Indian Journal of Pharmacy and Pharmacology 2022;9(2):77–80

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Review Article

Ecopharmacovigilance: Need of the hour

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ARTICLE INFO

Article history:
Received 29-04-2022
Accepted 11-05-2022
Available online 12-07-2022

Keywords:
Pharmacovigilance (PV)
Ecopharmacovigilance (EPV)
Eco-directed sustainable prescribing (EDSP)
Active pharmaceutical ingredients (APIs)
Liquid Chromatography-Mass Spectrometry (LC-MS)
Non-steroidal anti-inflammatory drugs (NSAIDs)
Environmental Risk Assessment (ERA)
Gas Chromatography-Mass Spectrometry (GC-MS)

ABSTRACT

Pharmaceuticals in the environment have the potential to be hazardous to human beings. With each passing day it is becoming a major source of concern. Due to recent findings showing the availability of pharmaceutical components in the environment, particularly in ground water bodies, pharmaceuticals have gained a growing amount of attention from worldwide health regulatory bodies and have become one of the most significant water pollutants. The aim of this article is to review the environmental hazards of pharmaceuticals that have been reported in various literature sources to promote awareness on safe usage of medicines, to increase pharmaceutical manufacturers' knowledge on environmental safety aspects and to arrest the attention of pharmacovigilance practitioners to some of the emerging problems caused by medicines. Pharmaceutical waste has been a source of huge concern amongst environmental scientists. Pharmaceutical manufacturers and pharmacovigilance scientists should invest more attention to these increasing environmental concerns caused by medications. Ecopharmacovigilance is defined by the World Health Organization (WHO) as the science and activities concerned with the detection, assessment, understanding, and prevention of adverse events or other related problems caused by pharmaceuticals in the environment that affect people and other animal species. This review is an attempt to compile information on Ecopharmacovilance, with an emphasis on the Indian perspective.

1. Introduction

Scientists have become increasingly concerned in recent years about the potential hazardous consequences of pharmaceutical chemicals in the environment. Pharmaceuticals from many therapeutic groups (particularly antibiotics) have been found in the environment on a regular basis, usually at low concentrations in surface water bodies.

EPV is still in its early days in India compared to the other nations, and there is no clear regulatory structure in place to monitor potential detrimental effects of pharmaceuticals in the environment. If not properly disposed of, unused or expired medicines can constitute a threat to public safety and the environment, as many drugs have two lives (one in the body of animals/humans and one in the environment). Prescription and OTC drugs are amongst the products of concern.[1–3]

2. Materials and Methods

The process entailed a review of research articles, review articles, and other internet-based materials. Various publications, articles, and reports were combed over meticulously. The information gathered was useful in determining the current state of Ecopharmacovigilance.

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https://doi.org/10.18231/j.ijpp.2022.014

3. Ecopharmacovigilance: Need of the hour

3.1. Analysis of pharmaceuticals

Since the 1970s, when chemical analysis of pharmaceutical products began, examinations of pharmaceuticals in water have required the extraction of huge amount of water. The technology of Gas Chromatography/Mass Spectrometry (GC/MS) was used in those examinations. During this period, the data acquired was typically in the parts per billion (ppb) range, but often in the higher range, making this method unsuitable due to its low sensitivity. Furthermore, the number of pharmaceuticals detected was modest. By the mid of 1990s, a better approach was developed that had a higher detection rate. Solid-phase extraction was the name given to this process. While it performed better when combined with GC/MS analysis, the number of drugs discovered was limited. The GC/MS technology was phased out in favor of a more sensitive approach known as Liquid Chromatography-Mass Spectrometry in the late 1990s (LC-MS). Because of its increased and enhanced sensitivity, this has opened a new vista in pharmaceutical analysis. The World Health Organization (WHO) issued an article providing specifics on an analysis technique that is commonly used by researchers all around the world when analyzing the drugs. The study discusses the suitability of various approaches for the types of medications under consideration. For example, LC-MS/MS analysis is better for measuring polar chemicals that are highly soluble in water, whereas GC-MS/MS analysis is better for volatile target compounds.[3–6]

3.2. Eco-directed sustainable prescribing

Eco-directed sustainable prescribing (EDSP) is a method of lowering the environmental impact of active pharmaceutical ingredients (APIs). EDSP is certainly one of the most important steps in the ecopharmacovigilance (EPV) program. In some of the recent polls, majority of the physicians felt that there is a higher percentage of APIs in the environment. They were concerned about the potential environmental impact and ecological concerns linked with API residues, and they backed the effectiveness and necessity of EDSP under ecopharmacovigilance with the hopes of reducing API exposure in the environment. Physicians expressed an interest to get involved in EDSP practices in the future.[4]

3.3. Impact of antibiotics

Antibiotics, which are an important part of contemporary medicine for both humans and animals, are designed to have desirable or helpful effects on disease infections caused by pathogens. Antibiotics, like other pharmaceutical chemicals, are tiny organic polar molecules that are generally ionizable and must be removed by metabolism or biotransformation. These chemicals and their metabolites are mostly excreted by urine, faces, or a combination of both. Domestic home, urban, hospital, industrial wastewater, aquaculture, and extensive medicated livestock production are the main sources of antibiotic contamination. They may enter natural surface-ground water in measurable but very minute concentrations since present sewage treatment systems are unable to effectively remove them. Apart from other contaminants, antibiotics can disrupt the microecosystem by increasing the diversity of resistance. Ibuprofen, diclofenac, naproxen, acetaminophen, and ketoprofen were the top five most common non-steroidal anti-inflammatory drugs (NSAIDs) present in the environment, that led to the decrease in vulture population as per a study.(Table 1)[4–8]

3.4. Observation from adverse environmental impact of pharmaceutical compounds

1. Groundwater in Toansa village of Punjab, India has been observed to be contaminated up to a depth of 100 feet.
2. Diclofenac sodium caused vultures to die in the Indian subcontinent.
3. Male fishes were feminized by ethinyl estradiol.
4. Spawning in shellfishes by Fluoxetine.
5. Frogs were killed by contraceptive tablets.
6. Aggression caused in Lobsters due to antidepressants.

Pharmaceuticals are certainly prevalent environmental contaminants that can be released into the environment through a variety of methods, including patient excretion through the sewer system and manufacturer or hospital releases into waste waters. The study of antibiotic resistance in the environment is currently very significant to the researchers. The increasing sensitivity/resolution of chemical and analytical methods, such as ultra-high-performance liquid chromatography/quadrupole time-of-flight mass spectrometry (UHPLC-QqTOF-MS) and the long adsorption time detection of substances in passive samplers, has enabled the detection of antibiotics in water. Marketing authorization holders for both human and veterinary medicines have been required to submit an environmental risk assessment report since 2006, which is supposed to include a prospective exposure assessment to aid in determining the potential impact and occurrence of common antibiotics after years of use. Potential risks and dangers may not be adequately foreseen when marketing authorizations are granted and so it becomes increasingly important to generate new data, particularly to better understand the exposure assessments in a year-on-year basis.[9,10]

Because of their high frequency, prolonged leakage into the atmosphere, and possibly severe ecotoxicological impact, the presence of medicines in drinking water has

sparked popular outrage in India. Around 300 of the 4,000 pharmaceutical compounds used in the medical business have previously been detected in drinking water systems and are commonly found in aquatic settings, with concentrations ranging from ng/L to g/L. An obligatory provision in the medication development process may be made to establish safety in the context of environmental effect and research on the drug's impact over time. Before a medicine may be approved for sale in India, it must undergo an Environmental Risk Assessment (ERA). However, we must keep in mind that the results of ERA are influenced by a variety of parameters, including the drug's dose, chemical properties, metabolism, biodegradation profile, detected environmental concentration level, and ecotoxicology. The benefits of strict rules have been seen in countries such as the United Kingdom. The United States Senate has also enacted legislation to monitor drugs in the environment. As mentioned previously, several government and non-government organizations have also implemented actions in various other countries. [8,9,11–15]

3.5. Risk mitigation

The most effective strategy to mitigate the dangers posed by pharmaceutical APIs in the environment is to use a combination of measures:

1. Rational drug use program.
2. Pharmaceutical-return programs.
3. Raising awareness among stakeholders, i.e., patients, doctors, nurses, and pharmacists, regulatory bodies.
4. Introduction of Advanced effluent treatment with sophisticated sewage treatment system and wastewater treatment plants.
5. Product linked Incentives for the development of "green" pharmaceuticals, and improved regulations and guidelines for pharmaceutical waste management.

3.6. Knowledge and practice on Ecopharmacovigilance amongst students

Medical students should be aware of safe drug disposal, ecopharmacovigilance, and self-medication habits as future prescribers. The same holds good for the nursing and pharmacy students. In several affluent countries, there exist extensive protocols for proper pharmaceutical disposal. In developing nations, however, the situation is different. Various research studies from Bangladesh, Nepal, and other underdeveloped countries have revealed that medical and pharmacy students have a lack of understanding. According to a Nepalese study, pharmacists are uninformed of and lack appropriate information about proper medication disposal. Another study found that medical and dentistry students are aware of pharmaceutical expiration dates and are knowledgeable on how to safely dispose of expired medications. However, majority of them kept prescriptions at home and did not disclose how they disposed of unwanted or expired medications. Several papers have also emphasized the importance of increasing nurses' understanding of ecopharmacovigilance and encouraging them to use suitable safe medication disposal techniques. Administrators of nursing education should update their ecopharmacovigilance curricula. [16,17]

3.7. Progress of India towards ecopharmacovigilance

In India, ecopharmacovigilance is in a nascent state. It is not supported by enough data to reveal the information of pharmaceuticals found in the environment. Government of India has been analyzing the amounts of minerals and heavy metals as pollutants in environment but has not achieved any major success in detecting pharmaceuticals as pollutants. India is a hub of pharmaceutical companies and manufacturing units and has become one of the world's largest centers for bulk drug manufacture. This results to an unprecedented drug contamination of surface, ground, drinking water and the environment.

Table 1: Identified pharmaceuticals in Indian environment

Cetirizine	Antihistamine
Levocetirizine	Antihistamine
Ciprofloxacin	Antibiotic, fluoroquinolone
Citalopram	Selective serotonin reuptake inhibitor
Enalapril	Angiotensin-converting enzyme inhibitor
Enoxacin	Antibiotic, fluoroquinolone
Enrofloxacin	Antibiotic, fluoroquinolone
Lomefloxacin	Antibiotic, fluoroquinolone
Metoprolol	Beta-adrenoreceptor antagonist
Norfloxacin	Antibiotic, fluoroquinolone
Ofloxacin	Antibiotic, fluoroquinolone
Terbinafine	Antimycotic
Trimethoprim	Antibiotic, folic acid synthesis inhibitor
Aspirin	NSAIDs

Ecopharmacovigilance is very much necessary in India after considering the massive pharmaceutical activity. There is a need for joint research activities between government, industry, and academia. To increase scientific understanding of medicines in the environment and for a better environmental risk assessment, more studies are required. To identify, repair, and prevent the environmental problems caused by pharmaceuticals, an independent government-based individual program, or a program as a part of existing initiatives such as the Pharmacovigilance Program of India (PvPI) is required. [7]

4. Discussion and Conclusion

Human and animals exposed to drugs through the environment may be affected directly or indirectly. Microbial resistance is the most talked-about topic in the recent times. Antimicrobial resistance may develop

as a result of long-term exposure to very low doses of antimicrobials through drinking water. Pharmaceutical companies' falling interest in creating novel antimicrobials in favor of producing fancy medications may exacerbate the problem. Although the effect of very low doses from environmental cycling is unclear, certain populations, such as pregnant women, children, the elderly, and people with renal or hepatic diseases, may be more vulnerable to such exposure because their pharmacokinetics are altered in these groups, and even minor doses can be harmful. In the same way, some medications in tiny minuscule quantities may have a synergistic effect. The possibility of a nocebo impact from medications, even at subtherapeutic amounts in the environment, cannot be ruled out. Furthermore, adverse reactions of type B may occur at these doses. We conclude that some recommendations for implementing EDSP from the standpoint of introducing and strengthening ecopharmacovigilance related medical training and education are based on the aforesaid findings. Hospitals, medical centers, and colleges should create training and educational programs to educate physicians and medical students about APIs in the environment, environmental consciousness while prescribing, the environmental impact of their professions, ecopharmacovigilance, and EDSP. Furthermore, there is a need to promote rational prescribing to control over prescription of medications, which is a fair start in implementing EPV in the healthcare system. It is also recommended that the environmental constituent be incorporated into the rational prescribing principles. Additionally, building a database would also be helpful to allow obtaining the relevant information to select the effective and more environment friendly doses rather than prescribing some non-environment friendly hazardous drugs and understand the drugs' excretion profiles.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Dutta A, Banerjee A, Chaudhry S. Ecopharmacovigilance: Need of the hour. *Indian J Pharm Pharmacol* 2022;9(2):77-80.