PATTERNS OF PRESCRIPTION AND ADVERSE DRUG REACTION PROFILE OF NON- STEROIDAL ANTI-INFLAMMATORY DRUGS AT ORTHOPEDIC OUT-PATIENTS DEPARTMENT

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ABSTRACT

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are the most prescribed drugs all over the world. These are used in the treatment of pain and inflammation. Systematic evaluation of prescription patterns and monitoring of adverse drug reactions is required to increase the therapeutic benefit and decrease the adverse effects of these drugs. An observational, cross-sectional study was conducted for 6 months from September 2021 to February 2022 in 300 patients prescribed least one NSAID to assess the prescription patterns and adverse drug reaction profile (ADR) of NSAIDs prescribed in the orthopedic outpatient department. Among enrolled patients 52% were female and 48% were male. The most common age group was 20-39. The average number of drugs per prescription was 2.89. A total of 868 drugs were prescribed, out of which 402 were NSAIDs (46.31%). Naproxen was the most prescribed agent (45.02%), followed by Diclofenac (17.17%). ADR was reported in 12% of patients. Most of the ADRs were due to Naproxen (72.18%) followed by Ibuprofen (16.66%). The gastrointestinal system was involved in maximum patients and the most common ADR was abdominal pain. Most of the drugs were prescribed by brand name 95.18%. Naproxen was the most prescribed NSAID and responsible for most ADRs. There was a higher prevalence of irrational prescribing, polypharmacy, and underreporting of ADR. A strategy must be developed and implemented for prescribing and rational use of NSAIDs and monitoring their harmful effects.

KEYWORDS

Prescription pattern, adverse drug reaction, non-steroidal anti-inflammatory drugs, naproxen

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INTRODUCTION

A prescription is a written order of a registered medical practitioner, which is one of the most effective methods to assess and evaluate a physician's prescribing attitude and pharmacist's dispensing practice to increase therapeutic benefits and decrease the adverse effects.[1,2] Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common drugs prescribed around the globe.[3] Hence periodic evaluation of drug utilization patterns of NSAIDs is needed to enable suitable modification to maximize best therapeutic outcomes.

The NSAIDs are classified into several chemical classes. This chemical diversity yields a broad range of pharmacokinetic characteristics. Although there are many differences in the kinetic of NSAIDs, they have some general properties in common. Most of the NSAIDs are extremely metabolized, some by phase I followed by phase II mechanism and others by direct glucuronidation (phase II) alone.[4]

The effect of NSAIDs on two unique isoforms of cyclooxygenase (designated COX-1 and COX-2) has led to a bigger understanding of the mechanism of action of NSAIDs and has also explained their toxicity.[5] NSAIDs are utilized in the management of disorders associated with pain and inflammation. They have multiple indications for use, ranging from treatment of acute pain to more chronic conditions such as rheumatoid arthritis (RA), osteoarthritis (OA), low back pain (LBP).[4]

Conventional NSAIDs are nonselective, which bind and inhibit both the isoforms of cyclooxygenase, but cyclooxygenase-1 (COX-1) is inhibited more avidly than cyclooxygenase-2 (COX-2).[6] Inhibition of COX-1 is responsible for the ADRs and that of COX-2 for therapeutic effects. This has resulted in the introduction of the COX-2 selective drugs.[7] However, cardiovascular toxicity is more with selective COX-2 inhibitors.[8]

Adverse drug reactions (ADRs) are considered as the 4th to 6th leading causes of death among hospitalized patients. These are associated with significant morbidity, mortality, permanent disability and is a huge economic burden to the patients due to prolonged hospitalization.[9] In medical practice, there is growing concern regarding the irrational prescription pattern and use of drugs.[2] Periodic evaluation of drug utilization patterns needs to be done to enable suitable adjustment in the prescription of drugs to increase the therapeutic benefit and decrease the ADRs.

The study of prescribing patterns seeks to monitor, evaluate, and if necessary, suggest modifications in the prescribing behavior of medical practitioners to make medical care rational and cost-effective.[10] With this background, the present study was planned to investigate the prescription patterns and ADR profiles of NSAIDs prescribed in the orthopedic outpatient department of Karnali Academy of Health Sciences, Jumla, Nepal.

MATERIALS AND METHODS

An observational cross-sectional study was conducted for 6 months in 300 patients taking NSAIDs for the treatment of orthopedic problems from September 2021 to February 2022 after the approval of the Institutional Ethics Committee at Karnali Academy of Health Sciences. Sample size was calculated using the formula: Sample Size formula= Z2pq/d2 (Z=1.96 at 95%CI, p= 73.3% reference to a previous research article, q= 1-p, d= 5%.[11] Patients who were prescribed NSAIDs including surgical postoperative patients and routine follow-up attending orthopedic OPD were included, and patients who were prescribed NSAIDs in Casualty, ICU, other than in orthopedic OPD and wards were excluded.

Written informed consent was taken from all patients visiting the orthopedic OPD who were willing to participate in the study before their prescriptions were analyzed. The case sheet of patients was analyzed for the prescription pattern using WHO core drug use indicators. Simultaneously development of any ADR to a drug prescribed was observed with the present visit and a follow-up visit after 3 days. ADR was analyzed using the WHO-UMC causality assessment scale and Hartwig's Severity Assessment Scale. The data was entered in MS Excel. Data were transferred to SPSS-20 and were analysed using descriptive statistics as Mean ± SD and percentages.

RESULTS

Out of 300 prescriptions, 156 (52.0%) were female and 144 (48.0%) were male. The most common age group was 20-39 (51.0%). In this present study average number of drugs per prescription was 2.89 with a mean duration of 4 days.

Total 868 drugs were prescribed, out of which 402 were NSAIDs (46.3%), 258 (29.7%) were gastroprotective agents followed by 193 (22.2%)

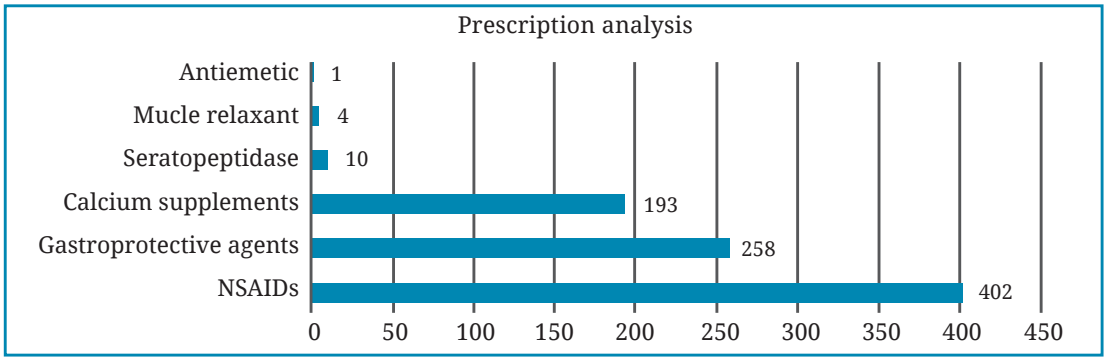

Fig. 1: Prescription patterns of drugs used in orthopedic OPD (n=868).

Table 1: Patterns of NSAIDs used in Orthopedics Outpatient Departments.

Name of Drug	No of drugs	% (out of 402 NSAIDs)	% (out of 300 prescription)
Tablet Naproxen	181	45.02	60.33
Tablet Aceclofenac	68	16.92	22.66
Gel Diclofenac	63	15.68	21.0
Tablet Diclofenac	6	1.49	2.0
Tablet Ibuprofen	39	9.7	13.0
Tablet Acetaminophen	39	9.7	13.0
Tablet Indomethacin	6	1.49	2.0
Total	**402**	**100**	

calcium supplements. Out of 300 prescriptions gastroprotective agents were prescribed in 86% (Fig. 1).

Table 2: Prescription analysis according to the WHO core drug use indicators.

Parameters	Number
Total no of prescriptions	300
Total number of drugs	868
Average number of drugs per prescription	2.89
Drugs from essential drug list	17.51%
Drugs prescribed by generic name	4.82%
Drugs prescribed by brand name	95.18%
Drugs administered by oral route	92.74%
Drugs administered by parenteral route	7.26%

Traumatic injury, musculoskeletal pain were common indications for the use of NSAIDs. Most of the drugs were prescribed by the oral route (92.74%).

Naproxen was the most prescribed agent among NSAIDs (45.02%), followed by diclofenac (17.17%) (Table 1).

Most of the drugs were prescribed by brand name (95.18%) and drugs prescribed from the essential drug list of Nepal[21] were 17.51%. Table 2 shows results of prescription analysis according to WHO core drug use indicators.[14]

Out of 300 patients 36 patients were reported ADRs showing a prevalence rate of 12%. Naproxen was found to be the commonest drug associated with ADR inclusive of single and combination therapy, followed by ibuprofen. Abdominal pain was the most common ADR reported with Naproxen followed by sedation.

Out of 36 ADRs 10 were certain (27.77%), 7 were probable (19.44%), 15 were possible (41.66%) and 4 were Doubtful after casualty assessment according to the WHO-UMC

Table 3: ADR profile of NSAIDs prescribed (n=402)

Drug	Adverse drug reaction	System involved	Number (%)
Naproxen	Abdominal pain	Gastrointestinal	14 (38.88)
	Vomiting	Gastrointestinal	3 (8.33)
	GI Bleeding	Gastrointestinal	1 (2.77)
	Diarrhea	Gastrointestinal	1 (2.77)
	Jaundice	Hepatobiliary	1 (2.77)
	Oliguria	Renal	1 (2.77)
	Sedation	CNS	4 (11.12)
	Headache	CNS	1 (2.77)
Ibuprofen	Abdominal pain	Gastrointestinal	1 (2.77)
	Rash, pruritus	Skin	5 (13.89)
Aceclofenac	Ologuria	Renal	1 (2.77)
Diclofenac	Rash, pruritus	Skin	1 (2.77)
Indomethacin	Headache	CNS	1 (2.77)
	Abdominal pain	Gastrointestinal	1 (2.77)
Total			36(100)

causality assessment method. Severity of ADRs was assessed by modified Hartwig and Siegel's scale for adverse drug reactions, 2 (5.55%) were severe, 7 (19.45%) were moderate and 29 (75%) were mild (Table 3).

DISCUSSION

Less studies have been conducted to determine the prescription pattern and ADR of NSAIDs in Nepal. To the best of our knowledge, there is no reliable report on the prescription pattern and adverse drug reaction of NSAIDs in Karnali province. This is the first prescription-based study that evaluates and analyzes the prescribing pattern and ADR of NSAIDs in the population of Karnali province.

The population most commonly attending outpatient department were young adults (21-39 yrs) Similar findings were also reported by Motgahre *et al.*[12] As KAHS is in rural areas of Nepal, many of the patients were farmers, laborers, by occupation, which could be the reason for the higher traumatic[13] orthopedic complaints in this age group. The average number of drugs per prescription was 2.89 which was similar to the study of El Mahalli who reported an average number of 2.4.[14] A high average number of drugs in our study might be due to financial incentives to prescribers to prescribe more, lack of therapeutic training of prescribers, or shortage of therapeutically correct drugs and trend of polypharmacy.[15]

Naproxen was (45.02%) the most commonly used NSAIDs in our study while a study conducted by Motgare *et al*[12] reported Ibuprofen (53.58%) and Gywali *et al.*[11] reported Aceclofenac (73.3%) as the most frequently prescribed NSAIDs. COX-2 selective inhibitors were developed with the assumption of a better safety profile (renal and GI) than nonselective NSAIDs that became very popular a few years back. However, the results of the present study point towards the reversal of trends back to the use of conventional non-steroidal anti-inflammatory drugs (NSAIDs). This shift might have come with the recent reported CVS toxicity with the use of selective COX-2 inhibitors.[16] Aceclofenac was the second most common NSAIDs prescribed by oral route. The use of Aceclofenac over Diclofenac might have come because Aceclofenac was found more superior to Diclofenac in terms of epigastric discomfort, dyspepsia, abdominal discomfort, and compliance was better with Aceclofenac.[17] Diclofenac gel topical was prescribed more in comparison to oral diclofenac.

Gastroprotective agents (Proton pump inhibitors) were the most commonly used adjuvant drugs in our study. It might be to avoid gastrointestinal ADRs associated with the use of NSAIDs. Proton pump inhibitors provide potent and long-lasting effects by inhibiting gastric acid secretion and help in healing NSAIDs related ulcers.[18]

Adverse drug reactions were reported in 36 patients showing a prevalence rate of 12%.

Maximum ADRs were due to Naproxen (72.18%) followed by Ibuprofen (16.66%). Our study is in contradiction with a study by Motgahre *et al*[12] who reported maximum ADRs with Ibuprofen (66%) followed by Diclofenac (33.33). This might be because of more prescriptions of naproxen in our study. The gastrointestinal system was involved in maximum patients and the most common ADR was abdominal pain. This could be because Naproxen inhibits both the constitutive COX-1 and the inducible COX-2 which causes decreased synthesis of COX-1 dependent cytoprotective prostaglandin in the stomach.[19,20]

We found that oral administration (92.74%) was the most common route of administration. This could be explained by the fact that the oral administration route is convenient, easy to use, safe, acceptable, and the cheapest available route. The majority of the prescription drugs were prescribed by brand name 95.18%. This signifies the need for educational programs on proper prescribing habits for doctors at all levels.

In conclusion, Naproxen was the most prescribed NSAID and responsible for most ADR. Gastrointestinal ADR was most frequently reported. Concomitant medication with gastroprotective agents (Proton pump inhibitor) was high. There was a higher prevalence of irrational prescribing, polypharmacy, and underreporting of ADRs. Pharmacovigilance programs should be promoted which is highly effective in increasing the reporting of ADRs as well as helping to identify infrequent adverse drug reactions caused by drugs. Thus, a strategy must be developed and implemented for prescription, and rational use of medications which includes continuing medical education regarding the potential risks of NSAIDs, the importance of their appropriate and rational use, and the necessity of appropriate prescription writing regarding both content and indication is noticeable.

Recommendations: Monitoring of prescription patterns and ADRs is an ongoing, ceaseless, and continuing process. Identifying the adverse drug events, recording them meticulously, and reporting them to the concerned authority is a valuable task in the medical profession. This practice will prove to be very valuable in making drug therapy safer and more rational. This study has paved the way to carry out further studies on a large population in the future. The institutional policy can be tailored on the prescription of NSAIDs to achieve a superior therapeutic outcome. Over and injudicious use of antibiotics should be discouraged.

Limitations of the study: The study was conducted on a limited number of patients and in a short period.

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