed at least one NSAID and those already receiving non-steroidal anti inflammatory drugs before the start of the study were also included in the study.

Exclusion criteria
The patients who were not treated with NSAIDs, mentally retarded, unconscious and patients unable to respond to verbal questions were excluded from the study

Sources of the data collection
Patients were interviewed after informed consent was obtained. Interviews were conducted by using structured questionnaire (Open Question method). Patients' prescriptions were also reviewed for analyzing the drug utilization pattern and adverse drug events. Morisky Medication adherence score was to use determine compliance by totaling the number of "NO" answer to the 4 questions of non-adherence;

1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicine?
3. When you feel better, do you sometimes stop your medicine?
4. Sometimes if you feel worse when you take medicine, do you stop taking it?

A higher score on the scale of 0-4 indicates better adherence to treatment.

Data collection
The following parameters were recorded:

1. Sex and age distribution of patients using NSAIDs.
2. Types of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed.
3. Route of administration of NSAIDs
4. Average number of NSAIDs per prescription.
5. Monotherapy and combination therapy
6. Patient compliance scores
7. ADRs associated with prescribed NSAIDs.

Results

Gender distribution in study population
Over a period of 4 months, 300 NSAID users were selected for the study. Among the 300 study subjects, 159 (53%) were males and 141 (47%) were females (Table1).

Age distribution of NSAIDs users
Among the 300 NSAID users, it was observed that maximum number, 78 (26%) were in the age range of 31 to 40 years followed by 66 (22%) patients were in the age range of 41 to 50 years. (Table1, Fig. 1)

Types of non-steroidal anti-inflammatory drugs prescribed
During the study it was observed that aceclofenac was the most commonly prescribed drug (31%) followed ibuprofen (15.64%), diclofenac (13.86%) and nimesulide (13%). Details of the drugs utilization pattern are given in Table 2.

Route of administration of NSAIDs
Overall 433 (87.74%) of NSAIDs were taken by oral route and 60 (11.88%) were given as topical therapy, whereas 12 (2.38%) medicines were administered by parenteral route.

Number of NSAIDs prescribed per prescription
Average no. of NSAIDs prescribed per prescription was found to be 1.68%.

Monotherapy and combination NSAID therapy
Prescription of NSAIDs users showed that a total of 167 patients (55.67%) received NSAIDs as monotherapy whereas 133 patients (44.33%) were on multiple drug therapy. Among those who were treated with drug combination, 40.33% received two NSAIDs, 4% patients received 3 drug regimen.Aceclofenac (29%) was the most commonly prescribed drug as monotherapy

followed by ibuprofen (17.34%) and diclofenac (9.33%) .Among the combination therapy aceclofenac + paracetamol was the most frequently prescribed combo (34.33%), followed ibuprofen + paracetamol (6%) and diclofenac + paracetamol (4%).

Patient compliance

Patient compliance was determined by Morisky medication adherence score method. Patient compliance was poor. Only 34% of patients were good in compliance and followed the physician and pharmacist instructions while using NSAIDs (Table 3).

Adverse drug reaction monitoring in NSAID users

Adverse drug reaction monitoring was also carried out simultaneously with drug utilization study in the study population. A total of 24 ADRs were reported in 300 patients. Among 24 patients who presented with ADRs, 9 (3%) patients were males and 15 (5%), were females. Seventeen ADRs were reported in patients receiving combination therapy against 7 in those on monotherapy.

Diclofenac (n=8) was found to be the commonest drug associated with ADRs inclusive of single and combination therapy, followed by nimesulide (n=6), ibuprofen (n=5), paracetamol (n=3).

Majority of ADRs (83.5%) observed were mild, which were well tolerated by the patients for e.g. abdominal pain, skin rashes, gastric discomfort, vomiting, constipation etc. A lesser number (12.5%) of ADRs were classified as moderate e.g. loose motion, pruritus, gastric ulceration and bleeding. Only 4.16% cases of severe ADRs were observed. The offending drug was withdrawn and/or specific/symptomatic treatment was given which reversed symptoms (Table 4).

Conclusion

The observations of the present drug utilization and pharmacovigilance study indicate that the average no. of non-steroidal anti-inflammatory drugs per prescription was optimum with aceclofenac being the most frequently prescribed drug followed by diclofenac. Oral route was predominantly preferred mode of administration of NSAIDs.

Twenty four 24 (8%) cases of ADRs were reported in a pool of 300 patients in the 4 month study period. The incidence of ADRs on long term use of NSAIDs has been reported to be high in previous studies and hence long term pharmacovigilance studies are needed in order to formulate strategies to minimize prevent incidence of ADRs. Patient compliance was found to be poor in the study subjects which could be improved with proper patient counseling by clinical pharmacists.

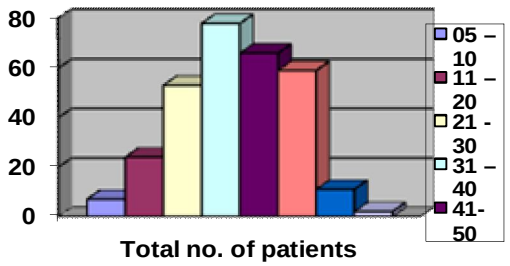

Fig. 1: Age distribution of NSAID users

Table 1: Age and gender distribution of NSAIDs users

Age	Male	Male%	Female	Female%	Total no. of patients	Total %age of patients
05 – 10	14	1.33	03	1.00	07	2.33
11 – 20	14	4.67	10	3.33	24	8.00
21 -30	28	9.33	25	8.33	53	17.67
31 – 40	43	14.33	35	11.67	78	26.00
41-50	34	11.33	32	10.67	66	22.00

51-60	30	10.00	29	9.67	59	19.67
61-70	05	1.67	06	2.00	11	3.67
71-80	01	0.33	01	0.33	02	0.67
Total	159*	53.00	141*	47.00	300	100.00
Mean Age = 37.225; P < 0.0001; S.D= 14.426 *p value is < 0.0001 (highly significant).						

Table 2: Types of non-steroidal anti-inflammatory drugs prescribed

Class	Drug	No. of NSAIDs prescription	%age prescription.
Aryl Acetic acid	Aceclofenac	156	31.07%
	Diclofenac	70	13.945
	Total	226	44.75%
Propionic Acid derivatives	Ibuprofen	79	15.64%
Preferential COX-2 inhibitor	Nimesulide	67	13.27
Combination	Aceclofenac + Paracetamol	103	20.39%
	Ibuprofen + Paracetamol	18	3.56%
	Diclofenac + Paracetamol	12	2.37%
Grand Total		505	100%

Table 3: Assessment of patient compliance

No. of Patients	Morisky score	Percentage of compliance
54	4	18
48	3	16
96	2	32
102	1	34

Table 4: ADRs, suspected drug and intervention

Class	Drug	Adverse reaction	No. of ADRs	Intervention
Aryl Acetic acid Derivative	Diclofenac	Abdominal pain, G.I.T. irritations	8	Mucosa protecting agent was used
	Aceclofenac	Pruritus	2	Therapy stopped
Propionic Acid derivatives	Ibuprofen	Gastric discomfort, Vomiting	5	Dose reduced
Preferential COX-2 inhibitor	Nimesulide	Loose motion, Hepatotoxicity	6	Therapy stopped
Paraaminophenol derivative	Paracetamol	Skin rashes.	3	Therapy stopped
Total			**24**	

REFERENCES

1. Alanko K, Stubb S and Kauppinen K. Cutaneous drug reactions: clinical types and causative agents. Acta Derm Venereol. 1989;69:223-226.
2. Avorn J. Reporting Drug Side Effects: Signals and Noise (ed.) JAMA. 1990; 263(13):1823.
3. Caruso I and Bianchi Porro G. Gastroscopic evaluation of anti-inflammatory agents.Br Med J. 1980;280:75-78.
4. Day RO and Brooks PM. Variations in response to non-steroidal anti-inflammatory Drugs. Br J Clin Pharmac.1987;23:655-658.
5. Pullar T and Wright V. Pattern of non-steroidal anti-inflammatory drug prescribing in a teaching hospital rheumatology unit. Proceedings of the BPS, 12-14 July, 1989;750.
6. Beard K, Walker AM, Perera D and Jick H. Non-steroidal anti-inflammatory drugs and hospitalization for gastroesophageal bleeding in the elderly. Arch Int Med. 1987; 147:1621-23.
7. Guess HA, West R, Strand LM, Helston D, Lydick EG, Bergman U and Wolski K. Fatal upper gastrointestinal hemorrhage or perforation among users and nonusers of anti-inflammatory drugs in Saskatchewan, Canada 1983. J Clin Epidemiol. 1988;41(1):35-45.
8. Sommerville K, Faulkner G and Langman M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. Lancet. 1986;462-64.
9. Amstrong CP. Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulcerations. Gut. 1987;28:527-32.
10. Caradoc-Davies TH. Non-steroidal anti-inflammatory drugs, arthritis, and

gastrointestinal bleeding in elderly inpatients. Age and Ageing 1984;13:295-298.
11. Bollini P, García Rodríguez LA, Pérez Gutthann S and Walker AM. The impact of research quality and study design on epidemiologic estimates of the effect of NSAIDs on upper gastrointestinal pathology. Arch Int Med, in press.
12. Griffin MR, Piper JM, Daugherty JR, Snowden M and Ray WA. Non-steroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Int Med.1991;114:257-63.
13. Laporte JR, Carné X, Vidal X, Moreno V and Juan J. Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal anti-inflammatory drugs. Lancet.1991; 337:85-89.
14. Dukes MNG. The Laws and Ethics of the Pharmaceutical Industry. 1. Amsterdam: Elsevier; 2006.
15. So Relle R. Withdrawal of Posicor from market. Circulation. 1998;98:831–832.
16. EMEA. Sertindole. [13 October 2006]. http://www.emea.en.int/pdfs/human/referral/sertindole/2852002en.pdf.
17. Vioxx HR. The implosion of Merck, and the aftershocks at the FDA. Lancet 2004; 364:1995-1996.
18. Loke Y, Price D, Derry S and Aronson JK. Case reports of suspected adverse drug reactions – systematic literature survey of follow-up. BMJ. 2006;332:335–339.
19. Aronson JK and Hauben M. Anecdotes that provide definitive evidence. BMJ. 2006; 333:1267–1269.
20. Carter RS, Ebner D, Brenner D and Bruppacher R. Journal of clinical epidemiology. 1997;50(2): 217-218.
21. Ajavi FO, Sun H and Perry J. J Clin Pharmac. 2000;40(10):1093-1101.