J. Pharm. Res. 2026;25(2):112-115

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

ORIGINAL ARTICLE

Adverse Drug Reactions of Non-Steroidal Anti-Inflammatory Drugs in a Tertiary Care Hospital in Kerala

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ARTICLE INFO

Article history:
Received 29-03-2026
Accepted 04-05-2026
Published 03-06-2026

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https://doi.org/10.18579/jopcr/v25.i2.67

ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most prescribed drugs in modern medicine. NSAIDs are very effective in decreasing the pain, inflammation and many patients world-wide have found relief in their use. However, they cause various side effects including cutaneous, gastrointestinal (GI) disorders (from minor dyspepsia through to major ulcers, bleeding and perforation), kidney effects and cardiovascular effects. Objective of the study is to study the pattern of Adverse Drug Reactions (ADRs) of NSAIDs in a tertiary care hospital. This was an observational study done in the Dept. of Pharmacology, Government T.D. Medical College, Alappuzha over a period of one year (July 2014- 2015). As a part of pharmacovigilance programme, all ADRs were collected in CDSCO forms and retrospective data was entered from the ADR forms. A total of 255 ADRs were identified during a one-year period, of which 39 (15.29%) cases were due to the use of NSAIDs. The age group was 31-40 years. Males were 35.9% and females were 64.1% with M:F ratio 1:1.8. The drugs involved in ADRs were Diclofenac (38.5%), Paracetamol (30.8%), Aspirin (15.3%), Ibuprofen (5.1%), Piroxicam (2.6%), Ketorolac (2.6%), Indomethacin (2.6%) and Nimesulide (2.6%). Skin was the most commonly affected organ system (71.8%), followed by GIT (15.3%), Renal (7.7%), Respiratory (7.7%) and CNS (5.1%). Causality assessment showed that 71.8% ADRs were possible and 28.2% were probable according to Naranjo's scale. Severity assessment using the Modified Hartwig and Siegel Scale showed that 76.9% reactions were mild, 15.4% were moderate and 7.7% were severe, out of which one case was reported with Stevens-Johnson Syndrome (SJS). The causative drugs were stopped, and the patients were managed conservatively. No case fatalities were reported. Since ADRs due to NSAIDs may vary from self- limiting rash to severe life-threatening condition, the prescribing clinicians should be aware of the toxic potential of drugs and be vigilant in the spontaneous reporting the ADRs.

Keywords: Adverse Drug Reactions, Non-Steroidal Anti-inflammatory Drugs, pharmacovigilance, Naranjo's scale, Causality assessment, Severity assessment

INTRODUCTION

The WHO defines an Adverse drug reaction (ADR) as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.' ADRs are one of the major causes of iatrogenic disease. Historically, there are various examples of patients having come to harm through the use of prescribed medicines. The thalidomide tragedy was one of the worst examples. In healthcare, today the risk of ADRs influences every decision to prescribe and ultimately to take a medicine[1]. ADRs can cause negative patient outcomes, increase healthcare utilization, and contribute to rising healthcare costs[2]. We used Naranjo's causality algorithm to

determine the likelihood of whether an ADR was actually due to drug identified by the clinical event monitor, rather than the result of other factors[3]. Causality assessment is the method by which the extent of the relation between a drug and a suspected reaction is established.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed class of medications globally and they account for approximately 5–10% of all medications prescribed each year[4]. They are widely used to treat for their analgesic, anti-inflammatory, and antipyretic effects. These drugs possess different chemical and clinical profiles but essentially exert the same therapeutic properties and are associated with similar adverse effects. Gastrointestinal injuries, which range from dyspepsia to fatal upper gastrointestinal tract bleeding and perforation, are among the most common ADRs associated with the use of NSAIDs[5-7]. Other important ADRs include skin reactions, renal complications, allergic reactions, alteration in hepatic enzyme levels and, rarely, hepatopathies[8-11]. Hepatic ADRs associated with NSAIDs are quite uncommon when compared with other pharmacological classes such as antibiotics[10, 12]. Epidemiological studies have reported the incidence of acute liver injury to be 1–9 cases per 100 000 NSAID users[10, 11].

As recommended by the European Medicine Agency (EMA)[13], NSAIDs should be prescribed at the lowest effective dose and for the shortest time necessary to control symptoms. Differences in safety profiles between NSAIDs are a key discriminator for choosing between one NSAID and another, and not all NSAIDs have the same level of risk for inducing gastrointestinal ADRs. Gastrointestinal ADRs are important indicators when evaluating the overall risk profile of NSAIDs because of the risk of gastrointestinal bleeding and perforation. The elements of risk for gastrointestinal complications include age over 65 years, the use of corticosteroids, aspirin or anticoagulants, serious comorbidity or a history of upper gastrointestinal issues[14].

The first-generation NSAIDs block the activity of both COX-1 and COX-2 receptors. The second-generation drugs - the COX-2 inhibitors, were developed to reduce the incidence of gastrointestinal adverse effects by sparing the gastrointestinal protective functions of COX-1 while still inhibiting inflammation[15, 16]. However, it was beyond doubt, after their wide-spread use that their was associated with increase in cardiovascular risk, thereby resulting in their withdrawal from the market[17, 18]. A number of studies evaluating the gastrointestinal tolerability of COX-2 inhibitors did not demonstrate a lower risk of upper or lower gastrointestinal events[19]. This study was done to identify and quantify the ADRs resulting from the use of NSAIDS and to know the individual propensity of each drug towards causing ADRs as well as the type of ADR, which may help the treating clinicians in understanding the toxic profile of NSAIDs and the significance of promptly reporting the ADRs.

MATERIALS AND METHODS

This was an observational study done in the Dept. of Pharmacology, Government T.D. Medical College, Alappuzha over a period of one year (July 2014- 2015). Approval was taken from the Institutional Ethics Committee (IEC) before commencing the study. All ADRs were collected in CDSCO forms and retrospective data was entered from the ADR forms. Data entry was undertaken in Excel 2010 and analysis was done using SPSS 24. The quantitative continuous variables were expressed as the Mean ± Standard deviation.

RESULTS

A total of 255 ADRs were identified during a one-year period, of which 39 (15.29%) cases were due to the use of NSAIDs. The age group was found to be 31 - 40 years. Males were 35.9% and females were 64.1% with M:F ratio of 1:1.8 given in Fig. 1.

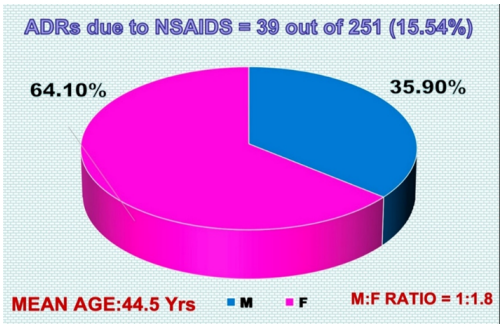

Fig. 1: Male:Female ratio of ADRs due to NSAIDs

The drugs involved in ADRs were Diclofenac (38.5%), Paracetamol (30.8%), Aspirin (15.3%), Ibuprofen (5.1%), Piroxicam (2.6%), Ketorolac (2.6%), Indomethacin (2.6%) and Nimesulide (2.6%), shown in Fig. 2.

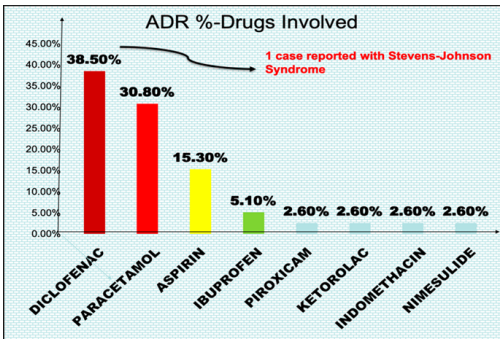

Fig. 2: Drugs that are involved in causing ADRs among NSAIDS

Skin was the most commonly affected organ system (71.8%) followed by GIT (15.3%), renal (7.7%), respiratory (7.7%) and CNS (5.1%) due to intake of NSAIDs, shown in Fig. 3.

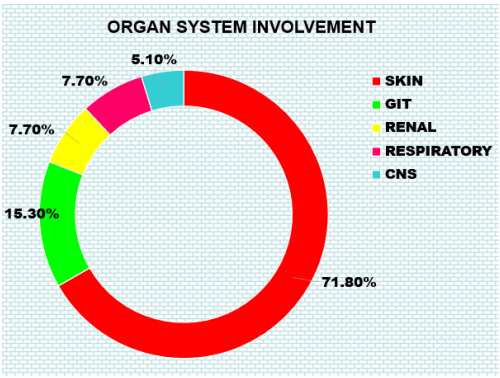

Fig. 3: Various organ systems involvement due to NSAIDs intake

Causality assessment revealed that 71.8% of ADRs were possible and 28.2% were probable, according to Naranjo's scale. Severity assessment using the Modified Hartwig and Siegel Scale showed that 76.9% reactions were mild, 15.4% were moderate and 7.7% were severe, out of which one case was reported with Stevens-Johnson Syndrome (SJS), shown in Fig. 4.

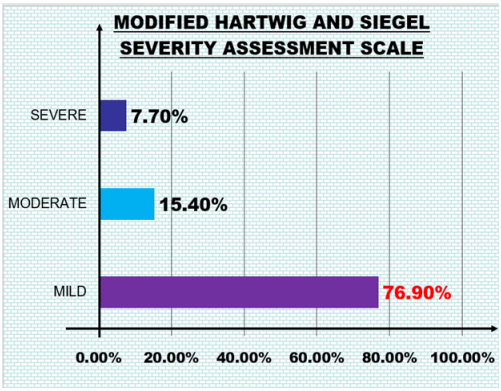

Fig. 4: Modified Hartwig and Siegel Scale showing severity assessment of ADRs

The causative drugs were stopped, and the patients were managed conservatively. No case fatalities were reported.

DISCUSSION

In the present study, a total of 255 ADRs were identified during a one-year period, of which 39 (15.29%) cases were due to the use of NSAIDs with M:F ratio of 1:1.8. Several publications indicate that the female gender experiences a higher incidence of ADRs than does the male gender[20].

In this study, it was found that Diclofenac, Paracetamol, Aspirin, Ibuprofen, Piroxicam, Ketorolac and Indomethacin were the most prescribed NSAIDs. Out of these drugs Diclofenac showed the highest side effects as it was the mostly prescribed drug. One review article suggested that an agent with comparatively less GI side effects, like Ibuprofen and Diclofenac, should be preferred for indomethacin, piroxicam or naproxen, which are more gastro toxic[21]. A review suggests that in situations like osteoarthritis where inflammation of joint is minimal, analgesics like paracetamol should be preferred over anti-inflammatory drugs like ibuprofen[22].

Two studies published from the same centre before and after the study period of this study highlight that NSAIDs are among the top 5 drugs which are suspected to cause ADRs. During the period of 2012- 2014, NSAIDs contributed to 14.5% ADRs reported from the centre, second to antibiotics and from 2017-2020 it was the third top offender group after beta lactam antibiotics and anti-tuberculous drugs. Among ADRs due to NSAIDs, the maximum was affecting the skin and appendages[23, 24].

In our study, skin was the most commonly affected organ system followed by GIT, renal, respiratory and CNS due to intake of NSAIDs. A six month study on pharmacovigilance of cutaneous ADRs show that NSAIDs were second to antibiotics in causing cutaneous adverse drug reactions, diclofenac and paracetamol being the most common drugs[25].

Limitation of this study is the relatively small sample size and short period of study without follow-up. Moreover, the study was a retrospective observational study. To prevent ADRs by NSAIDs, a protocol for their early detection and prevention should be established.

CONCLUSION

Pharmacovigilance is an essential tool for the treating clinician to develop safe medical practice. 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 be invaluable in making the medicines safer and rational. This study has paved the way for further studies on a large population in the future.

DISCLOSURE

Conflict of Interest: None.

Author contribution: All authors have contributed in the manuscript.

Author funding: Nil.

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