ORIGINAL RESEARCH PAPER | Pharma | Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

Drug Utilization Pattern of NSAIDs in Out Patient Department of Orthopedics of A Tertiary Care Hospital

KEYWORDS: Non Steroid Anti Inflammatory Drugs (NSAIDs), Cyclo- Oxygenase Enzyme, Drug utilization, Concomitant drugs.

Akshay Sadhotra
PG Resident, Department of Pharmacology, MMIMSR, MMU, Mullana, Ambala, Haryana.

*** Anshu Gupta**
Associate Professor, Department of harmacology, MMIMSR, MMU, Mullana, Ambala, Haryana.

Rani Walia
HOD, Department of Pharmacology, MMIMSR, MMU Mullana, Ambala, Haryana.

HS Sandhu
Professor, Department of Orthopedics, MMIMSR, MMU Mullana, Ambala, Haryana

ABSTRACT *Non Steroid Anti Inflammatory Drugs prevent the production of prostanoids by inhibiting the enzyme cyclo-oxygenase (COX) in the arachidonic acid pathway, with proven efficacy as analgesics, antipyretics & anti-inflammatory agents. Study was planned to analyse the drug utilization pattern of NSAIDs in OPD of Orthopedics.*
***Methods**: A prospective observational study was planned on 200 patients after obtaining IEC approval visiting Orthopedics OPD. The drug utilization pattern was recorded on proforma. Assessment of pain relief was done by using 11 point numeric metric scale (Visual Analogue Scale).*
***Observations**: The total number of males & females were 92 (46 %) & 108 (54 %) respectively. Out of a total of 200 patients, 177 (88.5 %) patients were in the 18-64 years age group (non-elderly) with the rest 23 (11.5%) present in the > 65 years age category (elderly). A total of 200 prescriptions after analysis showed that out of 200 patients, 98 % were on non selective NSAIDs & 2 % on preferential & selective NSAIDs. Aceclofenac alone or with Paracetamol is the most common prescribed drugs.*
***Conclusions**: COX-1 inhibitors NSAIDs are the most common drugs used among all the NSAIDs.*

Introduction

Anti-inflammatory drugs, historically were derived from the extracts of plants which contained salicylates, notably willow tree of genus salix which were known for their medicinal value in cases of pain, fever & inflammation.[1] Acetylsalicylic acid (ASA) or Aspirin was developed in 1897 by Felix Hoffman once it was found around the 19th century that salicylates are the active components of Willow spp.[2] Sir John Vane demonstrated that inhibition of the production of prostaglandins is the mechanism behind the effect of the non-steroidal anti-inflammatory drugs .[1] NSAIDs are a class of drugs which are one of the most frequently used drugs throughout the world with proven efficacy as analgesics, antipyretics & anti-inflammatory agents. These heterogeneous class of drugs include aspirin along with other non-selective & selective enzymatic inhibitors of cyclo-oxygenase enzyme.[3]

NSAIDs are the recommended therapy for rheumatological disorders like non-inflammatory & inflammatory degenerative diseases of the joint.[4,5] They are also frequently used treatment for acute pain after fracture or postoperative period after fracture fixation & other muscular-skeletal pain.[6]

Aspirin in-addition because of its action on decreasing the platelet aggregation is widely used prophylactically for the prevention of thromboembolic events in low dose (75-150mg).[7]

NSAIDs prevent the production of prostanoids by inhibiting the enzyme cyclo-oxygenase (COX) in the arachidonic acid pathway The inhibiting effect of NSAIDs on type 2 COX enzyme is the reason for the anti-inflammatory effect brought about by these drugs whereas the inhibition of type 1 COX leads to undesired side effects like gastritis & gastrointestinal erosions which is a major limitation of use of NSAIDs clinically.[5] Use of selective inhibitors of type 2 COX like celecoxib produces the same analgesic & anti-inflammatory effects but with reduced gastrointestinal (GI) toxicity & platelet abnormalities.[6] For this reason they were used widely for various orthopedic conditions like arthritis & inflammatory disorders but recently questions have been raised regarding the cardiovascular safety of this class of drugs & thus their long term use continuously in the elderly.[8]There is sufficient proof that indicates an increase in the risk of heart attack, thrombosis, and stroke.

Conventional NSAIDs are regarded to have the most damaging effect on the gastrointestinal mucosa which is dose dependent & drugs with longer half-life exhibit more tendencies for mucosal damage. This is confirmed by variability shown among individual NSAIDs which are used clinically in a recent 'Systematic Review and Meta-Analysis of Observational Studies' project (the SOS Project).[9] The present study is done to determine the drug utilization pattern of NSAIDs & identify ADRs of NSAIDs in patients attending the orthopedic out-patient department of a tertiary Care Hospital so that the pattern of NSAID use in our institution is known which will to an extent provide the usage pattern in the north India.

Methods

Study Design

A prospective observational study was conducted on patients attending the orthopedic department of MMIMSR (Mullana, Ambala) for drug utilization pattern and ADRs of NSAIDS after obtaining the approval of the Institutional Ethics Committee. The sample size taken in the study was 200 patients (assuming an error of margin of 7.5%, the effective sample size[10] came to be 171).

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

The study was conducted by Department of Pharmacology in association with Department of Orthopedics. All the concerned specialists in the orthopedic department were informed about the aim of the study to seek their cooperation and were assured of full confidentiality regarding the patient and treatment information.

Eligible patients were enrolled in the study after fully informing them about the study details and obtaining their written consent. Patient Information regarding demographic data, medical history, prescribed treatment details (drug name, dose and frequency, dosage form etc.) and diagnosis were obtained on designated proforma.

Examination and Assessment of Patients
Assessment of pain relief was done by using 11 point numeric metric scale (Visual Analogue Scale). It is an 11-point numeric metric scale (NRS 11) with 0 representing one pain extreme (e.g. "no pain") and 10 representing the other pain extreme ("worst possible pain"). It is 10 cm in length..Depending on the numeric scale, pain is categorized as no pain (0), mild pain (1-3), moderate pain (4-6), severe pain (7-10).[11]

Appropriate clinical examination & baseline (haemogram, LFT, RFT etc.) investigations were done on Day 0. Follow-up examination was done on 3rd, 7th and 10th day for pain relief and identification of ADRs. Data was collected and analysed using statistical software SPSS version 20.

Observations:
The total number of males & females were 92 (46 %) & 108 (54 %) respectively. Out of a total of 200 patients, 177 (88.5 %) patients were in the 18-64 years age group (non-elderly) with the rest 23 (11.5%) present in the > 65 years age category (elderly). A total of 200 prescriptions after analysis showed that out of 200 patients, 98 % were on non selective NSAIDs & 2 % on preferential & selective NSAIDs. The most common NSAID used was aceclofenac alone or aceclofenac-paracetamol fixed dose combination. It was used in 161 (80.5 %) patients followed by diclofenac in 21 (11 %) patients, indomethacin in 10 (5 %) patients, etoricoxib & ibuprofen 3 each (1.5 %) & meloxicam in 1 (0.5 %) patient. The prescribed doses and the frequency of doses is shown in **Table 1.**

Table 1: Drug Utilization Pattern of NSAIDs

Name of Drug	Prescibed Dose (mg)	Frequency (per day)	No. of Patients (%)
Aceclofenac/ Aceclo-PCM	100/100-325	twice	161 (80.5)
Diclofenac	50	twice	22 (11)
Etoricoxib	90/120	twice	3 (1.5)
Ibuprofen	400/800	thrice	3 (1.5)
Indomethacin	50	twice	10 (5)
Meloxicam	7.5	twice	1 (0.5)
Total			200 (100)

The **most common diagnosis** for which the patients were prescribed NSAIDs were low back ache (LBA-28 %), OA (19.5 %), trauma (9.5 %), pain neck (7 %). The other diagnosis were pain limbs (because of early osteoarthritic changes), bursitis, tendonitis, inflammatory conditions, RA, PIVD & miscellaneous.

The **concomitant drugs** (alone or as FDC) most frequently used were calcium-Vit D (51 %), thiocolchicide (41.5 % - used as FDC with aceclofenac), pantoprazole-domperidone (34 %), gabapentin-methylcobalamin (28.5 %), diacerin-glucosamine (25.5 %), trypsin-bromelain-rutopside (17.5 %), collagen peptide (9.5 %), deflazacort (9 %) & diclofenac gel (8.5 %). The findings are tabulated in **Table 2**.

Table 2: Concomitant Medication

Concomitant medication	No. of Patients	% age of Patients
Calcium-Vit D	102	51
Thiocolchicide	83	41.5
Pantoprazole-Domperidone	68	34
Gabapentin- Methylcobalamin	57	28.5
Diacerin-Glucosamine	51	25.5
Trypsin-bromelain-rutopside	35	17.5
Collagen peptide	19	9.5
Deflazacort	18	9
Diclofenac gel	17	8.5

Proton pump inhibitors (PPIs) were given prophylactically to only those patients who are eligible as per NICE guidelines, rest were given as rescue drugs in the event of development of gastric ADR.

The number of patients using less than 5 fixed dose combinations (FDCs) was 53 (26.5 %) & those using > 5 were 147 (73.5 %).**Table 3**

Table 3: Number of FDCs Used By Patients

No. of FDCs	No. of Patients	% age
<5	53	26.5
≥5	147	73.5
Total	200	100

The total number of patients having **co-morbid conditions** were 20 with 13 (65 %) having 1 co-morbid condition & 7 (35 %) having 2 or more.

Assessment of pain relief was done by using 11 point numeric metric scale (Visual Analogue Scale). After comparing the pre-treatment (day 0 **Mean ± SD;** 5.17 ± 1.23) & post-treatment (at Day 10 of follow-up **Mean ± SD;** 0.95 ± 0.87), the difference in the mean of VAS scores (Wilcoxson sign rank test; $p < 0.001$) was statistically significant.

ADRs & System Involved
A total of 28 (14 %) ADRs were reported from 200 patients enrolled in the study of which 20 (71.4 %) involved GIT system, 5 (17.8 %) involved skin & remaining 3 (10.8 %) were of renal system. Though after diclofenac causing 10 (45.6 %) ADRs, aceclofenac/acelofenac-PCM combination apparently caused the maximum number of 9 ADRs followed by indomethacin causing 5, etoricoxib 2, ibuprofen & meloxicam 1 each.

Discussion
Out of 200 patients in the present study, 98 % were prescribed non selective- NSAIDs & 2 % were on preferential & selective NSAIDs. ***Singh V et al 2014*** reported coxib use of 3.1 % (60) out of a total of 1908 NSAIDs used.12 ***Greenberg et al 2009*** also reported a decrease in the utilisation of COX-2 inhibitors in North America after the withdrawal of rofecoxib & valdecoxib from U.S markets. They reported a decline from 55.1 % in 2003 to 29.2 % in 2005 ($p < 0.001$) just after the withdrawal in 2004.13 Other similar studies on NSAIDs also have reported a decline in use of selective NSAIDs after the withdrawal of rofecoxib & valdecoxib because of CVS ADRs.8, 14, 15, 16 Selective inhibitors of type 2 COX enzyme were synthesised with the purpose of reducing the gastric toxic effects while maintaining the anti-inflammatory activity & their advent in the

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

market was seen as a significant breakthrough in achieving the reduction in NSAID-gastropathy resulting in marked increase in their sales from 1999 till 2004. However because of the adverse CVS event profile & greater cost as compared to nonselective-NSAIDs followed by rofecoxib & valdecoxib withdrawal in 2004, there was decline in their use.17,18

Aceclofenac alone (26 %) or in fixed dose combination with thiocolchicide (41.5 %) or paracetamol (14 %) was seen to be the most preferred NSAID prescribed (total-80.5 %), followed by diclofenac (11 %), indomethacin (5 %), etoricoxib & ibuprofen (1.5 % each) & meloxicam (0.5 %). FDC of NSAIDs was prescribed in 55.5 % as compared to mono-therapy in 44.5 % of patients. LBA was the most common diagnosis for prescription (28 %) followed by OA (19.5 %). ***Singh V et al 2014*** also reported diclofenac & aceclofenac as the two most commonly prescribed NSAIDs (46.5 %) in their study though in their study diclofenac was preferred over aceclofenac. Oral route was the preferred route in most prescriptions (96.4 %). FDCs with NSAIDs or other drugs (57.2 %) were more commonly prescribed than mono-therapy (42.8 %).73 After NSAIDs, the other most common prescribed drugs were gastro-protective drugs, multivitamins & skeletal muscle relaxants. In the present study also the most common concomitant drug prescribed was calcium-Vit D FDC & thioclohicide-skeletal muscle relaxant with anti-inflammatory action (51 % & 41.5 % respectively), followed by FDC of pantaprazole-domperidone (34 %), gabapentin- methylcobalamin (28.5 %) & diacerin-glucosamine (25.5 %).

7 The mean number of drugs in each patient (FDC) in the present study was 3.12 + 0.86 (mean + SD) and as individual drugs was 5.32 + 1.71. Though this was higher as compared to seen in ***Singh V et al 2014*** (3.19), ***Rahman et al 2007*** (2.47-3.25), ***Gupta M et al 2005*** (3) but ***Nidhi et al 2015*** reported that the number of drugs varied from 2-14 with < than 5 in 14.5 %, > 5 in 71 % (poly-pharmacy) & > 10 (high poly-pharmacy) in 14.5 %.12, 18, 19, 20

. Pelletier Jean-Pierre et al 2016 emphasized that NSAIDs provide an effective as well as safe treatment for degenerative joint diseases & are the key drugs in these diseases. This is despite the association of GI & CVS ADRs since these drugs have individual differences in the risk of above events on comparison.21. Efficacy of NSAIDs as analgesics done by NRS scale has shown significant pain relief after 10 days of treatment.

Conclusions

In conclusion the present study has shown that NSAIDs continue to be the drug of choice as analgesics & anti-inflammatory agents for musculo-skeletal pain & degenerative joint diseases in outpatient department of orthopaedics. Non selective COX inhibitors are preferred over the selective COX 2 Inhibitors. These drugs are proven to be efficacious as analgesics & anti-inflammatory agents though they have to be used rationally to minimize their ADRs.

References

1. Pountos Ippokratis, Georgoul Theodor. Nonsteroidal anti-inflammatory drugs: Prostaglandins, indications and side effects. International Journal of Interferon, Cytokine and Mediator Research. 2011;3:19–27.
2. Rainsford KD. Anti-inflammatory drugs in the 21st century. Subcellular Biochemistry. 2007; 42:3-27.
3. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Research & Therapy (internet). 2013;15(Suppl 3):S3. doi:10.1186/ar4175. Accessed on 28.8.14.
4. Conaghan G Phillip. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatology international. 2012;32:1491–1502. doi:10.1007/s00296-011-2263. Accessed on 29.8.14.
5. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: A full in vitro analysis. Proceedings of the National Academy of Sciences of the United States of America. 1999; 96(13):7563-8.
6. Li K-H, Cheng L, Zhu Y, Deng G-B, Long H-T. Effects of a selective cyclooxygenase-2 inhibitor (celecoxib) on fracture healing in rats. Indian Journal of Orthopaedics. 2013; 47(4): 395-401.
7. Fabijanic D Kardum D, Banic M, Fabijanic A. Nonsteroidal-anti-inflammatory drugs and serious undesirable gastrointestinal effects. Lijec Vjesn. 2007 Jun-Jul; 129(6-7):205-13. Accessed on 9.9.14.
8. Kulkarni S K, Jain N K. Coxibs: The new super aspirins or unsafe pain killers?.Indian J Pharmacol 2005; 37: 86-9.
9. Castellsague J, Riera-Guardia N, Calingaert B, et al. Individual NSAIDs and Upper Gastrointestinal Complications: A Systematic Review and Meta-Analysis of Observational Studies (the SOS Project). Drug Safety. 2012; 35(12):1127-1146.
10. Naing.L. Medical Statistics: Practical issue in calculating the sample size for prevalence studies. Archives of Oro-facial Sciences. 2006; 1: 9-14.
11. Hawker GA et al. Measures of pathology and symptoms: Measures of adult pain. Arthritis Care & Research (American college of Rheumatology). 2011; Vol (S11): 240-52.
12. Singh V, Yadav P, Deolekar P.. Current trends of prescribing patterns of NSAIDs in an orthopaedic OPD in a teaching hospital. International Journal of Pharma and Bio Sciences. 2014 April; 5(2): 486 – 91.
13. Greenberg JD, Fisher MC, Kremer J, Chang H, Rosentein ED, Kishimoto M et al. The COX-2 inhibitor market withdrawals and prescribing patterns by rheumatologists in patients with gastrointestinal and cardiovascular risk. Clinical and Experimental Rheumatology 2009; 27:395-401.
14. Mukherjee D, Nissen SE, Topol EJ. Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors. JAMA. 2001;286(8):954-959. doi:10.1001/jama.286.8.954. Accessed on 3.2.15
15 Koffeman AR, Valkhoff VE, Jong GW, et al. Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints. Scandinavian Journal of Primary Health Care. 2014; 32(2): 90-8. doi:10.3109/02813432.2014.929810. Accessed on 6 Jan 2016.
16. M. Teeling, H. O'Connor, J. Feely, K. Bennett, What therapies have replaced rofecoxib in Ireland?. British Journal of Clinical Pharmacology.2007; 64(4): 536 – 41.
17. Cairns A John..The coxibs and traditional nonsteroidal anti-inflammatory drugs: A current perspective on cardiovascular risks. Canadian Journal of Cardiology 2007 Feb; 23(2): 125–31.
18. Gupta M, Malhotra S, Jain S, Aggarwal A, Pandhi P. Pattern of non-steroidal anti-inflammatory drugs in orthopaedic outpatient clinic of a North Indian tertiary hospital. Indian J Pharmacol, December 2005; 37(6): 404-405.
19. Rahman MS, Begum ZA, Samad MK. Prescribing pattern of non-steroidal anti-inflammatory drugs at outpatient departments of teaching hospitals. Bangladesh Journal of pharmacology 2007; 2: 1-6.
20. Patel Nidhi S, Shah RB, Buch JG. Drug utilization pattern of NSAIDs assessed with the anatomical therapeutic chemical classification/defined daily dose system in an orthopedic department. Drug & Therapy perspectives.2015 October; Volume 31 (10): 358-64.
21. Pelletier Jean-Pierre, Pelletier JM, Rannou F, Cooper C. Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Seminars in Arthritis and Rheumatism.2016; 45(4): 22-7