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A Review on Eco-Pharmacovigilance

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Abstract

Pharmaceuticals in the environment have the potential to be hazardous to human beings. The science related to understanding, detection, assessment, and activities for prevention of adverse effects or other problems due to the existence of pharmaceutical pollution in the environment is Ecopharmacovigilance. Drug use in both the human and veterinary population is escalating day by day. The potential routes of environmental entry are patient excretion, direct release into waste water system, terrestrial deposition. Exposure of human beings and animals to drugs through environment imposes a great threat. The important one is microbial resistance due to continuous exposure to low dose of antimicrobial through drinking water. The difficult part of Ecopharmacovigilance is to determine relationship between cause and effect. In order to reduce the Pharmaceutical exposure; the approaches that have been taken are to reduce generation of pharmaceutical waste, use of green pharmacy, increase the efficiency of sewage treatment plants, better drug disposal programs. Both PV and EPV aim to monitor the adverse effects of Pharmaceuticals. The drug regulations for Ecopharmacovigilance in various countries are ERA, RCRA, and RMM which govern era of pharmaceuticals. As India is a hub of Pharmaceutical companies, it is the reason that leads to precedent drug contamination of surfaces, ground drinking water. To reduce the effects of pharmaceuticals there is need to setup a strong law concerning EPV. Increasing transparency and availability of environmental data for medicinal products is a key element in successful EPV.

Keywords: Ecopharmacovigilance, Microbial Resistance, Relationship between cause and effect, Drug regulations, Transparency

Introduction

The definition of Eco-pharmacovigilance is the science related to understanding, detection, assessment, and activities for prevention of adverse effects or other problems due to the existence of pharmaceutical pollution in the environment. This definition of EPV reflects the approach communicated at the International Society of Pharmacovigilance annual meeting in Ghana in November 2010(8).

The science of eco-pharmacovigilance can be discussed under following objectives-

1. Pharmaceuticals in the environment
2. Consequences of environmental pollution by pharmaceuticals
3. Approaches to reduce amount of pharmaceuticals released in the environment
4. Ecopharmacovigilance and Drug regulations.

Pharmaceuticals in the Environment:

Drug use in both the human and veterinary population is escalating day by day.

According to one estimate 100,000 tons of antimicrobials are consumed every year. More than 30 billion doses of non-steroidal anti-inflammatory drugs are consumed annually in the United States only.

The potential routes of environmental entry include-

1. Patient excretion either as parent compound or metabolites via the sewer system,
2. Direct release into the waste water system from manufacturing, hospitals or disposal via toilets/sinks, and
3. Terrestrial depositions, for example via sludge application to land, leaching from solid waste landfills, or irrigation with treated or untreated wastewaters (7).
4. Terrestial deposition EX: via sluge application to land, leaching from solid waste landfills.

Disposal of unused drugs can be managed effectively by guidance for patients take back schemes and disposal practices.
A pharmaceutical residue in the environment from human use is an unavoidable consequence of patient drug use and it is much more difficult to prevent.

As it can be tackled by effective sewage treatment which may prevent significant environmental contamination, but still there are some residues remaining.

Consequences Of Environmental Pollution:

Exposure of human beings and animals especially aquatic life to drugs through environment imposes a great threat.

The important one is microbial resistance due to continuous exposure to low dose of antimicrobial through drinking water may cause resistance.

When compared to normal population, the special population like pregnant females, children, elderly kidney and liver disease patient remain at greater risk to exposure.

The most difficult part of the ecopharmacovigilance is to determine the relationship between the cause and effect.

Few examples, impact of drugs through environment on various aquatic and terrestrial animals –
1. Vulture population has been declined over a decade due exposure of contaminated 'diclofenac' a NSAID in the treated ill animals. When vultures feed carcass of animals treated with diclofenac , they die from kidney failure within the days of exposure.
2. Levonorgestrel progesterone can cause sterility in female frogs when threshold limit in the environment is higher than normal (2). Mainly causing immature ovarian egg cells and lacked oviducts.
3. In a study, diabetes drug metformin makes male minnows more female at levels common in wastewater effluent (3).
4. Synthetic estrogens like 17-α- ethinyl-estradiol, which is widely used in contraception is shown to enter the water bodies, its very low concentration in aquatic environment causes feminization of male fish(4)(5).
5. Ivermectin can affect dung bettle such as reduction of growth rate, inhibition of pupation and the disruption of mating (6).
6. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) is widely identified in streams and lakes from sewage effluent water.
7. Raloxifene and bazedoxifene medications used to help prevent osteoporosis—showed the potential to reach drug concentrations in fish tissue that exceed potency levels.

Approaches To Reduce Amount Of Pharmaceuticals Released In The Environment:

Drug has become an inevitable part of our lives but it is not imperative to compromise with the balance of ecosystem on any grounds. Some remedial measures can be projected to reduce the amount of drugs entering the environment.

To reduce generation of pharmaceutical waste:

Reducing the amount of pharmaceutical waste addresses the root cause of the problem as well as reducing overall health cost.

To increase the efficiency of sewage treatment plants:

Sewage treatment plants are generally not equipped to routinely remove medicines. Thus , measures should be taken to improve the efficiency of these sewage treatment plants so that pharmaceutical can be removed from sewage before it enters local water ways.

Use of green pharmacy:

It is a design of pharmaceutical products and processes that eliminate or reduce significantly the use and generation of hazards substances and the prevention or reduction of environmental safety and health impacts. Thus new Eco compatible ways should be adopted to synthesize drugs.

Developing better drug disposal programs:

Over the counter and prescription medications should not be disposed down the drain because waste water treatment facilities are not designed to remove pharmaceutical compounds and they may end up in local water ways and may eventually found in drinking water. Proper disposal of unwanted and expired prescriptions and over the counter medications in the trash promotes a healthy aquatic environment and prevents accidental poisoning and intentional abuse.

Return to donor or manufacturer:

Possibility of returning unusable drugs for safe disposal by the manufacturer should be explored.

Landfill:

Landfill means to place waste directly into a land disposal site without prior treatment or preparation. Properly constructed and operated landfill sites offer a relatively safe disposal route for municipal solid wastes, including waste pharmaceuticals.

a) Waste immobilization: It is done by two ways

Encapsulation involves immobilizing the pharmaceuticals in the solid block with in a plastic or steel drum.

Inertization it is a variant of encapsulation and involves removing the packaging materials, paper, cardboard and plastic, from the pharmaceuticals.

Comparison Of Pharmacovigilance With Eco-Pharmacovigilance:

Both PV and EPV aim to monitor the adverse effects of pharmaceuticals, pharmacovigilance in patients and eco-pharmacovigilance in the environment.

Exposure to the drugs in humans is well defined through clinical trials by knowing the dose given and also by measuring plasma levels.

Conversely, drugs and their metabolites can be detected in the environment and their concentrations measured or predicted.

Drugs that are prescribed to the patients are monitored, and ADRs identified, discussed and clarified as necessary through the pharmacovigilance process.

In contrast, species in the environment are not routinely monitored and there is no equivalent to the doctor patient interaction that is so important for identifying ADRs in patients.

Determining a causal relationship between a drug or a combination of drugs, and a possible ADR in an individual patient or a population group is not always straight forward but it is now here near as difficult as attributing adverse environmental impacts on environmental species to a single cause such as an individual drug, combination of drugs or a drug metabolite.

Ecopharmacovigilance And Drug Regulations:

Environmental Risk Assessment (ERA) of pharmaceuticals:

There are various countries- Europe, America having regulatory requirements which governs of era of pharmaceuticals.
It assess environmental fate and effects produced by these pharmaceuticals.

The European Commission is currently reviewing data on pharmaceutical in environment and potential impact on the environment and public health and veterinary drugs.

Environment risk management plan as a centralized source to assess and manage the environment risk of a drug throughout it's life cycle.

It is assessed by risk quotients which is ratio of the Predicted Environmental Concentration (PEC) to the Predicted No Effect Concentration (PNEC).

Ratio estimates maximum concentration anticipated to occur in the environment.

If (PEC:PNEC) is less than 1, no further information is required; if it is greater than 1 then additional testing is required and appropriate risk management is needed.

ERA have to be done in Eco-pharmacovigilance before approving a new drug.

Resource Conservation and Recovery Act (RCRA):

This act since 1974 is for regulating the disposal of health care waste.

It regulates and tracks the disposal of solid waste, setting forth strict rules for facilities that generate, transport, store and dispose off hazardous waste.

This act defines hazardous waste as chemicals or formulations so detrimental to the environment that they must be separated for special disposal and cannot be introduced into sewers or placed in landfills.

Risk Mitigation Measures (RMM):

If the ERA of a veterinary medicinal product indicates an unacceptable risk to the environment that is the risk quotient consisting of the ratio of PEC to PNEC is equal to or larger than one, and /or the risk-benefit balance is negative, i.e., the therapeutic benefit is outweigh by risks to the environment, safety or efficacy, the authorization can be refused.

RMM can be applied to improve the prevention of exposure and the protection of the environment.

RMM can also be applied to the human pharmaceuticals.

Global Scenario of Ecopharmacovigilance:

In recent years, human pharmaceuticals from numerous therapeutic classes have increasingly been detected in the environment, typically at nanogram per liter low microgram per liter in surface waters.

A vast array of pharmaceutical ingredients an enter environment.

They may be of medical importance or for which a possible pharmaceutical use has not yet been discovered.

A study has found that nineteen pharmaceuticals of the twenty seven human pharmaceuticals investigated, have been identified in aquatic environment.

Drug	Group
Erythromycin	Antibiotics
Trimethoprim	Antibiotics
Ketoconazole	Antibiotics
Amoxicillin	Antibiotics
Diclofenac	NSAIDs
Ibuprofen	NSAIDS
Paracetamol	NSAIDs
Naproxen	NSAIDs
Propranolol	B blockers
Atenolol	B blockers
Metaprolol	B blockers
Tamoxifen	Hormonal drugs
Ethinylestradiol	Hormonal drugs
Levonorgestrel	Hormonal drugs
Fluoxetine	Anti-depressants
Citalopram	Anti-depressants
Carbamazepine	Miscellaneous
Benzafibrate	Miscellaneous

Not only pharmaceuticals are identified in the environment, but also in the portable water sources.

In USA, the studies have detected very low levels of pharmaceuticals in finished drinking water. The highest concentration reported was 40ng/l for Meprobamate.

In tap water, concentration ranges from nanograms to low micrograms per liter in countries like Germany, Italy.

Even ground waters are also affected by a variety of sources; with landfills, septic systems and agricultural fields representing the most

significant potential sources of anti-infective contamination.

Indian Scenario:

In India, Ecopharmacovigilance is in a budding state.

In India, government has been measuring the amounts of minerals and heavy metals as pollutants in environment but has not succeeded to detect pharmaceuticals as pollutants.

As India is as hub of pharmaceutical companies and manufacturing units has become one of the world's largest centers for bulk drug production. This is the reason that leads to precedent drug contamination of surface, ground drinking water and environment.

A Swedish research team revealed that pharmaceutical levels in water downstream of a waste water treatment plant in Patancheru, Andhra Pradesh, India was 150 times the highest levels of that found in the USA. There have been several reports from cities like Hyderabad, Bangalore, Coimbatore.

Need for Ecopharmacovigilance in India:

Though it is impossible to eliminate pharmaceutical entry into environment through human and animal excretion, it is impossible to reduce the entry through hospital wastes, improper disposal of unused drugs and wastes emerging from manufacturing industries. Considering the detrimental effects caused by pharmaceuticals entering the environment, there is a need for setting up 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 should take up the measures to initiate and strengthen ecopharmacovigilance in India.

A significant cooperation is required from Bulk Drug Manufacturer's Association of India representing the pharmaceutical industries.

Certain measures are to be implemented by the government of India to prevent the misshapes of entry of pharmaceuticals in the environment. The greatest challenge concerns signal detection in the environment and the difficulty of identifying cause and effect. Testing or monitoring in the environment need to be done when the risk is identified. Studies need to be done in the laboratories simulating real environment to assess the effect 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.

Conclusion:

Drug use has become inevitable part of our lives which leads to the accidental poisoning or intended poisoning to the human beings and animals including aquatic life. Biopharmaceuticals may be an alternative but we still lack a scientific evidence to accept them as a complete substitute of drugs in practice. We need to monitor the effects of drugs not only as a good medical practice, but also to safeguard our environment. If we don't begin to address the environmental damage we are causing, it will be at the far greater cost of accelerated species extinction and disruption of the food chain. The research community, EPA, FDA and pharmaceutical manufacturers should work together to design educational programs to better inform investigators, health care providers and patients about the potential environmental impacts of pharmaceutical use and appropriate disposal methods.

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