



# A Review On Adverse Drug Reaction Of Ibuprofen

Harish R. Kayatwar, Aboli A. Dagamwar, <sup>3</sup>Sneha S. Kamatwar, <sup>4</sup>Shital N. Thengane.

<sup>1</sup>Satish B. Kosalge

Hi-Tech College of Pharmacy, Chandrapur, India.

**Abstract:** In this review article we discussed about the adverse drug reactions and its types and risk factors of adverse drug reaction, also we discussed about the role of pharmacovigilance in adverse drug reactions. Ibuprofen is an analgesic and antipyretic medication that is a derivative of phenyl propionic acid. It may be utilised both alone and in combination. There are numerous adverse effects that are dose-related. Higher dosages and chronic use may have adverse effects on the liver, kidneys, heart, blood vessels, gastrointestinal tract, and immune system, among other things. Surveillance, monitoring, and patient education are essential for decreasing adverse drug reactions. This side effect can be treated. ADR needs to be discussed to patients and documented in files. It should be illegal to manufacture combinations of two or more medications. Prescriptions should be properly audited, and ADR notification should be made legally required. Patients should receive education about how to avoid using self-medication. Clinical pharmacologists', doctors', or neurologists' suggestions are highly valued for better care that can hasten the patient's recovery.

**Index Terms – Ibuprofen, Antipyretic, Analgesic, NSAID'S ADR'S**

## I. INTRODUCTION

### Adverse Drug Reaction

Worldwide, adverse drug reactions (ADRs) are a significant cause of illness and mortality. According to the World Health Organisation (WHO), an adverse drug reaction (ADR) is a reaction to a poisonous and unexpected substance that happens at dosages given to humans for the purpose of preventing, diagnosing, and treating of disease.<sup>[1]</sup> Adverse drug responses, or ADRs, are defined as: "A response to a drug that is noxious and unanticipated, and that occurs at levels ordinarily employed for the prevention, diagnosis, or treatment of disease, or for the change of physiological function."<sup>[2]</sup> Growing research indicates that ADRs are occurring more frequently and severely, which has a detrimental effect on patients' health state. ADRs also place a major strain on healthcare facilities, extending hospital stays and occasionally necessitating further care. For the therapy of disorders and symptoms brought on by the patient, research and medication therapies are used.<sup>[3]</sup> ADRs have developed to be a serious issue for people taking several drugs, including the elderly. According to a research, up to 75% of elderly inhabitants took medication. differences following the change from a hospital setting to a primary care one. According to a study, as many as 75% of all elderly residents had prescription errors after transferring from the hospital to a primary care setting.<sup>[4]</sup> The most frequent form of medical treatment, drugs are largely employed to ease suffering. But it has long been known that drugs themselves can be fatal; as the adage "Drugs are Double Edged Weapons" says, "Drugs are deadly." Monitoring and reporting of adverse reactions are essential in finding the negative reaction tendencies in the community.<sup>[5]</sup>

## History of adverse drug reaction

ADRs are a prevalent manifestation in clinical practise, including as a cause of unscheduled hospital admissions, occurring during hospital admission, and manifesting consequently, according to ground-breaking research conducted in the United States and the United Kingdom in the late 20th and early 21st centuries. discharge.<sup>3-6</sup> While research indicates that between 5% and 10% of patients may experience an ADR at admission, during hospitalisation, or at discharge, despite numerous prevention measures, the incidence of ADRs has remained largely stable over time.<sup>[6]</sup> The volume of ADR reports in China has rapidly expanded in recent years. In 2020, China's Adverse Drug Reaction Monitoring System received 1.676 million ADR complaints, which represents 10% of all reports (1251 instances per million people). 9 ADRs lengthen patients' treatment times and raise the expense of their medical care.<sup>[7]</sup>

## Types of adverse drug reaction <sup>[8]</sup>

Type of ADRs	Characteristics	Examples
Type A	-Dose-related -Related to a pharmacological action of drug -Predictable from known pharmacology	-Nephrotoxicity caused by aminoglycosides -Anticholinergic effects of tricyclic antidepressants
Type B	-Not dose-related -Uncommon -No relation to a pharmacological action of the drug	-Penicillin- induced urticaria -Anticonvulsant hypersensitivity syndrome reaction
Type C	-Uncommon -Long term exposure of drugs	-Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
Type D	-Uncommon Long term exposure of drugs	-Tardive dyskinesia caused by antipsychotic medication
Type E	-Termination of treatment	-Tachyphylaxia

## Pharmacovigilance

"The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" is the meaning of pharmacovigilance. Therefore, the purpose of pharmacovigilance is to warn about potential hazards associated with a medicine. Pharmacovigilance therefore seeks to raise awareness of a drug's possible hazards. the effectiveness of pharmacovigilance procedures is thus constrained by the underreporting of medical practitioners. The health authorities of numerous nations have in the past organised the collection of data directly from patients. Studies have demonstrated that some reports from patients can be of comparable quality to those from medical experts, but patient reporting is still insufficient because few patients are aware of the reporting system.<sup>[9]</sup>

The Government of India established the Pharmacovigilance Programme of India (PvPI), whose contribution to the WHO-UMC Pharmacovigilance database is somewhat limited because to the lack of a strict monitoring mechanism and a lack of knowledge on ADR reporting among health care providers. Furthermore, unlike some nations, such as Spain and Sweden, the Indian government does not require ADRs reporting. As a result, a strong pharmacovigilance system must be established as a requirement for the drug safety process. This system should support not only the collection, surveillance, and analysis of data related to ADRs, but also the development of strategies for risk minimization and drug utilisation.<sup>[10]</sup>

## Aims of pharmacovigilance

1. Identification of severe and unforeseen adverse drug reactions to known medications, as well as even modest ones

to newer medications.

2. Determining the risk variables linked to the emergence of negative drug responses, mechanisms of Type A, Type B,

Type C, etc. that cause them.

3. Quantitative estimation of the incidence, prevalence, and risk factors for negative drug reactions. estimation of the

ADR-related pharmacoeconomic data, for example:

a. How much do ADRs lengthen hospital stays?

b. How much does managing ADRs ultimately cost (directly and indirectly), and how much does it cost the country and the hospital?

c. How much do ADRs contribute to hospital admissions?

d. How widespread is morbidity and mortality overall?<sup>[11]</sup>

## Definations

1. “any undesirable or unintended consequence of drug administration”.<sup>[12]</sup>

2. defined as “an undesirable effect, reasonably associated with the use of the drug that may occur as a part of the pharmacological action of a drug or may be unpredictable in its occurrence”.<sup>[13]</sup>

3. Adverse drug reactions (ADRs) are any unwanted/uncomfortable effects from medication resulting in physical, mental, and functional injuries.<sup>[14]</sup>

## Reasons for adverse reactions

1. Dispensing and Medication administration errors
2. Failure to set therapeutic end point
3. Bioavailability differences
4. Patient factor<sup>[15]</sup>

## Classification of adverse drug reaction.<sup>[16]</sup>

Adverse reaction is classified in to two types

### 1 predictable or type 1 or non immunological

- Excessive pharmacological effect.
- Side effects.
- Toxic effects
- Secondary pharmacological effect
- Rebound response after discontinuation. effects.
- Toxic effects
- Secondary pharmacological effect
- Rebound response after discontinuation.

### 2 Unpredictable or Type B or Immunologic Reactions

- Idiosyncrasy or Pharmacogenetics
- Genetically determined toxicity.
- Allergic drug reaction (hypersensitivity reaction).
- Super sensitivity
- Photosensitivity.
- Intolerance.

## Risk Factors Of ADR

### 1. Drug Related Factors

- a) Drug Dose and Frequency
- b) Poly Pharmacy

### 2. Patient Related Factors

- a) Age
- b) Gender
- c) Pregnancy
- d) Renal function
- e) Disease Related Factors

### 3. Social factors

- a) Race and Ethnicity
- b) Alcohol
- c) Smoking<sup>[17]</sup>

## II. IBUPROFEN

Stewart Adams made the discovery of ibuprofen in 1961, and it was first sold under the name Brufen.[18] Ibuprofen is a nonsteroidal anti-inflammatory medicine (NSAID) that treats a variety of conditions, curing the temperature, discomfort, etc. It is used to treat mild to moderate pain, inflammation, and fever brought on by a wide range of illnesses. It is used to treat osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and menstrual cramps (dysmenorrhea). Ibuprofen has certain drawbacks besides its benefits. Failure of the heart, kidneys, and liver are all made more likely by it. It doesn't seem to increase the risk of heart attack at low doses, but at greater doses, the risk might go up. The World Health Organization's list of essential medications, which includes the chemical medicine in question.

### Structural formula

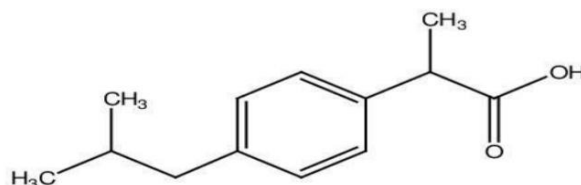


Fig. Structure of ibuprofen

**Molecular Formula:** C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>

**Molecular Weight:** 206.29 g/mole

**IUPAC name:** (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid

**Density:** 1.03 g/ml g/cm<sup>3</sup>

**Melting Point:** 75–78°C (167–172°F)

**Boiling Point:** 157°C (315°F)

**Odour:** Characteristic odour

**Colour:** Colourless, crystalline stable solid

### Solubility

1. Readily soluble in most organic solvents.
2. Very soluble in alcohol.
3. 21 mg/L (at 25°C).

### Pharmacology

Ibuprofen has antipyretic and analgesic effects. From a pharmacological perspective, its effects are comparable to those of other traditional NSAIDs. Ibuprofen is an NSAID produced from propionic acid that possesses anti-inflammatory, analgesic, and antipyretic properties in addition to having aspirin's cardioprotective properties. The activity of cyclooxygenase I and II is inhibited by ibuprofen, which reduces the production of precursors to prostaglandins and thromboxanes. The main physiological effect of the medicine is a reduction in prostaglandin synthesis, which results from this. Additionally, thromboxane synthase's production of thromboxane A<sub>2</sub> is reduced by ibuprofen, which prevents platelet aggregation. When used orally, the medication is quickly and completely absorbed. After biotransformation into glucuronide conjugate metabolites, which are expelled in urine, ibuprofen is eliminated.

### Mechanism of action

Arachidonic acid is converted in the body into prostaglandin H<sub>2</sub> by the enzyme cyclooxygenase (COX), which is necessary for prostaglandin synthesis via the arachidonic acid route. Additionally, anticoagulant effects are brought about by inhibiting COX, which changes arachidonic acid into thromboxane A<sub>2</sub>, an essential component in platelet aggregation that results in blood clot formation. Because the maintenance of the gastric mucosa is altered, an excessive dose of NSAID may result in the long-term inhibition of COX-1, a subtype of COX that may induce gastric toxicity.

## Contraindications

- Active peptic ulcer.
- Aspirin.
- Breastfeeding.
- Gastrointestinal bleeding.
- Hypersensitivity.
- Neonates with congenital heart disease.
- A study of pregnant women suggests that those taking any type or amount of NSAID (including ibuprofen, diclofenac, and naproxen) were 2.4 times more likely to miscarry than those not taking the drugs.<sup>[18]</sup>

## Dosage

- People of age between 20 to 45 years suffering from fever and minor aches are treated with 200-400 mg for every 4-6 hours.
- A person with arthritis is treated with 300–800 mg 3 or 4 times daily. Individuals should not use ibuprofen for more than 10 days for the treatment of pain or more than 3 days for the treatment of a fever unless directed by a physician.
- Children from 6 months to 12 years of age usually are given 5–10 mg/kg of ibuprofen every 6–8 hr. for the treatment of fever and pain. The maximum dose is 40 mg/kg daily.
- A person suffering from juvenile arthritis is treated with 20-40 mg/kg/day in 3–4 divided doses.<sup>[19]</sup>
- Combination of ibuprofen and paracetamol (200/500 mg) tablets is frequently indicated for temporary relief of mild to moderate pain associated with migraine, headache, back- ache, period pain, dental pain, rheumatic and muscular pain.<sup>[20]</sup>

## Uses

1. Ibuprofen is used as a simple analgesic and antipyretic in the same way as low dose of aspirin. It is particularly effective in dysmenorrhoea in which the action is clearly due to PG synthesis inhibition. It is available as an 'over-the-counter' drug.
2. Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders, especially where pain is more prominent than inflammation.
3. They are indicated in soft tissue injuries, fractures, vasectomy, tooth extraction, postpartum and postoperatively: suppress swelling and inflammation.

## Adverse effect of ibuprofen

Aspirin is less well tolerated than ibuprofen and all of its equivalents. Side effects are less severe and less common. Though less frequent than those from aspirin or indomethacin, nausea, vomiting, and gastric discomfort are still the most frequent side effects. Both gastric erosion and covert bleeding are uncommon. Headache, wooziness, blurred vision, tinnitus, and depression are CNS side effects. It is unusual to experience rashes, itching, or other hypersensitivity problems. However, these medications exacerbate asthma brought on by aspirin. Fluid retention is not as noticeable. They should not be prescribed to expectant mothers, and peptic ulcer patients should not take them.<sup>[21]</sup>

### 1. Hepatic side effect

Not typically. Ibuprofen and other NSAIDs hardly ever have liver side effects. According to estimates, between 1 and 10 out of every 100,000 people who take NSAIDs develop liver impairment. The majority of users have little risk of liver damage from NSAIDs currently on the market. NSAIDs increase the risk of liver issues. People who already have a higher risk of developing liver disease are more likely to experience it. They have a history of liver issues like hepatitis C, for instance. Additionally, the danger is increased if you simultaneously take other medications that are hard on the liver.<sup>[22]</sup>

### 2. Allergic reactions

Ibuprofen use can result in a severe allergic reaction, which is particularly common in people who are aspirin allergic. Immunoglobulin E (IgE)-mediated or non-IgE-mediated allergic responses associated with ibuprofen are two possible outcomes. Ibuprofen allergy symptoms could include the following: Hives, a swollen face, rashes, and asthma (wheezing), Breathing difficulties, shock, skin reddening, and blister.<sup>[23]</sup>

### 3. Gastrointestinal Side Effects

According to a significant research, unfavourable GI effects from oral NSAID treatment are expected to be 15% more common than those from topical NSAID use. Oral care was provided to 1100 patients who were admitted to the hospital with upper GI bleeding or ulcers in a case-controlled study.

### 4. Renal Side Effects

Comparing topical NSAIDs to their oral counterparts, there are fewer studies that have specifically examined the renal side effects. Prior research indicates that topical treatment may be significantly more effective than oral ibuprofen in the 24-hour renal excretion of 0.57 and 97%, respectively. safer in people who have kidney impairment.

### 5. Cardiovascular Side Effects

There is limited research on the cardiovascular side effects, similar to the renal side effects. of ibuprofen applied topically. However, it has been consistently shown that ibuprofen taken orally impairs aspirin's capacity to inhibit platelet aggregation, hence it should be avoided by athletes. are taking aspirin as a preventative measure to prevent negative consequences like myocardial or cerebral infarction. [24]

According to estimates, 1 in 5 people who use NSAIDs chronically over an extended length of time will experience silent stomach injury. Less often reported ibuprofen side effects include others. They consist of impaired vision, rashes, headaches, and thrombocytopenia. eyesight, fluid retention, and edoema, as well as toxic amblyopia in rare circumstances. Ibuprofen use should be stopped by patients who experience eye problems. Acute renal failure, interstitial nephritis, and nephritic syndrome are kidney-related side effects (as with all NSAIDs), but these conditions are extremely rare. [25]

### 6. Drug-Drug Interactions

Ibuprofen and NSAIDs have known pharmacokinetic or pharmacodynamic interactions.79,80 The most dangerous interactions include the use of NSAIDs with lithium, warfarin, oral hypoglycemics, high dose methotrexate, antihypertensives, angiotensin converting enzyme inhibitors,  $\beta$ -blockers, and diuretics. When these medications are taken together, anticipation and careful monitoring can frequently prevent serious events.

### 7. Food-Drug Interaction

The simultaneous consumption of meals had an impact on the absorption of oxycodone and ibuprofen when given as a combo tablet. Ibuprofen absorption was unaffected by food intake prior to the administration of a single dosage of the combination, but it did slightly increase the extent but not the rate, of oxycodone ingestion. Investigations have been done on how food affects the plasma concentration-time profile of ibuprofen dose forms with sustained release. following a night of fasting or with a hearty vegetarian breakfast. On the plasma concentration-time curve, the formulation showed several peaks. Ibuprofen's bioavailability was unaffected by meals, although its mean concentration rose statistically significantly. The results showed that while the type and character of the formulation have the biggest impact on qualitative changes in the plasma concentration versus time curves, bioavailability of a meal is influenced by the drug's absorption properties as well. [26]

## III. CONCLUSION

From the above review we concluded that, ibuprofen is a phenyl propionic acid derivative, used as antipyretic and analgesic drug. It can be used as single or in combination. It shows many adverse effect which are dose related. In higher doses and usage for prolonged period, it may cause Hepatic side effect, Renal Side Effects, Cardiovascular Side Effects, Gastrointestinal Side Effects, Allergic reactions etc. This adverse effect can be managed by, Surveillance, monitoring and education of patients are important in preventing adverse drug reactions. ADR should be recorded in file and communicated to patients. Manufacture of combination of two or more drugs should be banned. There should be proper audit of prescriptions and notification of ADR should be made mandatory. Patients should be educated on prevention of self-medication. Inputs from clinical pharmacologists, physicians or neurologists are most welcomed for improved management which can help in faster recovery of the patient.

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