WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 21, 485-500. Review Article ISSN 2277–7105

THE CORNERSTONE OF PHARMACOVIGILANCE: DRUG SAFETY AND ADVERSE EVENT

[1]*Revati I. Dapurkar, [2]Sampada S. Jadhav, [3]Nikita V. Mahalle and [4]Harigopal S. Sawarkar

Dr. Rajendra Gode College of Pharmacy, Amravati, Maharashtra-444602, India.

Article Received on
09 September 2024,

Revised on 30 Sept. 2024,
Accepted on 21 October 2024

DOI: 10.20959/wjpr202421-34431

***Corresponding Author**
Revati I. Dapurkar
Dr. Rajendra Gode College of Pharmacy, Amravati, Maharashtra-444602, India.

ABSTRACT

Pharmacovigilance, or Drug Safety, encompasses the science and activities aimed at detecting, assessing, and preventing adverse drug reactions (ADRs) to enhance patient safety and treatment outcomes. ADRs can vary from mild side effects to severe, life-threatening conditions. Effective monitoring and reporting are essential for improving drug safety. ADRs are classified into six types: Type-A (Augmented), Type-B (Bizarre), Type-C (Continuous), Type-D (Delayed), Type-E (End-of-dose), and Type-F (Failure of Therapy). The field emerged in response to the Thalidomide tragedy of the late 1950s, prompting stringent drug safety regulations, including the Kefauver-Harris Amendment and the WHO Programme for International Drug Monitoring. Current PV systems include the Spontaneous Reporting System (SRS), which relies on voluntary reports; Cohort Event Monitoring (CEM), which actively investigates specific medications; and Targeted Spontaneous Reporting (TSR), focusing on specific patient groups. Additionally, the use of proton pump inhibitors (PPIs), widely prescribed for acid-related conditions, has been linked to adverse effects such as gastrointestinal issues, nutrient malabsorption, kidney problems, and potential gastric cancer. These findings underscore the critical need for ongoing monitoring and cautious prescribing practices in pharmacotherapy. Proton pump inhibitors (PPIs) are commonly used to treat gastrointestinal conditions, but long-term use may lead to adverse reactions. This case report describes a patient who developed thrombocytopenia after initiating PPI therapy, which resolved upon discontinuation. This highlights the importance of considering PPIs as a potential cause of idiopathic thrombocytopenia.

KEYWORDS: Pharmacovilance, Adverse Drug Reaction, Spontaneous Reporting, Cohort Event monitoring, Targeted Spontaneous Reporting.

INTRODUCTION

PHARMACOVIGILANCE

According to the World Health Organization, "Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem, particularly long term and short term adverse effects of medicines." Pharmacovigilance is also known as Drug Safety and abbreviated PV or PhV. The etymological roots for the word "pharmacovigilance" are: Pharmakon (Greek word for 'drug') and vigilare (Latin word for 'to keep watch'). Pharmacovigilance greatly focuses on adverse drug reactions (ADRs) which are defined as any reaction to a drug which is harmful and unintended including lack of efficacy used for the prophylaxis, analysis or therapy of illness.

ADVERSE REACTION

An Adverse substance Reaction (ADR) is any unexpected or adverse response to a prescription or substance. Adverse Drug Events (ADEs) can range from minor side effects to potentially fatal consequences. ADRs can arise owing to variables such as individual differences in drug metabolism, interactions with other drugs, allergies, dose errors, or underlying medical disorders. Common adverse reactions (ADRs) include nausea, dizziness, skin rashes, gastrointestinal difficulties, and allergies. In severe circumstances, ADRs can cause organ damage, anaphylaxis, and even death.

Monitoring and Understanding ADRs are significant in healthcare, affecting patient safety and treatment outcomes. PV the monitoring and evaluation of drug safety, is crucial for identifying and controlling adverse drug responses. PV allows healthcare providers and regulatory agencies to gather and evaluate data on adverse drug reactions (ADRs) to improve drug safety, update labels, and make informed decisions about prescription use.

Reporting adverse drug responses is crucial for identifying potential safety issues, protecting patients, and improving overall drug safety. Healthcare personnel and patients should report suspected adverse drug reactions (ADRs) to improve patient care and promote safe medication practices.

CLASSIFICATION OF AN ADVERSE REACTION

1. **Type-A (Augmented):** It is the most common (up to 70%) and is dose-dependent. Severity increases with dose. Slowly introducing low dosages can mostly prevent this issue. Pharmacological mechanisms, such as beta-blockers are causing hypotension, insulin causing hypoglycemia, or NSAIDs causing gastric ulcers, might predict potential side effects.
2. **Type-B (Bizarre):** conditions are rare, unique, genetically driven, and unpredictable, with unclear underlying mechanisms. Serious and potentially fatal side effects of medications, such as hepatitis from halothane, aplastic anemia from chloramphenicol, and neuroleptic malignant syndrome from various anesthetics and antipsychotics, are not dose-related.
3. **Type-C (Continuous drug usage)**: A condition caused by continued drug use. Antipsychotic medicine can cause irreversible and unforeseen side effects, such as tardive dyskinesia and dementia**.**
4. **Type-D (Delayed) ADRs:** It occurs after treatment termination, such as corneal opacities from thioridazine, ophthalmopathy from chloroquine, or pulmonary/peritoneal fibrosis from methyserzide.

- **Type-E (end-of-dose):** Withdrawal symptoms. Occurs with depressant medications, such as hypertension and restlessness in opiate abstainers, seizures during alcohol or benzodiazepine withdrawal, and first-dose hypotension from alpha-blockers (Prazosin or ACE inhibitors).
- **Type-F (Failure of Therapy):** It refers to ineffective treatment results, such as accelerated hypertension due to inefficient control, which were previously omitted from the WHO criteria. Adverse medication reactions can be treated similarly to other medical conditions.

HISTORICAL BACKGROUND OF PV

Thalidomide tragedy (Late 1950s-Early 1960s): The thalidomide Tragedy stands as a pivotal event in the history of PV. Thalidomide was a drug prescribed to pregnant women for morning Sickness and sleeplessness. However, it was later discovered that Thalidomide caused severe birth defects, leading to limb deformities in thousands of newborns. This tragic incident highlighted the need for rigorous drug safety evaluation and monitoring.

Kefauver-Harris Amendment (1962): Following the thalidomide tragedy, the US enacted

the Kefauver-Harris Amendment, which tightened drug laws and mandated that pharmaceutical firms prove the products' safety and efficacy before approving them.

World Health Organization's (WHO) Programme for International Drug Monitoring (PIDM)(1968): which was carried out in association with the Uppsala Monitoring Centre (UMC) in Sweden. In order to promote international collaboration in drug safety, PIDM sought to gather and evaluate data on adverse drug reactions from different nations.

Development of adverse drug reaction reporting systems (1970s–1980s): During this time, numerous nations created their own national pharmacovigilance and adverse drug reaction reporting systems. By enabling the public and medical experts to report suspected adverse reactions, these platforms helped to expand the database of data on medication safety. Pharmaceutical industry and regulatory authorities worldwide came together to form the ICH. Since then, several facets of PV and safety reporting have been covered by ICH standards, which have streamlined procedures globally.

In the 2000s, regulatory bodies like as the FDA and EMA focused on strengthening PV systems: This involved creating risk management policies, upgrading safety labeling, and enhancing signal detecting methods.

Recent technological advancements: Technological advancements have led to major gains in PV data collecting, detection, and analysis. Electronic health records, data mining, and AI have improved the efficiency and accuracy of monitoring adverse medication reactions.

ROLE OF PV IN DRUG REGULATION

The basis for both public trust in medicines and a national approach to drug safety is strong regulatory frameworks. The jurisdiction of drug regulatory bodies must cover a greater variety of matters pertaining to the safety of pharmaceuticals in order for them to be effective, beyond only approving new drugs. These matters include:

- Clinical Trials
- The security of biological medications, vaccinations, and complementary and alternative therapies
- The establishment of communication channels amongst all stakeholders with a stake in medication safety to guarantee their ability to operate effectively and morally, especially during emergencies.

- PV programs must, on the one hand, continue to have close ties with drug regulatory bodies in order to make sure that these bodies are kept informed about safety concerns in routine clinical practice, regardless of whether these concerns are pertinent to upcoming regulatory actions or concerns that become public knowledge. Regulators must, however, be aware of the unique and crucial role that PV plays in guaranteeing the continued safety of pharmaceutical products.

Management of Adverse Drug Reactions

- Understanding and Recognizing Adverse Drug Reactions
- Documentation
- Avoiding Harmful Drug Reactions
- Handling Adverse Drug Reaction Management

Recognition/Identification Of Adverse Drug Reaction

- Verify that the patient has received and consumed the medication at the recommended dose.
- Confirm that the medication was taken after the suspected ADR started.
- Establish the duration between the drug's administration and the event's start.
- Assess the possible adverse drug reaction (ADR) following drug discontinuation or dosage reduction, and track progress.
- Examine the potential cause (apart from the medication).
- Make use of a knowledgeable physician opinion and information center.
- File an ADR report

Reporting

Adverse drug reaction reporting helps the drug monitoring system to detect the unwanted effects of those drugs which are already in the market. ADR Reporting is a process of continuously monitoring of undesirable effect suspected to be associated with use of medical products. ADR reporting covers all pharmaceutical products, biological, herbal drugs, cosmetics and medical devices.

What to Report?

- Any undesirable adverse event suspected to be associated with use of drug.
- Include – All ADRs as a result of prescription and non-prescription.

- All ADRs – irrespective of the used (acc with PI provided by company).
- Unexpected reactions – regardless of their nature or severity.
- ADRs-in special field – drug abuse, drug use – pregnancy / lactation.

Information required for ADR case reporting

Patient information

- Patient identifier
- Age at time of event or date of birth
- Gender
- Weight

Product problems/Adverse effect

- Description of event or problem
- Date of event
- Date of this report
- Relevant tests/laboratory data (if available)
- Other relevant patient information/history.

Suspected medication (s)

- Name (brand name)
- Dose, frequency
- Route used
- Therapy date
- Diagnosis for use
- Event abated after use stopped or dose reduced
- Batch number
- Expiration date
- Event reappeared after reintroduction of the treatment.

Reporter

- Name
- Address and telephone number
- Speciality and occupation

WHO Should Report?

- Doctors
- Pharmacists
- Assistant medical officers
- Clinical officers
- Pharmaceutical assistants
- Traditional medicine practitioners
- Others health care providers

When to Report?

- Any suspected ADR should be reported as soon as possible.
- Delay in reporting will make reporting inaccurate and unreliable.
- If possible, report while the patient is still in the health facility this gives a chance to reporter to clear any ambiguity by re-questioning or examining the patient.

Where to Report?

- Please return the completed form to the nearest Adverse drug reaction Monitoring Centre (AMC) or to National Coordinating Centre.
- The Uppsala Monitoring Centre (Sweden) is the International collaborating centre. In India, the Central Drugs Standard Control Organization (CDSCO) is Coordinating the PV programme, under which peripheral, regional and zonal monitoring Centres have been set up along with National Pharmacovigilance advisory committee.
- The pharmacovigilance centres collect, communicate and disseminate ADR data by linking with hospitals as Well as practitioners and are also expected to provide expertise for assessing causality and severity of ADR.
- The information is submitted to the Steering Committee of PvPI constituted by the Ministry Of Health and Family Welfare. The Committee is Entrusted with the responsibility to review the data and Suggest any interventions that may be require

Prevention of Adverse Drug Reaction

- Anticipation by patient monitoring Ex- anaemia due to deficiency of G6PD, check the condition.
- Anticipation of dosage re-education Ex- impaired renal / liver function – dosage should reduce. Monitoring the serum levels (drug) Ex - theophylline, amino glycosides.

- Monitoring of pharmacological activity (extensive of Pharmacology activity) Ex- diuretics- to promote salt & water loss, but causes electrolyte depletion & dehydration.
- Minimizing of non-preventable- Idiosyncratic / hypersensitivity not preventable.
- Can be done by carful observation / monitoring of patient Ex- patient with meningitis

Management of Adverse Drug Reaction

Confirmation of the ADRs: indicate what assisted in confirming the suspected adverse reactions.

For example

- Drug reactions confirmed by disappearance of the reaction after stopping administration of the drug or reducing the doses.
- Recovery on withdrawal of suspected drug(s) if no other drug is withdrawn and no therapy given.
- Recovery follows treatment of the reaction in addition to withdrawal of drug.

Mention the criteria for regarding the reaction as serious

Mention any treatment given to the patient after experiencing the ADRs.

Outcome: indicate the outcome of the adverse reaction by marking X in the appropriate box with dates.

METHODS OF ADR REPORTING

Spontaneous reporting system

This is the PV system that is most commonly used and is also known as "voluntary" reporting. The ability of reporters to document and transmit their observations voluntarily rests on their motivation and level of education. All already employed healthcare workers and community members should receive training on how to raise awareness of the reporting culture in terms of about whom, what, where, when, and how to report a negative reaction. The adopted strategies for overcoming the recognized constraints of spontaneous reporting, particularly the underreporting, will be trained in the future.

It could serve as a method of detection for new, rare, or serious ADR events. One of the main advantages of SRS is that it applies to all drugs during its lifetime and not limited to a period of study.

Cohort event monitoring

A type of active PV system called Cohort Event Monitoring (CEM) 16–17 was mainly created for a few targeted medications in order to conduct a prospective, observational research of side effects related to those medications. A CEM program is mostly necessary for the study of a unique pharmaceutical in routine clinical practice. Moreover, it can be beneficial in determining the risk associated with marketed medications as well as in early phase IV clinical studies. Since CEM is the only system that demands thorough documenting of every clinical event along with specific ethical problems are involved. Since the primary goal of CEM is to determine the prevalence rate, it is crucial to avoid making duplicate entries; this can only be done if patients are accurately identified.

Targeted spontaneous reporting TSR

Targeted spontaneous reporting (TSR), as suggested by the WHO, is a methodology that expands upon the ideas of CME and spontaneous reporting while being implemented in a specific environment. This approach targets a particular patient group to report specific safety concerns related to suspected medication. TSR was created by WHO in 2010 and is currently being tested in three nations' HIV treatment programs (Kenya, Vietnam and Uganda). TSR can be used to track any suspected adverse reactions throughout the specified population or to focus on specific adverse reactions of particular concern, such as toxicity that poses a risk to therapy, etc. The aforementioned helps to restrict the recording of adverse events that matter most to patients and research.

PROTON PUMP INHIBITORS

The most widely used family of medications for the management of conditions relating to stomach acid is proton pump inhibitors (PPIs) . PPIs prevent the formation of gastric acid by blocking the hydrogen potassium ATPase required for the final stage of acid secretion in the gastric parietal cell. PPIs have a well-established therapeutic role in the treatment of illnesses connected to acid since they are the most effective inhibitor of this enzyme currently on the market. Peptic ulcer disease, gastro esophageal reflux disease (GERD), Zollinger-Ellison syndrome, Helicobacter pylori infection eradication, bleeding duodenal ulcers and esophageal strictures, and Barrett's esophagus maintenance therapy are among the conditions where PPIs are more effective and frequently used.

CASE REPORTS IN GASTROINSTESTINAL

35-year-old Hispanic woman was brought in due to increasing nausea, vomiting, and upper

abdominal pain. PPI was being used to treat her previous medical condition of heartburn. She was sent home on daily Omeprazole after being admitted to the emergency room for severe epigastric abdominal pain. When she was taking Omeprazole, she complained of identical symptoms when she went back to her primary care office two months later. She was moved to esomeprazole since Omeprazole was ineffective. She was evaluated for stomach ache when she returned to El Salvador two months later. She had a cholecystectomy because of her ongoing symptoms, but it didn't really help.

The patient stated that she was not taking any acid-suppressing drugs for the preceding two months and that she was unable to take the esomeprazole that was initially recommended due to financial difficulties. After then, an upper endoscopy revealed several stomach ulcers. After that, she was put on pantoprazole. She continued to experience pain after arriving back in the US, so she began using non-steroidal anti-inflammatory medicines (NSAIDs) to help. She then went to her primary care office because she was given dexlansoprazole during this clinic appointment and instructed to contact the emergency room if her symptoms persisted. The next day, she went back to the ER for more assessment of her deteriorating symptoms. She had stable hemodynamic and was a febrile at the time of her initial evaluation in the emergency room. She denied having hematemesis, Melina, or hematochezia, but she did report having significant abdominal pain and losing thirty pounds in the past year. The results of the laboratory analysis showed a platelet count of 116 × 103/mm3, hemoglobin of 13.8 g/dl, and white blood cell count of 26.5 × 103/mm3. According to laboratory data review, the patient's last platelet count, which was measured six months ago, was normal (264 × 103/mm3) and had been acquired before to the patient's initial PPI prescription. Prior to this most recent visit to the emergency room, no additional laboratory testing had been acquired. As a result, we were unable to determine how PPI affected the platelet count over the six months following the start of treatment. The results of the urinalysis, liver function, chemistry panel, and blood/urine cultures were all negative. Abdominal and pelvic CT images were normal except for diffuse steatosis.

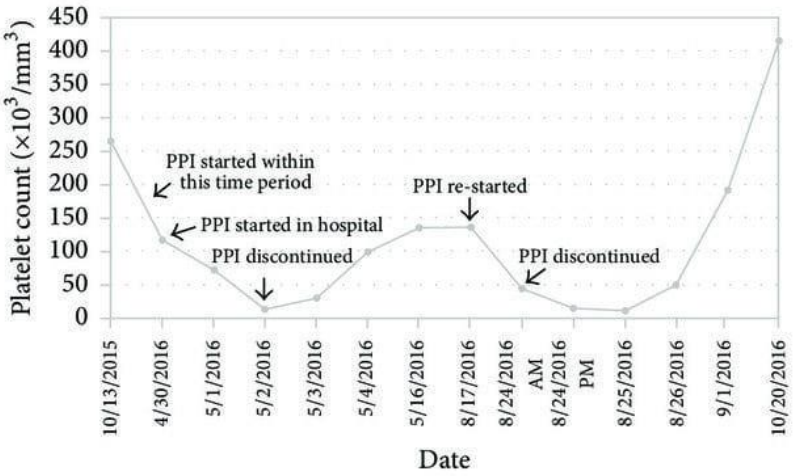
After consulting with gastroenterology, an upper endoscopy was suggested because of NSAID use, weight loss, and refractory abdominal pain. Additionally, twice-daily intravenous esomeprazole was initiated. Her platelet count kept declining, down to 12 × 103/mm3 the day after and 72 × 103/mm3 the following day. The quick decline in platelet count was sent to hematology, and it was believed that the cause was secondary to idiopathic

thrombocytopenic purpura, drug-induced thrombocytopenia, or infection. Notably, the patient had no prior history of clotting or bleeding problems Furthermore, the peripheral blood smear showed no signs of hemolysis, and the patient was not coagulopathic. According to the pharmaceutical review, the PPI should be held as there were no other medications (apart from a single preventive dosage of heparin) that could be linked to thrombocytopenia. After stopping the PPI, the platelet count returned to 99 × 103 /mm3 in just two days. At that time, an upper endoscopy showed nonspecific gastritis. Helicobacter pylori infection was not detected in the biopsies. Antibodies to the heparin-platelet factor 4 complexe were not examined to rule out heparin-induced thrombocytopenia because of the spontaneously improved platelet count. After quitting the PPI, our patient's platelet count returned to normal, and the present bout of thrombocytopenia was thought to be probably caused by the PPI.

After being sent home, our patient continued to experience chronic epigastric pain. Her symptoms barely improved after she used an H2 (histamine 2) receptor antagonist. The Gastroenterology Clinic was where she was next observed. The platelet count at this point was 135 × 103/mm3. Since heparin-induced thrombocytopenia was not ruled out, the question of whether the patient's thrombocytopenia was actually caused by PPI use was reexamined during this appointment. Due to her ongoing complaints, a PPI was deemed necessary, and dexlansoprazole was restarted with careful monitoring.

She ultimately got readmitted to the hospital 7 days later for persistent epigastric pain (while on PPI). T is time the platelet count was found to have decreased further to 43 × 103 /mm3. Te platelet count continued to drop, similar to her prior admission while on PPI, with the lowest count being 10 × 103 /mm3. PPI was held because of prior concern for PPI-induced thrombocytopenia. On this admission, our patient did not receive any heparin products and peripheral blood smear was not consistent with hemolysis. She did not receive any medications known to cause thrombocytopenia. Platelet count improved to 50 × 103 /mm3 while of PPI and she was discharged home. Patient’s symptoms improved on H2 antagonist, sucralfate, and pain control with morphine. On this admission, PPIs Seven days later, she was readmitted to the hospital due to ongoing epigastric pain (during her PPI). This time, it was discovered that the platelet count had dropped even more to 43 × 103 /mm3. Similar to her previous admission while on PPI, her platelet count continued to decline, reaching its lowest point at 10 × 103 /mm3. Due to earlier worries about PPI-induced thrombocytopenia, PPI was suspended. Our patient did not receive any heparin products throughout this admission, and

the peripheral blood smear did not show hemolysis. No drugs that are known to induce thrombocytopenia were administered to her. After receiving PPI, her platelet count increased to 50 × 103 /mm3, and she was sent home. After using an H2 antagonist, sucralfate, and morphine for pain management, the patient's symptoms improved. Regarding this disclosure PPIs were noted in the patient's medical file as a medication allergy. She was spotted in the Gastroenterology Clinic upon hospital discharge, and it was observed that scopolamine, sucralfate, and H2 antagonist—which she had acquired from her home country to treat nausea—were helping to somewhat control her symptoms. The platelet count eventually increased to 415 × 103/mm3. Given figure provides a comprehensive visual depiction of our patient's platelet count.



FigureNo-01: Platelet count trend of the patient. Thrombocytopenia developed after starting PPI for the first time and later on when it was restarted. Platelet count recovered after PPI was discontinued on both occasions [x-axis: actual date; y-axis: platelet count in103/mm3.

Adverse effect associated with proton pump inhibitors use

a. **Gastrointestinal Issues:** Diarrhea and constipation are common. Long-term use may increase the risk of Clostridium difficile infections, leading to severe diarrhea.
b. **Nutrient Malabsorption:** PPIs can interfere with the absorption of vital nutrients, including:

i. **Magnesium:** Low levels can cause muscle spasms and arrhythmias.
ii. **Calcium:** Impaired absorption may increase the risk of osteoporosis and fractures.
iii. **Vitamin B12:** Deficiency can lead to anemia and neurological issues.

c. **Kidney problems:** Long-term use has been linked to chronic kidney disease and acute interstitial nephritis.

d. **Gastric Cancer:** Some studies suggest a potential association between prolonged PPI use and an increased risk of gastric cancer, possibly due to altered stomach acidity and bacterial overgrowth.

e. **Gut Microbiome Alteration:** The suppression of stomach acid may disrupt the gut microbiome balance, leading to potential long-term health effects.

Table No. 01: Adverse effect associated with proton pump inhibitors use.

Drug Name	Brand Name	Dose	Routes of Administration	Side Effect
Omeprazole	Prilosec	20-40 mg/day	Oral (Tablet Capsule)	Rare kidnay issues, Low Magnesium, Clostridium difficile infection
Esmoprazole	Nexium	20-40 mg/day	Oral (Capsule), IV	Allergic Reaction, Vitamin B12 Deficiency
Lansoprazole	Prevacid	50-30 mg/day	Oral (Capsule Tablet)	Rare lupus like syndrome, Dizziness
Pantoprazole	Protonix	40 mg/day	Oral (Tablets),IV	Joint pain, Lupus erythematosus
Rabeprazole	Aciphex	20 mg/day	Oral(Tablets)	Hypomagnesemia, Skin reaction
Dexlansoprazole	Dexilant	30-60 mg/day	Oral (Capsule)	Liver enzyme abnormality, Severe Diarrhea

Importance of ADR reporting for drug safety

- **Unknown Adverse Reaction Identification:** The detection of uncommon or hitherto unreported adverse drug reactions (ADRs) is made possible by ADR reporting. Early identification of these events can result in timely intervention, shielding patients from more injury.
- **Post-marketing surveillance:** Because of small sample numbers and carefully regulated environments, clinical trials conducted prior to medication approval might not have caught every potential adverse event. After medications are prescribed, ADR reporting allows for ongoing monitoring of drug safety in practical contexts.
- **Risk assessment and signal detection:** A Combining ADR report from several sources facilitates the identification of trends or signals that can point to possible safety issues. By analyzing these signals, one may evaluate the risk-benefit profiles of medications and, if necessary, take the necessary regulatory action.

- **Updating medication labels and usage instructions:** ADR reports offer insightful information that might influence changes to medication labels, which may include cautions, warnings, and contraindications. This ensures that healthcare personnel and patients are educated about potential dangers and recommended uses.
- **Enhancing pharmacovigilance practices:** ADR reporting Contributes to the overall improvement of pharmacovigilance systems And practices. Regular analysis of ADR data can lead to enhancements In reporting processes and signal detection methodologies.
- **Comprehending drug interactions and comorbidities:** Adverse drug reaction (ADR) reporting facilitates the evaluation of drug interactions as well as the impact of underlying medical problems. This information is useful for customized treatment regimens and medicine.
- **Patient empowerment:** Encouraging patients to report ADRs empowers them to actively participate in their healthcare. Patient- driven ADR reporting can lead to improved patient safety and better healthcare outcomes. Post-approval safety assessment: ADR reporting helps regulators evaluate medication safety profiles. Reevaluating the risk-benefit balance of medications ensures their sustained safety and efficacy.

CONCLUSION

Pharmacovigilance plays a vital role in ensuring drug safety, particularly regarding the potential adverse reactions associated with widely used medications like proton pump inhibitors (PPIs). The case of a patient who developed thrombocytopenia after starting PPI therapy illustrates the need for healthcare providers to be vigilant in monitoring patients for adverse effects, even from commonly prescribed drugs. Ongoing evaluation and cautious prescribing practices are essential to enhance patient safety and treatment outcomes in pharmacotherapy.

RE9FERENCE

1. Rajkumar Soni1*, Bikrant Kesari2, A Review on Pharmacovigilance, nt. J. Pharm. Sci. Rev. Res., May–Jun, 2014; 26(2), 41: 237-241.
2. Al Dweik R, Stacey D, Kohen D, Yaya S. Factors affecting patient reporting of adverse Drug reactions: a systematic review. Br J Clin Pharmacol, 2017; 83(4): 875-83.
3. Ditto for AM. Drug allergy. In: Grammer LC, Greenberger PA, editors. Patterson's allergic illnesses. Lippincott Williams & Wilkins published the sixth edition in 2002; 295.

4. Waller P. An Introduction to Pharmacovigilance. Southampton, UK: Blackwell Publishing, 2010.
5. Hamza Y. Garashi1 · Douglas T. Steinke1 · Ellen I. Schafheutle, A Systematic Review Of Pharmacovigilance Systems In Developing Countries Using the WHO Pharmacovigilance Indicators, Therapeutic Innovation & Regulatory Science, 2022; 56: 717–743.
6. World Health Organization The importance of pharmacovigilance.; 2002.) (Dhikav V, Singh S, Anand KS. Adverse drug reaction monitoring in India. J Indian Acad Clin Med., 2004; 5(1): 27–33.
7. Gupta P, Udupa A. Adverse drug Reaction Reporting and Pharmacovigilance: knowledge, attitudes and perceptions amongst Resident doctors. J Pharm Sci Res., 2011; 1459(2): 1064–9.
8. Hussein G, Bleidt B, Belding B. Recognition evaluation and reporting Of adverse drug reactions. Clin Res Regul Aff., 1999; 16(3): 91–107.
9. Rao HP. Reporting of adverse drug reactions by consumers: rationale And potential. Pharmbit. Am J Hosp Pharm., 2010; 22(20): 110.
10. Coleman JJ, Ferner RE, Evans SJ. Monitoring for adverse drug Reactions. Br J Clin Pharmacol, 2006; 61: 371–9.
11. Hazell Lorna, Shakir Saad AW. Under-reporting of adverse drug reactions: A systematic review. Drug Saf., 2006; 29(5): 385-96. Doi: 10.2165/00002018-200629050- 00003, PMID 16689555
12. WHO. A practical handbook on the pharmacovigilance of antimalarial medicines. Geneva: WHO, 2008.
13. WHO. A practical handbook on the pharmacovigilance of antiretroviral medicines. Geneva: WHO, 2009.
14. Council for International Organizations of Medical Sciences (CIOMS). International Ethical guidelines for epidemiological studies. Geneva: CIOMS, 2009.
15. WHO. A practical handbook on the pharmacovigilance of medicines used in the Treatment of tuberculosis. Geneva: WHO, 2012.
16. Clarkson A, Ingleby E, Choonara I, Bryan P, Arlett P. A novel scheme for the Reporting of adverse drug reactions. Arch Dis Child., 2001; 84(4): 337-9. Doi: 10.1136/adc.84.4.337, PMID 11259235.

17. M. M.Wolfe and G. Sachs, "Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome," *Gastroenterology*, 2000; 118(2): S9–S31.
18. M. M. Wolfe, L. S. Welage, and G. Sachs, "Proton pump inhibitors and gastric acid secretion," *American Journal of Gastroenterology*, 2001; 96(12): 3467-3468.
19. Rudelli, I. Leduc, C. Traulle et al., "Thrombopenia following treatment with omeprazole," *Presse Medicale*, 1993; 22(20): 966.
20. S. D. Zondor, J. N. George, and P. J.Medina, "Treatment of drug induced thrombocytopenia," *Expert Opinion on Drug Safety*, 2002; 1(2): 173–180.
21. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm., 1992; 27(6): 538.