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Research Article

# PHARMACOVIGILANCE FOR ADVERSE DRUG REACTIONS IN PATIENTS ON NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND HEPATIC DYSFUNCTION IN ACECLOFENAC THERAPY IN SOUTH DELHI HOSPITAL

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**ABSTRACT**

**Objectives:** To carry out Pharmacovigilance for Adverse Drug Reactions in Non-Steroidal anti-inflammatory drugs therapy. And evaluate biochemical changes for hepatic dysfunction in patients using Aceclofenac.

**Setting:** 300 patients were the subjects in Orthopaedics Department of a Multispecialty Hospital, in South Delhi.

**Method:** It was a duly approved, pharmacovigilance study, in patients on NSAIDs therapy, conducted by competent professionals. The data was obtained from physicians' prescribing records and patients by individual interviews using the structured proformas as per World Health Organisation guidelines. Hepatic function was evaluated by enzymatic estimations **(SGOT, SGPT, γ-GTP).**

**Keyfindings:** In 300 patients, 23 cases of ADRs were reported, showing following demography; 39% males, 61% females, 30% were between 41-50 yrs, 21% between 31-40 yrs. 52% alcoholics, 48% non-alcoholics, 61% smokers, 39% non-smokers, 48% vegetarians, 52% non-vegetarians. ADR cases on combination therapy were 69%, on monotherapy 31%. ADR cases associated with Diclofenac 2.6%, aceclofenac 1%, nimesulide 1.6%, ibuprofen 1.6%, paracetamol 0.6%. On basis of severity of ADRs, 6.6% cases were mild, 1% were moderate. As per Naranjo's scale, 6% were classified as possible and 1.3% were classified probable & unlikely 0.3%. Majority of the patients, although experienced some physical signs of hepatic ADRs, did not have significant change in the biochemical parameters from that of the normal; SGOT 29 ± 1.823$^{NS}$, SGPT 30.94 ± 1.796$^{NS}$, γ GTP19.21 ± 1.806$^{NS}$.

**Conclusion:** The pharmacovigilance study demonstrated that the incidence of ADRs was found to be higher in elderly patients (> 40 yrs), in females, alcoholics, smokers, non-vegetarians. Most of the adverse effects were mild and tolerable. ADRs were higher with Combination against monotherapy; diclofenac was associated most with ADRs followed by nimesulide, ibuprofen, aceclofenac and paracetamol.

Aceclofenac did not produce hepatic dysfunction during the period of therapy.

**Keywords**: Pharmacovigilance, ADR, NSAIDs, Compliance, SGOT, SGPT, γ-GTP.

## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs having; analgesic, antipyretic and anti-inflammatory effects.[1] NSAIDs act by interfering with the production of prostaglandins by inhibiting the enzyme Cyclo-oxygenase (COX), both COX-1 and COX-2, reducing inflammation but at the same time blocking the protective role of COX-1, thus producing adverse effects, particularly on the gastric mucosa. NSAIDs COX-2 inhibitors are thought to act by selectivity blocking COX-2, thereby reducing pain and inflammation, but not blocking COX-1.

NSAIDs are associated with certain adverse drug reactions such as; allergic reactions, skin reactions, gastrointestinal effects, renal complications, alteration of hepatic enzyme levels and rarely hepatopathies.[2] These effects are dose-dependent, and in many cases severe enough to pose the risk of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAID therapy. Many of these events are avoidable; a review of physician visits and prescriptions estimated that unnecessary prescriptions for NSAIDs were written in 42% of visits.[3]

A prospective trail for hepatotoxicity, with 7,000 patients taking NSAIDs reported that, 3% had persistent abnormalities (elevations) on more than one liver function test. Abnormalities in liver function are almost always reversible with the cessation of NSAIDs.[4] Toxic hepatic reactions usually occur within three months. Some NSAIDs (Benoxaprofen, fenclofenac, Ibufernac, Bendazac, pirprofen) have been withdrawn from the market in the early 1980s because of fatal hepatotoxicity.[5] Nimesulide was withdrawn in 2002 because of a high frequency of hepatotoxicity.[6]

Aceclofenac is a well tolerated, potent NSAID, effective orally, at a dose of 100 mg b.i.d.Withdrawal rate for Aceclofenac due to gastrointestinal adverse effects is lower than Ketoprofen and Tenoxicam.[7] Aceclofenac is an effective analgesic and anti-inflammatory agent with a good tolerability profile. It has proved as effective as diclofenac, naproxen and piroxicam in patients with osteoarthritis.[8]

WHO defines 'adverse drug reaction' (ADR) as any response to a drug which is noxious and unintended and occurs at doses normally used in human for prophylaxis, diagnosis or therapy of disease or the modification of physiological function'. This definition excludes therapeutic failures, intentional and accidental poisoning and drug abuse.[9]

Management of ADRs adversely affects Pharmacoeconomics of the therapy of disorders.[10] Pharmacovigilance programmes aim at improving patient care and safety, contributing in assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective use with appropriate interventions in cases of ADRs.

WHO defines 'Pharmacovigilance' (ADR monitoring) as the science and activities relating to the detection, assessment, understanding and prevention of ADRs or any other medicines related problems (WHO, 2004). The overall purpose of pharmacovigilance is improvement in the safety of medicine. Among the paramedical staff Pharmacists have a more competent place in Pharmacovigilance.[11] Pharmacists may interact with patients and report more data on ADRs.[12]

Reports reveal that about 22.3% of the patients experience ADRs.[13] Also monitoring of ADRs show that of the total visits in medical department, 5.9% are due to drug related events, and 45% due to ADRs.

Current Pharmacovigilance study contains the result of a 4-month observation on monitoring ADRs in patients on NSAIDs therapy in Orthopaedics Department in a Multispecialty Hospital in South Delhi.

**MATERIALS AND METHODS**

Present Pharmacovigilace study was a duly approved by Jamia Hamdard Institutional Review Board, dated 08th December 2007. It was an open, non-comparative, 4-month study, January to April 2008, conducted at a Multispecialty Teaching Hospital in South Delhi. Suitably qualified and competent professionals were involved in conducting the study. Inclusion criteria - all patients using NSAIDs irrespective of age and sex; and Exclusion criteria - patients mentally retarded, unable to comply, refusing the consent; was observed for selection of the 300 patients. Informed Consent was signed by the selected patients. The data was obtained from physicians' prescribing records and patients by individual interviews using the proformas for; Informed Consent, ADR monitoring Form, Structured Questionnaire, as per World Health Organisation guidelines[14]. Hepatic function was evaluated by enzymatic estimations (SGOT, SGPT, γ-GTP) in blood samples of suspected patients using Aceclofenac therapy.

The evaluation of the probability of ADRs by Naranjo's Scale and by WHO causality Scale has been shown in Table 1 and Table 2 respectively.[15]The data were evaluated for statistical significance by applying Students't test.

**Table 1: Naranjo's Adr Probability Scale**

| S. No. | Questions | Yes | No | Do not know | Score |
|---|---|---|---|---|---|
| 1. | Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | |
| 2. | Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 | |
| 3. | Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 | |
| 4. | Did the adverse reaction reappear when the drug was re-administered? | +2 | -1 | 0 | |
| 5. | Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1 | +2 | 0 | |
| 6. | Did the reaction reappear when a placebo was given? | -1 | +1 | 0 | |
| 7. | Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 | |
| 8. | Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0 | |
| 9. | Did the patient have the similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | |
| 10. | Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | |
| | | | | Total Score | |

Assessment score: Highly probable ≥ 9; Probable 5-8; possible 1-4; Unlikely ≤ 0

**Table 2: WHO Causality Assessment Scales**

| Level | Criteria |
|---|---|
| Certain | • Event of laboratory abnormality, with plausible time relationship to drug intake<br>• Cannot be explained by disease or other drugs<br>• Response to withdrawal plausible (pharmacologically, pathologically)<br>• Event definitive pharmacologically or phenomenologically.<br>• Rechallenge (if necessary) |
| Probable | • Event of laboratory abnormality, with reasonable time relationship during intake<br>• Unlikely to be attributed to disease or other drugs<br>• Response to withdrawal clinically reasonable<br>• Rechallenge not necessary |
| Possible | • Event or laboratory abnormality, with reasonable time relationship during intake<br>• Could also be explained by disease or other drugs<br>• Information on drug withdrawal lacking or unclear |
| Inaccessible/ unclassifiable | • A report suggesting an adverse reaction<br>• Cannot be judged because of insufficient or contradictory information<br>• Report cannot be supplemented or verified |
| Unlikely | • Event or laboratory abnormality with a time to drug that makes a relationship improbable (but not impossible)<br>• Disease or other drugs provide plausible explanations |
| Conditional /unclassified | • Event or laboratory test abnormality<br>• More data for proper assessment needed or additional data under examination |

**RESULTS AND DISCUSSION**

A total of 23 cases of ADRs were reported in 300 patients. Higher numbers of ADRs cases were between 41-50 yrs and 31-40 yrs, 30% and 21% respectively (Table 3).

On the basis of 23 patients' demographics; a higher percentage of ADRs occurred in females 61% than in males 39%; alcoholics 52%, non-alcoholics 48%, smokers 61%, non-smokers 39%, vegetarians 48%, non-vegetarians 52%. ADR cases in combination therapy were 69% against 31% in monotherapy. ADR cases associated with

Diclofenac 2.6%, aceclofenac 1%, nimesulide 1.6%, Ibuprofen 1.6%, paracetamol 0.6% **(Table 4).**

As per Naranjo's scale, 6% were classified as possible and 1.3% was classified probable & unlikely 0.3% (Table 5).

Majority of the patients, although experienced some physical signs of hepatic ADRs, did not have significant change in the biochemical parameters from that of the normal; SGOT 29 ± 1.823$^{NS}$, SGPT 30.94 ± 1.796$^{NS}$, γ- GTP 19.21 ± 1.806$^{NS}$ (Table 6).

**Table 3: ADRs among various age groups in NSAIDs users**

| Age group | Male | Female | Total (%) |
|---|---|---|---|
| 10-20 | 1 | 2 | 3 (13.4%) |
| 21-30 | 1 | 2 | 3 (13.4%) |
| 31-40 | 2 | 3 | 5 (21.7%) |
| 41-50 | 3 | 4 | 7 (30.4%) |
| 51-60 | 2 | 3 | 5 (21.7%) |
| **Grand total** | **9** | **14** | **23** |

**Table 4: ADRs with classes of NSAIDs and with individual drugs**

| Class | Drugs | Adverse reaction | No. of cases of ADRs | | Intervention |
|---|---|---|---|---|---|
| | | | No. | %. | |
| Aryl acetic acid derivative | Aceclofenac | Dizziness | 2 | | Symtometic treatment |
| | | Diarrhoea | 1 | 13% | Dechallanged |
| | Diclofenac | Abdominal pain | 6 | 34.87% | Symtometic treatment |
| | | Dyspepsia | 2 | | Symtometic treatment |
| | | *Total (drugs class)* | *11* | 47.82% | |
| Propoinic acid derivative | Ibuprofen | Epigastric discomfort | 3 | 21.73% | Dose reduced |
| | | Vomiting | 2 | | Symtometic treatment |
| Preferential COX-2 inhibitor | Nimesulide | Loose motion | 5 | 21.73% | Dechallanged |
| Para-aminophenol derivative | Paracetamol | Skin rashes | 2 | 8.69% | Dechallenged |
| **Total** | | | **23** | **100%** | |

On basis of severity of ADRs, 6.6% cases were mild, 1% were moderate.

**Table 5: Classification of ADRs according to Naranjo's Scale**

| Assessment | No. of ADRs | % of ADRs |
|---|---|---|
| Unlikely ;<0 | 01 | 0.3 |
| Possible ;1-4 | 18 | 6 |
| Probable ;5-8 | 04 | 1.3 |
| Highly probable;9 | 0 | 0 |
| **Total** | **23** | **7.6** |

**Table 6: Biochemical parameters for hepatic function**

| | Baseline (mean ± SEM) | After$^{4th}$ week (mean ± SEM) |
|---|---|---|
| SGOT | 21.316 ± 1.08 | 29 ± 1.823$^{NS}$ |
| SGPT | 22.47 ± 1.519 | 30.94 ± 1.796$^{NS}$ |
| GGT | 15.42±1.45 | 19.21 ± 1.806$^{NS}$ |

NS = Non significant when P > 0.05

Values after 4$^{th}$ Week are compared with those of baseline.

## DISCUSSION

To our knowledge, considering prescription drugs this is the first study providing comprehensive information on the prevalence and the pattern of ADRs in patients using NSAIDs.

A total of 23 cases of ADRs were reported in 300 patients using NSAIDs. Higher numbers of ADRs cases were observed in patients above 40 yrs, females', alcoholics, smokers, non-vegetarians, on combination therapy. Similar observations have been reported in few of the studies.[16] A previous study had already showed that the percentage of ADR was higher in females compared to males.[17]

Aryl acetic acid derivatives (Diclofenac, aceclofenac) were the class of NSAIDs, most associated with mild ADRs inclusive of monotherapy and combination therapy. Individually Diclofenac was most associated with ADRs. This is in confirmation with an earlier report.[18,19]

Most of the ADRs were mild and tolerable, did not require withdrawal of therapy.

As per Naranjo's scale, 6% were classified as possible and 1.3% was classified probable & unlikely 0.3%.

A report reveals that aceclofenac does not affect the liver function adversely.[20] Current study also evaluated liver function after four weeks of aceclofenac therapy using γ-GTP as biochemical parameter for the first time in addition to SGOT, SGPT. Majority of the patients using Aceclofenac, although experienced some physical signs of hepatic ADRs, did not have significant change in the biochemical parameters from that of the normal.

## CONCLUSION

The prime objective of this study was to monitor ADRs in patients on NSAIDs therapy and improve drug utilization pattern in a hospital setting. Also to measure ADR incidence in various patients

demographics and educate them about life style, diets, alcohol intake, Smoking, etc.

The following are the major findings of this study:

- Care should be exercised while prescribing NSAIDs for long term and in elderly patients as ADR incidents are higher in patients above 40 yrs in age and female.
- Monotherapy with NSAIDs should be preferred to Combination therapy.
- Paracetamol may preferably be prescribed unless others become very essential.
- Aceclofenac may be considered safe in terms of adverse effect on liver.
- The limitation of the present study is the small sample size, and short duration of study.

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