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Review Article

"India's progress towards Ecopharmacovigilance"

Dr Niroop Revannasiddaiah, Dr Chandani Ashok Kumar

MBBS, M.D.

Assistant professor, Pharmacology

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ABSTRACT

Ecopharmacovigilance is the science and activities associated with the detection, evaluation, understanding, and prevention of adverse effects of pharmaceuticals in the environment. The adverse effect of medicinal wastes on environment is yet to be understood in detail and addressed seriously in India, since India stands as one of the country with highest pharmaceutical activity. In this study, an assessment is done on India's contribution towards ecopharmacovigilance, the impact of pharmaceuticals on the environment and the seriousness of this issue which inquires for a need to implement ecopharmacovigilance in Indian government policy.

Keywords: Ecopharmacovigilance, Policy, India, Indian Scenario.

INTRODUCTION

India is a country of diverse ecology and so also known as a subcontinent. It also has records of possessing world's most polluted cities and environments [1]. The pollutants vary from gases namely carbon monoxide to solid wastes such as plastics. Not only are the cities and its surrounding areas polluted, but also forests due to mining, tourism and isolated civilizations. In the recent times there has been an awareness regarding medicines and their products, contaminating the environment. However, the adverse effect of medicinal wastes on environment is yet to be understood and addressed seriously in India. The pollution of water and soil bodies with pharmaceutical residues is an emerging environmental problem. Many of these substances, including human pharmaceuticals, may have little, if any, impact on human health or the environment, though for some substances there may be a significant risk and in these cases appropriate action should be taken.

The solution for the problem of undertaking effective ecopharmacovigilance in India is yet to be found. There is need for key roles from pharmaceutical industry, medical organizations, environmental regulators and academia for successful ecopharmacovigilance. Indian legislation should consider measures to monitor and evaluate the risk of environmental effects of such medicinal products for human use, including those which may have an impact on public health.

World Health Organization [WHO] defines ecopharmacovigilance as "the science and activities associated with the detection, evaluation, understanding, and prevention of adverse effects of pharmaceuticals in the environment".

Entry of Pharmaceuticals in the environment:

There are many ways for a pharmaceutical product to enter into environment. It enters through the excreta of a patient.[2] Another main channel is through release of waste system from hospitals. [3]Faulty disposal from manufacturing companies is also a big reason for pharmaceuticals to enter environment. [4]Improper disposal of unused or expired medications is also a concern. [5,6] Beef and dairy cattle, chickens, pigs and other livestock are given pharmaceutical drugs to limit the spread of disease or to help the animals grow may also contribute to the problem.

Global scenario:

In recent years, human pharmaceuticals from numerous therapeutic classes have increasingly been detected in the environment, typically at nanogram per Liter to low microgram per Liter in surface waters in different studies conducted in different parts of the world [7].Although, human and environmental exposure to these contaminants will be low, all of them need to be subjected to risk assessment on a case by case basis. A vast array of pharmaceutical ingredients can enter environment. They may be of medicinal importance or for which a possible pharmaceutical use has not yet been discovered. For example, nitro-glycerine, warfarin and dimethyl fumarate, initially sold respectively as an explosive, a rodenticide and a mould inhibitor have

*Corresponding author: Dr Niroop Revannasiddaiah |E-mail: dr.niroop@gmail.com

subsequently all been used as pharmaceuticals.A study in Spain found that nineteenpharmaceuticals of the twenty seven human pharmaceuticals investigated, have been identified in the aquatic environment. [8]

Following is the list of identified pharmaceutical substances found in environment in various countries.

Table1: Table showing different group of drugs present in the global environment.

Drug	Group
Erythromycin Roxithromycin Azithromycin Clarithromycin Lincomycin Sulfonamides Trimethoprim Chloramphenicol Doxycycline Cefalexin Ketoconazole Clotrimazole Triclosan and triclocarban Amoxycillin Sulfamethoxazole Lincosamides	Antibiotics [9,10,11,12,13,14]
Diclofenac Ibuprofen Indomethacin Mefenamic acid Paracetamol Naproxen	NSAIDs [9,10,11,12,15]
Propranolol Atenolol Metaprolol	β-blockers [11,12]
Tamoxifen Ethinylestradiol Levonorgestrel Endogenous estrogen excreted from women	Hormonal drugs [13,16,17,18,19,20]
Fluoxetine Norfluoxetine Citalopram	Antidepressants [12,21]
Carbamazepine Bezafibrate Gemfibrozil Clofibrate Theophylline Dextropropoxephene Cetirizine Cocaine	Miscellaneous [12,21,22]

Not only is the pharmaceuticals identified in the environment, but also in the potable water sources. Studies in USA have even detected very low levels of pharmaceuticals in finisheddrinking-water. The highest

concentration reported was 40 ng/l for meprobamate.[23] Studies have also found several pharmaceuticals in tap water atconcentrations ranging from nanograms to low micrograms per litre in several countriesin Europe, including Germany, the Netherlands and Italy [24]. Two separate studies in Germany found phenazone and propylphenazone(an analgesic andan antipyretic drug, respectively) in Berlin drinking-water, with the highest concentrationbeing 400 ng/l for phenazone.[25, 26]In the Netherlands, traces of antibiotics, antiepileptics and beta blockers weredetected in the drinking-water supply at concentrations below 100 ng/l, with mostconcentrations below 50 ng/l.[27] Even Groundwaters are affected by a variety of sources, with landfills, septic systems, and agricultural fields representing the most significant potential sources of anti-infective contamination. A recent study of groundwaters in the United States detected three anti-infectives of the twenty one targeted. [28]

Indian Scenario

InIndia, ecopharmacovigilance is in a budding state. It is not backed up by adequate data to reveal the information of pharmaceuticals found in the environment. Indian government has been measuring the amounts of minerals and heavy metals as pollutants in environment but has not succeeded to detect pharmaceuticals as pollutants. India is a hub of pharmaceutical companies and manufacturing units and has becomeone of the world's largest centers for bulk drug production, supplying over 65 countries. This leads to unprecedented drug contamination of surface, ground, drinking water and the environment.

A Swedish research team revealed that pharmaceutical levels in water downstream of a wastewater treatment plant in Patancheru, Andhra Pradesh, India was 150 times the highest levels of that found in the USA. Water samples were also taken from wells in six nearby villages. The samples were analyzed forthe presence of 12 pharmaceuticals with liquid chromatography–mass spectrometry. All wells were determined to be contaminated withdrugs.[29]And most of these companies exported their manufactured drugs to other countries, including the major markets in Europe and the United States. [30]

Table 2: Table showing identified pharmaceuticals in Indian environment.

Drug	Group
Cetirizine [29]	Antihistamine
Levocetirizine[29]	Antihistamine
Ciprofloxacin [29]	Antibiotic, fluoroquinolone
Citalopram[29]	Selective serotonin reuptake inhibitor
Enalapril[29]	Angiotensin-converting enzyme inhibitor
Enoxacin[29]	Antibiotic, fluoroquinolone
Enrofloxacin[29]	Antibiotic, fluoroquinolone
Lomefloxacin[29]	Antibiotic, fluoroquinolone
Metoprolol[29]	Beta-adrenoreceptor antagonist
Norfloxacin[29.31]	Antibiotic, fluoroquinolone
Ofloxacin[29]	Antibiotic, fluoroquinolone
Terbinafine[29]	Antimycotic
Trimethoprim[29]	Antibiotic, folic acid synthesis inhibitor
Apirin[32]	NSAIDs

The let off of wastes from manufacturing industries into water bodies have led to severe microbial resistance to antibiotics. There have been several reports from all parts of India in cities like Hyderabad, Bangalore and Coimbatore and stretches of Bay of Bengal. [33, 34, 35, 36]

Impact of pharmaceuticals in environment

The most difficult part of ecopharmacovigilance is determining the relationship between cause and effect in the environment. Indian authorities must initiate to conduct scientific studies for the same. Despite the widespread detection of pharmaceuticals in the environment and the potential for effects in wildlife species, there are few identified cases in which adverse environmental impact in the field has been solely attributed to a pharmaceutical. Environmental and human harms of such pollution are not only extensive to humans but may also have serious adverse effects on the

development of tadpoles and zebrafish which form an important constituent of ecological cycle. Studies have been conducted in other parts of the world and have led to conclusive detrimental results of pharmaceuticals entering environment.

Diclofenac, a non-steroidal anti-inflammatory drug, has resulted in an adverse population-level impact on non-target populations in the wild.[37] This was through its veterinary application in South-East Asia to treat inflammation and fever in domestic livestock. Vultures ingested diclofenac when feeding on the carcasses of livestock that had been treated with high doses shortly before their deaths. It is estimated that somewhere between 10 and 40 million vultures have been poisoned, and that three species of *Gyps* vultures are now critically endangered.[38] *Gyps* vultures are extremely sensitive to diclofenac and exposure to the drug causes abdominal gout and acute kidney failure. Acute effects have also been observed in the African white-backed vulture [*Gyps africanus*] and the Eurasian griffon vulture [*Gyps fulvus*] as a result of diclofenac exposure. The below table shows the various drugs and its effects on different species of animals.[39]

Table 3: Table showing the effect of pharmaceuticals on wild life

DRUG	Animal	Impact
Diclofenac	Gyps vultures[39]	Abdominal gout and acute kidney failure leading to death.
	Fish[40]	Histological changes in the liver, kidney, and gills of fish.
Oral contraceptives[41]	Frogs	Sterility
Ivermectin	Dung Beetle	Death
Sex hormones	Male fish	Feminization

Certain studies have assessed the environmental risks associated with propranolol and atenolol, Ethinyl estradiol, Tamoxifen, Anastrazole, Bicalutamide, Levonorgestrel and drospirenone. [41, 42, 43, 44, 45, 46]

Need for EPV in India

Though it is impossible to eliminate pharmaceutical entry into environment through human and animal excretion, it is possible to reduce the entry through hospital wastes, improper disposal of unused drugs and wastes emerging from manufacturing industries. Considering the established facts of detrimental effects caused by pharmaceuticals entering the environment, there is a need for setting up of a strong law concerning ecopharmacovigilance.

Currently, there are no established programs taken up by the government of India to monitor ecopharmacovigilance. In 1985, Indian government formed the Ministry of Environment and Forests. This ministry is the central administrative organization in India for regulating and ensuring environmental protection. The ministry should take up measures to initiate and strengthen ecopharmacovigilance in India. There is a body called Environment Protection and Training Research Institute [EPTRI] which should actively take up EPV into their perspectives. A significant cooperation is required from Bulk Drug Manufacturer's Associationof India [BDMA] representing the pharmaceutical industries. Academic institutions must participate and should include assessment of pharmaceuticals and its risk in environment as a part of academia.

Certain measures are to be implemented by the government of India to prevent the mishaps of entry of pharmaceuticals in the environment. Ecopharmaco-vigilance is still a developing science and is currently very unclear what it might mean in practice. The greatest challenge concerns signal detection in the environment and the difficulty of identifying cause and effect. The process of EPV starts from the launch of the drug and continues throughout the product life cycle. Assessments can be made by tracking environmental risks after launch of the product, via literature monitoring for emerging data on exposure and effects. Further research, testing or monitoring in the environment needs to be done when a risk is identified. Studies need to be done in the laboratories simulating real environment to assess the effects of pharmaceuticals. Increasing transparency and availability of environmental data for medicinal products is a key element in successful EPV. Keeping a global EPV perspective ensures higher chances of success rates. [47]

In the past, measures were taken by the governmentto minimize the harmful pollutant entry into environment. A

few pharmaceutical companies were banned after proven that improper waste management was leading to the entry of harmful substances which included pharmaceuticals. In one instance during July 2013, Government of Andhra Pradesh permanently banned certain polluting industries in Medak, Ranga Reddy, Mahboobnagar and Nalgonda districts in their G.O. Ms. No. 64. [48]A strong law with a proper foundation is now required to establish EPV in India which can stop and prevent further damage to the environment.

Conclusion

Necessity of Ecopharmacovigilance is absolute in India after considering the immense pharmaceutical activity. There is a need for individual and collaborative research between industry, academia and government acting in a proactive manner to improve the scientific understanding of EPV. Research is needed to improve scientific understanding of pharmaceuticals in the environment and environmental Risk Assessment. A government based individual program or as a part of existing programs such as Pharmacovigilance Program of India[PvPI] is essential to identify, solve and avoid the mishaps occurring in the environment due to the entry of pharmaceuticals.

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