

ADR Monitoring of NSAIDs among the in-Patients of the Orthopaedic Ward in a Tertiary Care Centre: A Prospective Observational Study

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ABSTRACT

Background: The non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all the drugs. Despite their wide clinical use, their gastro-intestinal toxicity is a major limitation. A number of studies describe NSAIDs as the leading causes of adverse drug reactions (ADRs). To augment an adverse drug reaction monitoring system, an active surveillance was planned and a pilot study was started in a tertiary care teaching hospital in Chennai.

Objectives: The main aim of this study was to identify the incidence of the ADRs of the NSAIDs among the in - patients of the orthopaedic ward. It also aimed to assess the causality and the severity of the adverse effects with the monitoring of rational prescribing.

Materials and Methods: This prospective, observational study was conducted among 200 in-patients of the orthopaedic ward over a period of 6 months. The incidences of the ADRs were collected and analyzed. The causality was analyzed by using Naranjo's Algorithm and the severity was analyzed by using the Hartwing and Siegel scale.

Result: Totally, 200 in- patients were studied, among which 5.5% (n=11) reported the occurrence of ADRs. Nearly 63.64% (n=7) of the ADRs were reported by men and 36.36% (n=4) were reported by females. The reactions which were observed were nausea, vomiting, gastritis, abdominal pain, diarrhoea, headache, rashes and oliguria. The most commonly reported ADR was gastritis and the system which was involved was the gastro-intestinal system. With the given drugs, Tablet (Tab) Diclofenac accounted for 72.73% (n=7) and Tab.Ibuprofen for 27.27% (n=3) of all the ADRs. As per Naranjo's Algorithm, 63.63% of the adverse reactions were "possible" and 36.37% were "Probable". The severity assessment showed that 72.73% of the adverse effects were mild and that 27.27% were moderate.

Conclusion: The incidence rate of the ADRs in the orthopaedic ward was found to be 5.5% and the ADRs were mild in nature. This shows that rational drug therapy and better prescription practices had brought down the ADRs to minimal in our tertiary care teaching hospital in Chennai.

Key Words: Adverse drug reactions, rational drug therapy, Naranjo's Algorithm, NSAIDs

INTRODUCTION

An 'adverse drug reaction', as defined by the World Health Organization, is a noxious, unintended effect of a drug, which occurs at normal doses in humans for the prophylaxis, diagnosis, or the therapy of the disease or for the modification of its physiological function [1]. ADRs are considered as the 4th to 6th leading causes of death among hospitalized patients. These are associated with significant morbidity, mortality and permanent disability and are a huge economic burden on the patients due to prolonged hospitalization [2]. It has been estimated that the incidence of ADRs throughout the world is 5% and 5-6% of all the hospital admissions which are caused by drug - induced problems [3]. In south Indian hospitals, ADRs accounted for 0.7% of the total admissions and 1.8% of the total deaths [4].

An important risk factor for developing ADR is the previous occurrence of ADR. Re-exposure to offending drugs due to poor documentation can cause the patient to experience the same ADR again, thus emphasizing the importance of the accurate

documentation of ADR at the time of the event and providing relevant information to the patient about the ADR to help prevent its further occurrence.

Pharmacovigilance deals with the detection, assessment and the prevention of adverse drug reactions [5]. Adverse drug reactions can occur in any treatment regimen [6]. Multiple drug therapy, increasing age (>70yrs) and co-morbid diseases were identified as the major predisposing factors for the occurrence of ADRs [7]. There are very few centres in India which can monitor ADRs and hardly have any detailed ADR surveys which have been done in India been published [8]. Lack of awareness and poor reporting resulted in inadequate ADR monitoring in India [9]. Effective pharmacovigilance programs are needed in India, as genetic diversity is present [10]. To augment an adverse drug reaction monitoring system, an active surveillance was planned and a pilot study was started in our hospital. Since the in-patient stay was prolonged in orthopaedic patients, the orthopaedic ward of a tertiary care teaching hospital of Govt. Kilpauk Medical College,

Chennai, Tamilnadu, was chosen to evaluate the various ADRs to NSAIDs.

AIM

The main aim of this study was to identify and report the adverse drug effects of NSAIDs among the in-patients of the orthopaedic ward. It also aimed to assess the causality and the severity of the adverse effects with the monitoring of rational prescribing.

MATERIALS AND METHODS

A prospective, observational study was carried out in the Department of Orthopedics, in collaboration with the Department of Pharmacology, Kilpauk Medical College, Chennai. Totally, 200 orthopaedic in-patients were selected. The study was conducted for 6 months from January 2010 to June 2010. All the patients of either sex, of the ages of 18 years and above, who were on NSAIDs therapy for inflammatory disorders like ankylosing spondylitis and osteoarthritis, were included for the study. Patients with cardiovascular diseases, liver disorders and kidney damage, pregnant women, patients who were shifted to other wards, those who were severely ill, outpatient cases and those who were not willing to take part in the study were all excluded. Written informed consent from all the patients and necessary approval from the Institutional Ethical Committee were obtained.

The patient's demographic details, their past history of adverse events, details of their examination, details of regular investigations like blood sugar, urea and creatinine and details of drug therapy and concomitant medication use were collected and recorded in the proforma. The subjects and their accompanying family members were interviewed and their past prescriptions and case notes were noted. The data which was collected on ADRs included the drugs which were received, the nature of the ADRs, the drugs which were implicated, the reaction time and the time of reverting in accordance to the proforma. A structured questionnaire was used to record the adverse effects of the commonly used NSAIDs which were relevant to the in-patients of the orthopaedic ward. The monitoring of the adverse effects was done, as the investigator visited daily, so that all the patients had the opportunity to convey the details about the adverse effects. The drugs were purchased from the hospital pharmacy. The Kilpauk Medical College Government hospital receives drugs from the Tamilnadu State Medical Services Corporation, Chennai, which is the central body that purchases drugs and surgicals for the entire state, based on the Essential Drug list of the State Government. The patients were asked to submit the empty foils of the past ADRs and the current drug which was responsible for the ADR was obtained from the staff nurse. The rechallenge test was not done due to ethical reasons. The causality was assessed by using Naranjo's Algorithm, which is one of the most widely used methods for evaluating adverse reactions [11]. It consists of ten objective questions with 3 types of answers – Yes, No or don't know. Scores are given accordingly and the drug reaction can be classified as definite (total score - >9), probable (total score -5-8), or possible (total score- 1 -4). The severity of the drug was assessed by using the Hartwing and Siegel scale, which classified the severity of the ADRs as mild, moderate or severe according to factors like the requirement for the change in treatment, duration of the hospital stay and the disability which was produced by the ADR [12]. No follow-up was done. The data which was collected

was compiled and tabulated. The data were analyzed by using the Chi-square(χ^2) test. A P value of <0.05 was considered as significant. Simple frequencies and percentages were obtained for various variables.

RESULTS

Out of the 200 in-patients, 11 had developed ADR. The male:female ratio of the study group was 1.8:1 and the demographic features are listed in [Table/Fig 1].

Out of the 11 patients who experienced adverse effects, 7 (63.63%) were males and 4 (36.36 %) were females. Nine ADRs were reported in the age group of 18-65 years and 2 were reported in the age group of above 65 years. According to our study, age and gender have no effect on the occurrence of ADRs due to NSAIDs and this was statistically insignificant [Table/Fig 2 and 3].

The reactions which were observed in the study subjects were nausea (n=2), vomiting (n=1), gastritis (n=4), abdominal pain (n=1), diarrhoea (n=1), rashes (n=1), headache (n=1) and oliguria (n=1). The most common adverse effect which was reported in our study was gastritis and the most common system which was involved was the gastrointestinal system. The ADRs and the implicated drugs are shown in [Table/Fig 4].

Among the NSAIDs, Tab. Diclofenac, Tab. Ibuprofen and Tab. Paracetamol were commonly prescribed in our hospital's orthopaedic ward. In the 200 prescriptions, Tab. Diclofenac was given to 152 patients (76%), Tab. Paracetamol was given to 25 patients (12.5%) and Tab. Ibuprofen was given to 23 patients (11.5%). Out of the 11 ADRs, 8 (72.73%) were caused by Tab. Diclofenac and 3 (27.27%) were caused by Tab. Ibuprofen. No ADR was found to be caused by Tab. Paracetamol. A gastro protective agent (GPA) was used with the NSAIDs in 172 (86%) prescriptions. Tab. Ranitidine was given to 128 patients and Tab. Omeprazole was given to 44 patients to prevent gastritis and the remaining 28 patients did not receive any gastro protective agents [Table/Fig 5].

In the present study, the incidence rate of the ADRs was found to be 5.5%. The causality assessment revealed that 7 ADRs (63.64%) belonged to the "possible" category, whereas 4 (36.36%) were "probable" reactions according to the Naranjo's Algorithm. Due to ethical reasons, a rechallenge was not performed in our study [Table/Fig 6]. The Hartwing and Siegel scale severity assessment showed 77.7% of the adverse effects were mild and that 22.3%

| Age group | Males (%) | Females (%) | Total number (200) |
|----------------|-----------|-------------|--------------------|
| 1. 18-65 years | 122 | 66 | 188 |
| 2. > 65 years | 8 | 4 | 12 |
| Total | 130 (65%) | 70 (35%) | 200 |

[Table/Fig-1]: The Patient's Demographic Features (total n=200)

| Age group | Number of patients with ADR | Number of patients without ADR | Total number (200) |
|----------------|-----------------------------|--------------------------------|--------------------|
| 1. 18-65 years | 9 | 179 | 188 |
| 2. > 65 years | 2 | 10 | 12 |
| Total | 11 | 189 | 200 |

[Table/Fig-2]: Age of the patients and Adverse Drug Reactions
Chi-square test $\chi^2 = 3.06$. Degree of freedom (1) P >0.05.

| Sex group | Number of patients with ADR | Number of patients without ADR | Total number (200) |
|----------------|-----------------------------|--------------------------------|--------------------|
| 1. Males (%) | 7 | 123 | 130 |
| 2. Females (%) | 4 | 66 | 70 |
| total | 11 | 189 | 200 |

[Table/Fig-3]: Sex of the patients and Adverse Drug Reactions
Chi-square test $\chi^2 = 0.95$. Degree of freedom (1) $P > 0.05$.

| S. No. | ADRs | Total number of Patients | Drug Causing the Adverse Effect (number of patients) |
|--------|----------------|--------------------------|--|
| 1 | Nausea | 2 | Ibuprofen (n=1) Diclofenac (n=1) |
| 2 | Vomiting | 1 | Diclofenac |
| 3 | Gastritis | 3 | Diclofenac (n=2) Ibuprofen (n=1) |
| 4 | Abdominal pain | 1 | Diclofenac |
| 5 | Diarrhoea | 1 | Diclofenac |
| 6 | Rashes | 1 | Ibuprofen |
| 7 | Head Ache | 1 | Diclofenac |
| 8 | Oliguria | 1 | Diclofenac |

[Table/Fig-4]: ADRs detected and implicated drugs
*ADR: Adverse Drug Reaction.

| Name of the drug | Number of patients Prescribed (%) | Number of ADR (%) |
|------------------|-----------------------------------|-------------------|
| NSAIDs | | |
| 1. Diclofenac | 152 (76 %) | 8(72.73) |
| 2. Ibuprofen | 23 (11.5%) | 3(27.27) |
| 3. Paracetamol | 25 (12.5%) | – |
| GPA's | | |
| 1. Ranitidine | 128 (64 %) | – |
| 2. Omeprazole | 44 (22%) | – |

[Table/Fig-5]: Drug utilization and ADR
*GPAs – Gastro Protective Agents, *ADR – Adverse Drug Reaction.

| S. No. | ADRs | No of ADRs (Possible) | No of ADRs (probable) | No of ADRs (Definite) |
|--------|----------------|-----------------------|-----------------------|-----------------------|
| 1 | Nausea | 1 | 1 | – |
| 2 | Vomiting | 1 | – | – |
| 3 | Gastritis | 2 | 1 | – |
| 4 | Abdominal pain | 1 | – | – |
| 5 | Diarrhoea | 1 | – | – |
| 6 | Rashes | 1 | 1 | – |
| 7 | Head Ache | 1 | – | – |
| 8 | Oliguria | – | 1 | – |
| | | 7 (63.64%) | 4 (36.36%) | 11(100%) |

[Table/Fig-6]: Causality assessment of individual Adverse Drug Reaction by Naranjo's Algorithm
Possible (total score 1 to 4), Probable (total score 5 to 8), definite (total score >9).

were moderate in nature. They were managed symptomatically by using routine treatment protocols.

DISCUSSION

The present study has reported the incidence of ADRs to NSAIDs in the orthopaedic in-patient setting in the Indian scenario. According to our study, the incidence of ADRs was found to be 5.5%. A recent study on the adverse drug reactions of non-steroidal anti inflammatory drugs in orthopaedic patients in a tertiary care teaching hospital, Delhi, showed that the prevalence rate of the ADRs was 26% [13]. A study which was conducted on orthopaedic patients in Mumbai showed that the incidence rate of various kinds of ADRs of NSAIDs ranged from 28 to 33 % [14]. Our study showed a lower incidence of ADRs as compared to the findings of the above studies. This may probably be due to the proper selection of the NSAIDs and their rational use.

Among the in-patients, 2 out of 12 who were above the age of 65 years and 9 out of 188 who were in the age group of 18 to 65 years experienced ADR. This finding differed from that of Egger et al study, where the elderly were more commonly affected [15]. Of the patients who experienced ADRs during the study period, 7 (63.63%) were males and 4 (36.37%) were females. Reports from various studies showed a female preponderance, while our study did not show much difference with respect to gender, as our study had only limited number of patients.

Epidemiological studies showed that gastro-intestinal tract (GIT) complications were the most common ADRs with ketoprofen and piroxicam and that they had a lower incidence with ibuprofen, diclofenac and paracetamol [16]. One study reported that 20% of the patients experienced side effects due to Tab.Diclofenac, but that only 2% discontinued the drug [17]. On the administration of Tab.Ibuprofen, 5 to 15% of the patients experienced side effects. Bates et al, in a study on 247 patients, found that 30% of the ADRs were caused by analgesics, 24% by antibiotics, and 8% by sedatives [18]. As our study was carried out in the orthopaedic department, the ADRs which were caused by NSAIDs were studied, where 8 cases reported ADRs due to Tab.Diclofenac out of 152 prescriptions (5.26%) and 3 reported ADRs due to Tab. Ibuprofen out of 23 prescriptions (13.3%). Since the number of patients who received Tab.Diclofenac was more than those who received other NSAIDs, the ADRs were more with the same drug. The pattern of NSAID usage was very similar in different places, where Tab.Diclofenac was commonly used, followed by Ibuprofen and Paracetamol. In our setup, only low risk drugs were prescribed, which were related to gastro protection. Gastro protective agents were also given in 86% of the total patients, which minimized the GIT complications in our study, as has been described in evidence based medicine.

According to Naranjo's Algorithm, 63.63% ADRs were assessed as "possible" ADRs and 36.37% as "probable" ADRs. These results were comparable with the findings of Davies et al's study and Shanmugam Sriram et al study [7]. Both the above mentioned studies showed that 63% of the ADRs were possibly drug related, whereas 37% were classified as probably or definitely related to the drug. The severity assessment scale revealed that 72.73% were mild and that 27.27% were moderate adverse reactions. A study which was conducted by Arulmani et al on ADR monitoring in a secondary care hospital in South India, showed that 53.7%

were mild ADRs, whereas our study showed more number of mild cases. No severe ADRs were found in our study [9]

In a recent study review, Pir Mohamed et al reported ADR frequencies between 10 and 20% in in-patients [19].

A number of studies have described NSAIDs as the leading causes of ADRs, while others have shown that they ranked 4th or 5th in causing ADRs. Two studies by Chan denotes that NSAIDs were responsible for 28% of the drug related admissions in Hong Kong and that NSAIDs related GIT bleeds were about 18% in an another study [20]. An Australian study of 5623 admissions reported a high incidence of GI bleeds which were associated with NSAIDs [21]. In a Scottish study, 17 patients reported ADRs due to NSAIDs [22]. Our study showed that GIT side effects were common and that they were mild in nature. When compared with the above studies, the incidence rate of the adverse drug effects in our orthopaedic in-patients was 5.5%, which was lower than that which was found in the above mentioned studies.

As our study involved active surveillance for adverse effects, we could detect 11 adverse effects, which in a routine set up, would have gone unrecorded. The treating doctors were considering risk factors like peptic ulcer in the patients. They prescribed drugs to prevent adverse effects whenever they anticipated adverse effects. So, the adoption of rational drug therapy by the treating doctors in a tertiary care teaching hospital where the study was done, might have contributed to the lower incidence of the adverse effects.

The prevention of adverse reactions by identifying persons who are at a high risk is important to improve patient care [23]. In our study, we found only a 5.5% incidence of adverse reactions which were caused due to rational drug uses. Despite the study being limited to one department, it has provided baseline data for further larger studies and it has ascertained the importance of prospective ADR monitoring in pharmacovigilance studies.

CONCLUSION

The present study has reported the incidence of ADRs of NSAIDs among the orthopaedic patients in the south Indian population. Overall, the incidence rate of ADRs in the orthopaedic ward was 5.5% and the ADRs were mild in nature. It showed that rational drug therapy had brought down the adverse effects to minimal and that it had attributed to the better prescription practice which was followed in our tertiary care teaching hospital in Chennai.

The pharmacovigilance system usually consists of notification forms, drop boxes and a coordinated Drug Information Centre [5]. The main sources of the ADR data include the ADR monitoring schemes of hospitals [24]. This has been validated in our study. The physician's considerate prescription of NSAIDs with a good understanding of each patient's GI risk factors is strongly encouraged, in order to maximize the cost effectiveness and to prevent serious GI complications. Therefore, the setting up of an ADR monitoring centre at a more regional or hospital level and integrating it with a sound network can reveal unusual or rare ADRs which are prevalent in the Indian population.

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