PROSPECTIVE STUDY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUG INDUCED ADVERSE DRUG REACTION IN A TERTIARY CARE HOSPITAL

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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed class of drugs having anti-inflammatory, antipyretic and analgesic properties. Because of their significant efficacy, low abuse potential and long-term clinical use to relieve various types of pain, they are one of the most widely used drugs in primary healthcare.NSAIDs are very effective in treating pain due to inflammation and unlike morphine, they do not depress CNS, do not cause physical dependence, have no addiction potential or any other negative effects. NSAIDS are also known as Non-narcotic, non-opioid and aspirin-like analgesics. This study is utilized to evaluate and analyze the Adverse Drug Reaction associated with non-steroidal anti- inflammatory Drugs. During the study period, totally nine adverse events were documented. More frequently reported adverse drug reactions were due to Diclofenac followed by Aceclofenac which were similar to the study conducted by Padmanabha et al., which revealed that proportion of ADR such as skin rash and gastritis, were more frequent with Diclofenac. The major risk factors which induce adverse drug reactions include age, concomitant illness, gastric ulcer, peptic or duodenal ulcer, polypharmacy, and drug interactions. Adverse drug reactions especially gastrointestinal distress developed in patients who were not prescribed with gastric protectants. Rashes and allergic reactions such as urticaria developed secondary to gastric complications. The incident rate of ADR in this study was found to be 4.08%

Keywords: NSAIDs, Adverse Drug Reaction, Causality Assessment

INTRODUCTION:

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed class of drugs having anti-inflammatory, antipyretic and analgesic properties. Because of their significant efficacy, low abuse potential and long-term clinical use to relieve various types of pain, they are one of the most widely used drugs in primary healthcare (1) NSAIDs are very effective in treating pain due to inflammation and unlike morphine, they do not depress CNS, do not cause physical dependence, have no addiction potential or any other negative effects. NSAIDS are also known as Non-narcotic, non-opioid and aspirin-like analgesics (2)NSAIDs are used to relieve pain and discomfort associated with chronic conditions such as rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, fever, gout, headache, back pain, abdominal pain and dysmenorrhea. (1)NSAIDs blocks prostaglandin synthesis through cyclooxygenase enzymes inhibition (COX-1 and COX-2). COX-1 produces prostaglandins and thromboxane A2 (TXA2) which control mucosal barrier in gastrointestinal tract, renal homeostasis and platelet aggregation. COX-2 produces prostaglandins which are related to inflammation, pain and fever. (1)Mostly they are weak organic acids with pKa in the range of 3–5. They contain an acidic group mostly carboxylic acids or enols and the COX inhibitory action of the compound depends on the acidic moiety.(3) NSAIDs are readily absorbed when administered orally. In acidic environment of the stomach, NSAIDs are dominantly in unionized form so, only a small amount of them gets absorbed through the stomach wall. Because of its large surface area, the small intestine is the primary site of NSAID absorption. They are not significantly affected by food in terms of bioavailability. The majority of NSAIDs undergo extensive metabolism; some through phase I reactions followed by phase II reactions, while others undergo direct phase II (glucuronidation) reactions only. The NSAIDs are dominantly metabolized in the liver, by CYP3A or CYP2C families of P450 enzymes. (3)Most of NSAIDs (95–99%) are highly bound to plasma proteins, they may displace other medications that may results in clinically significant interactions. NSAIDs are widely distributed throughout the body and mostly excreted by kidney.According to the half-lives, NSAIDs can be classified as the ones with shorter t1/2 (<6 h, e.g., diclofenac, aspirin, ibuprofen) and longer t1/2 (>10 h, e.g., celecoxib, naproxen,

oxicams).(3)Side effects have a greater influence in terms of morbidity, mortality quality of life and also increase healthcare resource utilization, such as diagnostic testing, doctor visits, hospitalizations and medications. Identification of specific risk factors and precise determination of NSAID induced adverse effects will help us to develop appropriate management strategies for patients taking NSAID therapy, leading to maximum potential benefits and minimum adverse events. (4)Among all studies most common adverse reactions included rash, urticaria and other allergic reactions followed by gastrointestinal complications such as ulcer, abdominal pain, nausea and vomiting and dyspepsia. Certain syndromes were also reported like Stevenson Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic syndrome (DRESS).Diclofenac, ibuprofen and etoricoxib were the most common ADR causing drugs

ADVERSE DRUG REACTION:

WHO defines ADR as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiologic functions” (19)

ADVERSE DRUG EVENT:

ADE is any untoward medical occurrence presenting during the administration of drug.(19)A key contrast between an ADE and an ADR is that an ADE is related with inappropriate use of the drug or other confounders that occur during drug therapy but are not always caused by the pharmacology of the drug itself, whereas an ADR occurs despite proper prescribing and dosing. A causal relationship is not required for an ADE but suspected for an ADR. ADE may also results from medication error. The National Coordinating Council For Medication Error Reporting And Prevention defines as “any preventable event that may cause or lead to inappropriate medication is in the use or patient harm while the medication is in the control of the health care professional, patient or consumer” (20)

ASSESSMENT:
A New or worsening symptom is the first sign of an ADR in inpatients as well as inoutpatients.Laboratory monitoring helps in the diagnosis of an ADR.A new order of laboratory or diagnostic procedure may indicate that an adverse drug reaction hasoccurred.Obtaining baseline laboratory values before initiation of therapy assists in anticipation of adverse drug reactions. Laboratory monitoring can assist in determining improvement or decline after a change in therapy

CAUSALITY ASSESSMENT OF ADR-WHO SCALE:

Causality assessment (CA) is method of evaluation to find out the relationship between drugs exposed and reported Adverse Drug Reaction (ADR). It will be categorized based on several criteria as given below

- Time relationship between the drug use and adverse reaction
- Absence of other competing causes
- Response to drug on withdrawal or dose reduction (de-challenge)
- Response to drug on re-administration (re-challenge)

Causality assessment will be classified into: Certain, Probable, Possible, Unlikely, Conditional (unclassified) and Unassessable.

RESULTS

1.PATIENT DEMOGRAPHICS

A total of 147prescriptions prescribed with NSAIDs were studied. The demographics of the patients are elucidated in Table.1 of which57 patients (38.8%) were males and 90 patients (61.2%) were females. Among which5 patients (3.4%) belonged to 18-30 years age group, 17 patients (11.6%) belonged to 29-38 years age group, 49 patients (33.3%) belonged to 39- 48 years age group, 46 patients (31.3%) belonged to 49-58 years age group,25 patients (17%) belonged to 59-68 years age group, and 5 patients (3.4%) belonged to 69-8 years age group which is depicted in the table 2

Table:1-Gender distribution

GENDER	FREQUENCY(N=147)	PERCENTAGE (%)
MALE	57	38.8
FEMALE	90	61.2
TOTAL	147	100

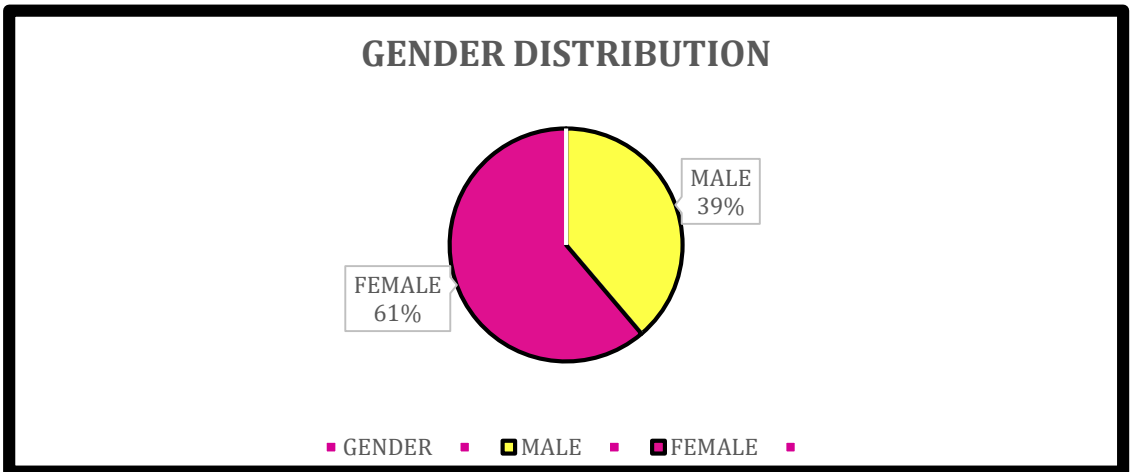

Figure: 1-Gender distribution

Table: 2-Age distribution

AGE (years)	FREQUENCY(N=147)	PERCENTAGE (%)
19-28	5	3.4
29-38	17	11.6
39-48	49	33.3
49-58	46	31.3
59-68	25	17.0
69-78	5	3.4
TOTAL	147	100

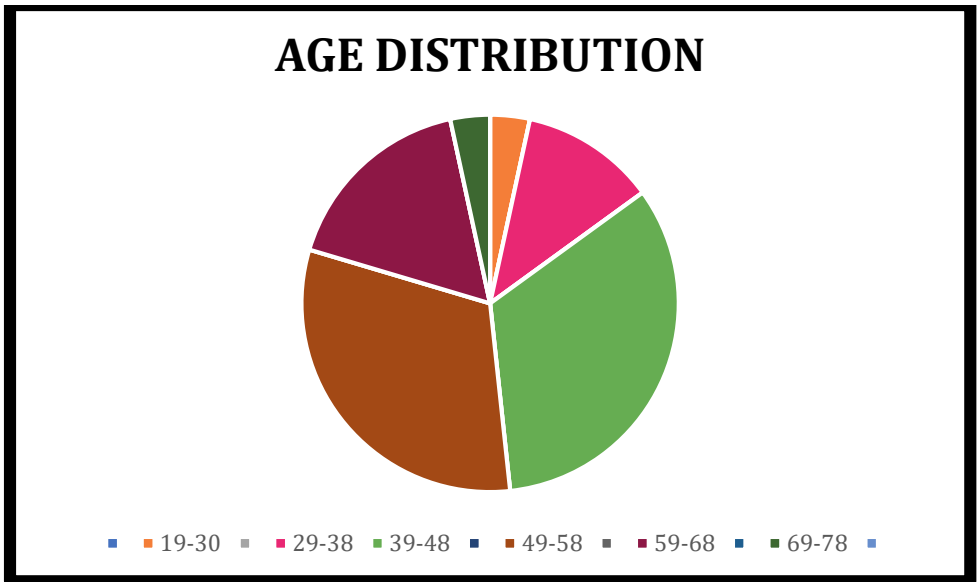

Figure: 2- Age distribution

3.INDICATIONS:

Out of 147 patients, the most common indication for which NSAIDs were prescribed was Fever (51.7%) followed by Diabetic foot ulcer (36%)

TABLE: 3-INDICATIONS

INDICATIONS	FREQUENCY	PERCENTAGE (%)
FEVER	76	51.7
OSTEOARTHRITIS	5	3.4
TRAUMA	10	6.9
RHEUMATOID ARTHRITIS	2	1.3
DIABETIC FOOT ULCER	54	36.7

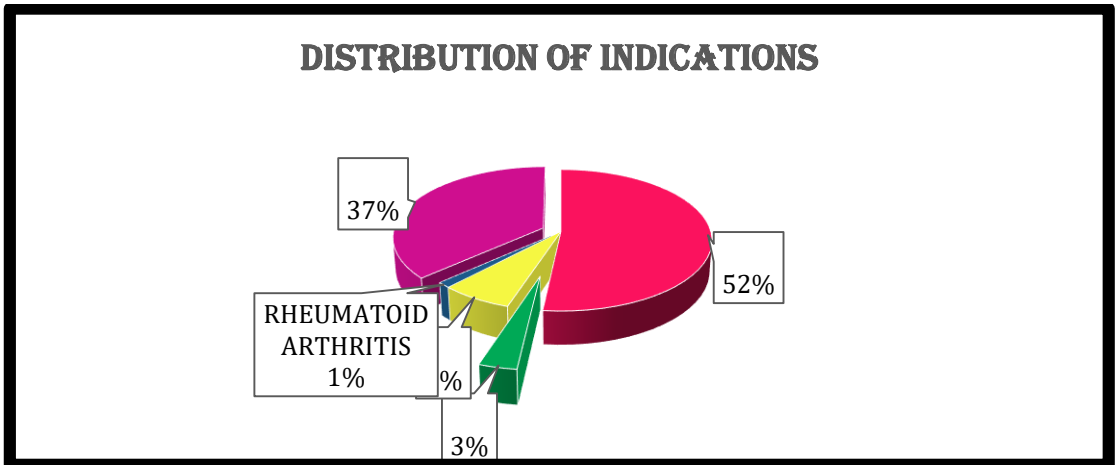

Figure: 3- INDICATIONS

4.Types of NSAIDs prescribed

The most common type of NSAIDs prescribed in OPD of orthopedic was Paracetamol (59.8%) and Diclofenac (44.8%) followed by Aceclofenac (4.0. %), Tramadol + Paracetamol combination (5.4%)

Table: 4 -Types of NSAIDs prescribed

NSAIDs	FREQUENCY(N=147)	PERCENTAGE (%)
ACECLOFENAC	6	4
DICLOFENAC	66	44.8
TRAMADOL+ PARACETAMOL	8	5.4
PARACETAMOL	88	59.8

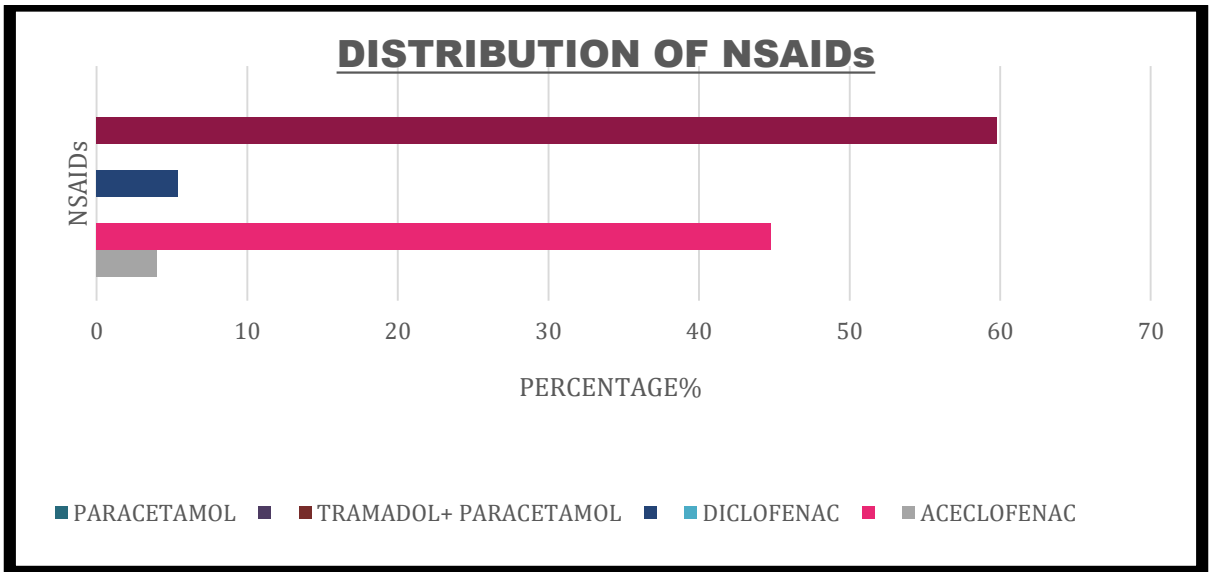

Figure: 4—Distribution of NSAIDS

5.Route of administration of NSAIDs:

Majority of NSAIDs were prescribed by oral route (94.8%) and least prescribed route was found to be parenteral (5.2%)

TABLE: 5- Route of administration

ROUTE OF ADMINISTRATION	FREQUENCY(N=147)	PERCENTAGE (%)
ORAL	145	94.8
PARENTERAL	8	5.2

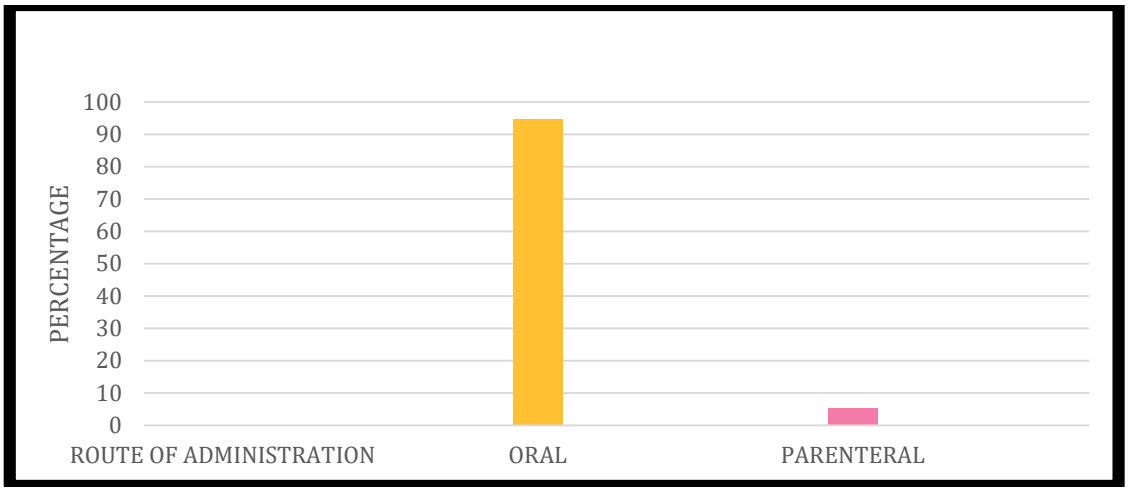

Figure: 5 - ROUTE OF ADMINISTARTION

6.Gastric protectants:

Gastric protectants are given as preventive co therapy in NSAIDs containing prescription. In this study 69 prescriptions included Omeprazole (49%) and 62 prescriptions included Pantoprazole (44%) and 10 prescriptions included Rabeprazole (7 %)

TABLE: 6-Gastric protectant

GASTRIC PROTECTANTS	FREQUENCY	PERCENTAGE (%)
RABEPRAZOLE	10	7
PANTOPRAZOLE	62	44
OMEPRAZOLE	69	49

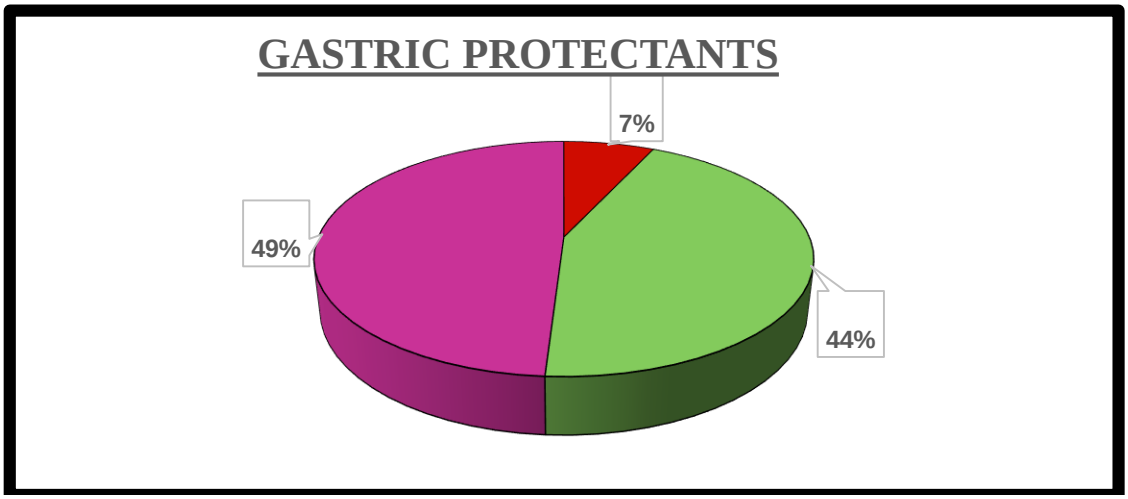

Figure: 6-GASTRIC PROTECTANTS

7.Distribution of Other drugs:

The concomitant therapy given along with NSAIDs include Antibiotics (34.2%), multivitamin (26.9%), Anti-diabetic drugs (21%) and Antihypertensive drugs (17.9%)

TABLE: 7-Distribution of other drugs

OTHER DRUGS	FREQUENCY	PERCENTAGE (%)
ANTIBIOTICS	65	34.2
MULTIVITAMIN	51	26.9
ANTIDIABETIC DRUGS	40	21.0
ANTIHYPERTENSIVE DRUGS	34	17.9
TOTAL	**190**	100

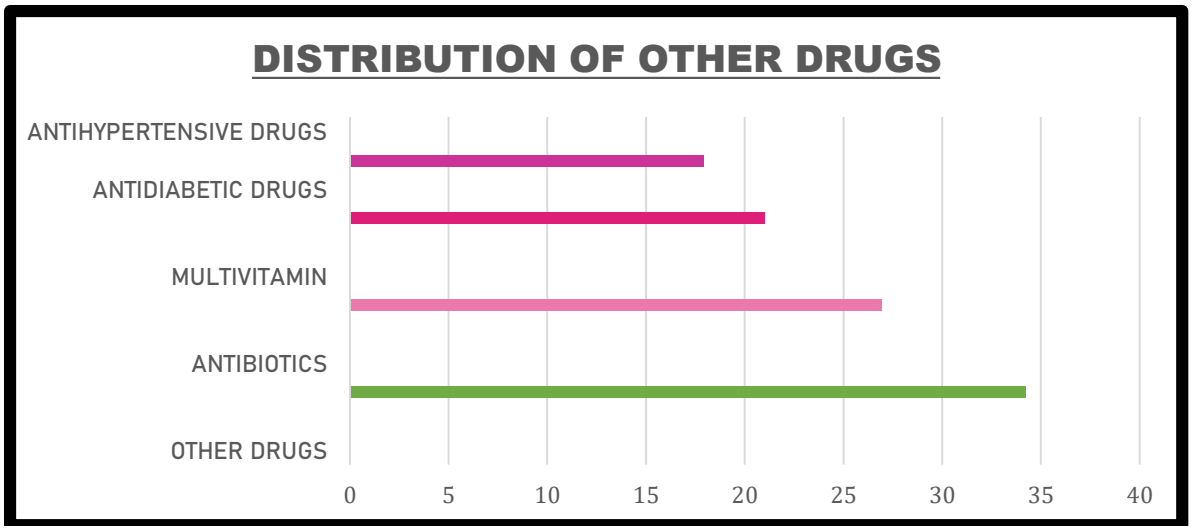

Figure: 7 DISTRIBUTION OF OTHER DRUGS

8.ADVERSE DRUG RAECTIONS:

In our study totally six adverse drug reactions were reported. Among all NSAIDs prescribed Diclofenac tends to cause more no of adverse reactions, followed by Aceclofenac and least caused by Paracetamol

TABLE: 8- ADVERSE DRUG REACTIONS

NSAID	ADR	WHO SCALE	NO.OF ADR	INDICATION
Diclofenac	Steve Johnson syndrome	Certain	1	Pain and Inflammation
Aceclofenac	Acute kidney injury	Probable	1	Pain and Inflammation
Paracetamol	Gastritis	Probable	3	Fever
Aceclofenac	Abdominal pain	Probable	1	Pain and Inflammation
Diclofenac	Gastritis and GI distress	Probable	1	Pain and Inflammation
Diclofenac	Rashes	Certain	2	Pain and Inflammation

DISCUSSION:

Precise determination of NSAID induced adverse effects helped us to develop appropriate management strategies for patients taking NSAID therapy, leading to maximum potential benefits and minimize adverse events.

A total of 147 subjects were enrolled during 6 months of study period. The study subjects were enrolled based on designed inclusion and exclusion criteria.

Among the study population female patients [61.2%] were more predominant than male patients [38.8%] . This study is consistent with a study done by ShidhaniAetal., in which most of the patients under NSAID therapy were females [56%].

Within the study population, most of the patients prescribed with NSAIDs were belonging to the age category of 39-48[33.3%] followed by the age category of 49-58 [31.3%]which is similar to the findings of Bhaskar R et al., (2015) in his study in Bengaluru, Karnataka

In our study population, NSAIDs were predominantly prescribed for fever [n=76] followed by pain and inflammation[n=54]. This is consistent with the study done by Kumar S et al., were NSAIDs are mostly prescribed for pain followed by inflammation.

Among our study population, Paracetamol [59.8%] was the most prescribed NSAID, followed by Diclofenac [44.8%]. This is consistent with the study conducted by Vaishnavi PR et al., in which the study concluded that paracetamol [27.03%] was prescribed more followed by diclofenac

Among the study population, NSAIDs were mostly administered via oral route [94.8%] and were followed by parenteral routes [38.8%]. This is similar to the findings reported in a study conducted by Bahreini A et al., where oral therapy was found to be the most commonly used route of administration with a frequency of 47.34%, followed by parenteral therapy with 31.02%.

NSAIDs are co-prescribed with PPI and H2 receptor antagonists to prevent NSAID-induced GI adverse effects. During the study period, Omeprazole (49%) was given more commonly as a gastro-protective agent followed by Pantoprazole (44%) and ranitidine (7%).

During our study period, totally nine adverse events were documented. More frequently reported adverse drug reactions were due to Diclofenac followed by Aceclofenac which were similar to the study conducted by **Padmanabha et al.,** which revealed that proportion of ADR such as skin rash and gastritis was more frequent with Diclofenac.

CONCLUSION:

In this study majority of the middle-aged patients were given NSAIDs for symptom alleviation. Diclofenac was the most widely prescribed NSAID, according to our study and Oral formulations were most frequently prescribed than parenteral formulations. Non- Selective NSAIDs were found to be the least commonly prescribed whereas Preferential COX2 Inhibitors were found to be the most commonly prescribed. Combination therapy is preferable to monotherapy. Despite the clinical benefits of NSAIDs in pain and inflammatory conditions, they are mostly associated with gastrointestinal complications. In this study gastric protectants are given as a preventive co therapy along with NSAIDs. Only few patients were not prescribed with NSAIDs.
The major risk factors which induces adverse events include age, concomitant illness, gastric ulcer, peptic or duodenal ulcer, polypharmacy, and drug interactions. Adverse drug reactions especially gastric distress developed in patients who were not prescribed with gastric protectants. This implicates the necessary measure to follow the preventive co-therapy in every NSAID prescription. Rashes and allergic reactions such as urticaria developed secondary to gastric complications. The incident rate of ADR in this study was found to be 4.08%. Pharmacovigilance enhances the recognition of reporting Adverse drug reactions by health care professionals. It is an important tool to reduce the incidence of adverse events and improve patient care and enhance rational prescribing. Thus compliance to pharmacovigilance guidelines reduces the ADR and economic burden on patients.

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