REVIEW ARTICLE

ECOPHARMACOVIGILANCE: ITS IMPORTANCE AND CHALLENGES

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ABSTRACT

Active pharmaceutical ingredients represent a group of emerging environmental contamination. Even in trace amounts, they are of great concern due to then continuous introduction into the environment, their impact an ecosystem and human and vetenery health is of great importance. This has given birth to the science of Ecopharmacovigilance (EPV). It aims to ensure that significant environmental issues associated with pharmaceuticals in the environment are identified and managed appropriately. EPV has become a research hotspot in Europe and North America. Environmental Risk assessment (ERA) is now a regulatory requirement prior to launch of any new drug. The biggest difference and greatest challenge concerns signal detection in the environment and the dilemma of identifying cause and effect. In the background of growing Indian pharmaceutical industry and drug consumption, India should shoulder responsibility for its own environment and people along with the world ecosystem. Compared to the west EPV in India is in infancy ERA is now a regulatory requirement prior to launch of any new drug. However there is no formal frame-work to monitor for potential adverse effects in the environment, once a product has been launched. There should be laws and regulations on EPV, rational medication, drug take back programs, strengthening policy guided and scientific researches on EPV by pharmaceutical firms and academia.

Key words: Ecopharmacovigilance (EPV), Active pharmaceutical ingredients (API), Environment risk Assessment (ERA).

INTRODUCTION:

In recent years great concern has been expressed over the potential impact of pharmaceuticals in the environment. As stated by AL Groce in New York times in 2007 "our home earth, is in danger". What is at risk of being destroyed is not the planet itself, but the condition that has made it hospitable for human beings[1]. Human pharmaceutical from various therapeutic classes have increasing being detected in the environment typically at ng/L to low ug/L in Surface water[2-8]. In 2009 Edward HL and others stated that there is presence of widely dispersed drugs and drug metabolites in the environment which posses a potential direct and indirect risk to humans. It emphasized that-

- The nature and extent of the potential risk must be further investigated and assessed.

- Safe disposal of drugs must be promoted and for that appropriate facilities to be provided and used.

- Measures should be taken to reduce drug discharge into environment and education about it to be provided.

- The promotion of rational drug use should reduce the volume of medicine funding their way into the environment[19]

Thousands of chemicals have been in used have been introduced into the market for everyday life in industry and everyday life. This was blindly carried out without considering the direct and indirect consequences on human and animal health and environment. Every year an estimated 100000 tons of antimicrobial are used all over the world[20]. Many pharmaceuticals chemicals are nondegradable by the acid environment in the stomach not metabolized or metabolized to an active compound are passed as such by humans and animals and thus pose a special risk when they enter through sewage system into water resources and food chain leading to an unwitting re-entry of drugs into humans. The long term exposure to these environment pharmaceutical pollutants could be responsible for chronic toxicity and subtle effects in animals plants and microbial resistance, endocrine disruption, growth inhibition, disruption of microbial ecosystem, cyctotoxicity, mutagenicity,

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teratogenicity and so on[21]. Vulture have been poisoned and even critically endangered due to veterinary diclofenae use when feeding on carcass of live stock[22]. In this alarming situation the concept of Ecopharmacovigilance (EPV) has emerged as an issue of great interest. This has had to the emergence of ecopharmavigilance (EPV) which was first coined by velo[23]. There are number of others similar terms like ecopharmacology, pharmacovigilance, pharmacoenvironmentology. Therefore EPV would describe the Science and activities associated with the dectection, evaluation understanding and prevention of adverse effects of pharmaceuticals in the environment[24,25]. Where as Pharmacovigilance has been defined by would health organization (WHO) as "the science and activities relating to the detection assessment, understanding and prevention of adverse effects or any other possible drug related problem"[26,27]. Environmental risk Assessment (ERA) is now a regulatory requirement prior to launch of any new drug. There are several challenges that has to met if EPV is to effective in practice like Environment risk management plan which provide a framework for recording any environmental risk of products from development to marketing and thereafter. It includes information like physiochemistry pharmacokinetics, metabolism, predinical toxicology and environmental data of the active pharmaceutical ingredient. However, there is no formal framework to monitor for potential adverse effects in the environment, once a product have been launched.

1. What is Ecopharmacovigilance:

It is a developing science and it is very unclear what exactly it means. EPV aims to monitor the adverse effects of pharmaceuticals in the humans through non-therapeutic environmental exposure. It derives from a compromise between a highly industralised chemical based society and need for protection of the environment. The definition of EPV by Holen et al[28] based on the WHO definition of PV. The approaches on EPV include green drug design, green chemistry in process development, development of biodegradable products, minimization of manufacturing emissions, education over rational use of drugs, improved prescribing practices the management of unused drugs etc[25,28-29]. And these new EPV approaches have been introduced into the environmental monitoring of antidepressant[21], antibacterial like fluroquinolones, hormones, paracetmol and diclofenac[25]. Due to the complexicity of pharmaceutical environmental exposure and special biochemical effects of drugs more studies on specific biological monitoring of different species, measurement, predication and identification of potential

effects of pharmaceutical pollutants are required to improve scientific understanding of pharmaceuticals in the environment. Some background is necessary about the Pharmaceuticals in the environment and Environmental risk Assessment of pharmaceuticals. Environmental risk Assessment (ERA) is now a regulatory requirement prior to launch of any new drug.

2.1 PHARMACEUTICAL IN ENVIRONMENT (PIE):

Sources of Entry:
The potential routes of environmental are-
(i) Patient excretion of the drug or its metabolities via the Sewage System.
(ii) Direct release from waste water System from manufacturing units.
(iii) Hospital or self disposal of unused, unwanted, expired drugs via trash or flushing.
(iv) Terrestial deposition for examples via sluge application to land, leaching from Solid waste landfills or irrigation with treated or untreated waste water [5,14,17,30,31]

Pharmaceutical from environment is usually from excretion of drugs after humans and veterinary therapeutic and also from manufacturing effluent discharge and disposal of unused drugs. Disposal of unused drugs can be managed effectively by guidance for patients take back schemes and disposal practices [32]. 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. It can be tackled by effective sewage treatment which may prevent significant environmental contamination. But there is still some residues remaining, so the doubt remains whether such residues present any significant risk and to what extent. This pertinent question is addressed for new drugs by understanding an environmental Risk assessment as part of regulatory approval to market a new drug.

2.2 ERA of pharmaceuticals:
There are various countries especially Europe and America there are regulatory requirements which governs ERA of pharmaceuticals. It assess the environmental fate and effects produce by these pharmaceuticals. The European commission EC is currently reviewing data on pharmaceutical in the environment and the potential impact on the environment and public health and veterinary drugs[32]. Some pharmaceutical firms in EU such as Astra Zeneca has used Environment Risk Management plans (ERMPs) as a centralized resource to assess and manage the environment risk of a drug throughout its life cycle which include information such as physicochemistry, human

metabolism pharmacokinetics, predinical toxicology and environmental data of the API. After launch Environment Risk Management Protocol (ERMP) is updated as necessary if any new or emerging environmental risk are identified as part of EPV process. It is assessed by risk quotients which is ratio of the predicted environmental concentration (PEC) to the predicted no effect concentration (PNEC). Ratio (PEC:PNEC) estimate the maximum concentration anticipated to occur in the environment. PENC is derived from ecotoxicological test normally in algae, daphnids and fish. If PEC :PNEC is less than one, no further information is required and if it is more than one then additional testing required and appropriate risk management is needed[2]. The society of Environmental toxicology and chemistry (SETAC) has recently published the outcomes of a collaborative workshop that identified the top 20 questions related to pharmaceutical in the environment[34] and has identified clear areas where future research is warranted. This ERA must be done in EU before a new drug is approved. There is no such regulatory in our country.

3. Consequences of Environmental pollution of the environment:

Exposure of human beings to drugs through environment pose a threat to humans and animals especially aquatic life, higher predators [25] . The most important of which is microbial resistance due to continuous exposure to low dose of antimicrobial through drinking water may cause resistance[36]. Decreasing interest of pharmaceutical companies in developing antimicrobial drugs as compared to "lifestyle drugs" may add to the problem [37] . Although effect of very low doses from the environmental cycling is not very char but special population like pregnant females, children, elderly, kidney and liver disease patient remain at greater risk to exposure from the environment and risk of toxic effects[38].

Diclofenae a non-steroidal anti inflammatory drug is an well documented example where a pharmaceutical has resulted in an adverse population level impact on non-target population in the wild [39]. In South-East Asia vultures ingested carcasses of live stock that has been treated with high doses of diclofenae. It is estimated that between 10 to 40 million vultures has been poisoned and that three species of Gyps vultures are now critically endangered [40] due to gout and acute and chronic renal failure. Effects on other species of vultures of Africa, North America, South America has been noticed.

Another, dassical example is the case of ethinylestradiol(EE2) that has shown to affect the sexual development of male fish in extremely low concentration in the laboratory [41-43]. Field survey have shown that intersex fish are wide spread in British river [44,45]. It is very difficult to attribute this phenomena of finished male fish to exposure to the presence of EE2 alone since there may be other chemicals in its environment that can also cause this. These include other estrogen like and anti-androgen like chemicals such as the nonyl-phenol, octylphenol, ethoxylate surfactants[46], leis phenol A[47] phthalates[46,48], phytoestrogens such as genistein and equol and endogenous estrogen excreted from women[49,50]. Population level impacts have been reported in the experimental lake studies by kidd et al[51] as a result of EE2 exposure albeit at level significantly above those found in rivers. This shows the complexity associated with linking cause and effect where several natural and synthetic chemicals are implicated, so researches are continuing working to make the picture dear which is not so yet.

4. EPV in use:

There are several challenges that has to met if EPV is to effective in practice like Environment risk management plan which provide a framework for recording any environmental risk of products from development to marketing and thereafter. It includes information like physiochemistry pharmacokinetics, metabolism, preelincecal toxicology and environmental data of the active pharmaceutical ingredunt .

It enables all available environmental data to be taken into account during drug development and provides early signals and warning of drugs that could pose a potential risk to the environment. This Risk Management plan includes number of measures to be taken to characterizing the safety profile, mitigating and mitigating and minimizing the risk to the patient of a particular pharmaceutical any identified risks can be managed with appropriate regulations from regulatory authorities and pharmaceutical companies. Follow up studies and ecological monitoring for environmental effects can be done.

Area of current concern and interest is whether it is possible to predict potential effects on environmental species from knowledge of the preclinical and clinical data for a compound. Winter et al [52] have reviewed some of the concepts and challenges faced in using preclinical data and knowledge of mode of action, drug discovery and development to help in the design of effective ERA. Such knowledge can help identify potentially sensitive species or sensitive life stages.

There are many individuals and collaboratory research between industry, academic and government acting together to improve the scientific understanding of PIE and ERA. The European commission (EC) has funded a number of specific projects. These include KNAPPE

knowledge and need assessment on pharmaceutical products in environmental water[53], ERA pharm[54], Pharmas[55] and cytothreat [53]. These projects are currently assessing the environmental risk associated with B-blockers, Selective serotonin uptake inhibitors, antibiotics and cyctotoxic drugs. MistraPharma[56] project aims to identify human pharmaceuticals likely to be affect aquatic environment and to address the risk of antibiotic resistance in the environment. Antimicrobial resistance (AMR) is a clinically important problem faced so is receiving particular attention. WHO has identified options to fight the evolving threat of antimicrobial resistance[57]. The control measures include reducing the use of antibiotic, look for antimicrobial use and resistance, but they do not appear to look at natural reservoirs of resistance and the impact that other chemicals co-selectors may have on the increased burden and transmission of AMR. There is evidence that demonstrates that the genes encoding for resistance in clinically relevant bacteria appear to be recruited from environmental bacteria [58,59,60].

Therefore more research is required to determine whether environmental use of human and veterinary antibiotic, antibiotic resistance bacteria biocides and metals (e.g. Copper and Zinc) from various uses cause an increase in the abundance of antibiotic resistance bacteria. Studies have also been conducted that demonstrate that antiviral drug oseltamivir (Tamiflu) is unlikely to have an impact on the environment as a result of widespread use due to bird flu pandemic[61].

The work of Huggett et.al. [62,63] suggests that the concentration of prapranolol in the environment may had to harmful effect in fish since then several research projects like ERA Pharma was done on B blockers which showed that prapranolol biodegraded in the environment, photodegraded [64,65] and unlikely to accumulate [66,67]. There are also ecotoxicity data including study on fish[67] which suggest that propanolol is not as toxic to fish as previously though. There are reason where the risk may be higher in some areas, for example if there is inadequate waste water treatment and /or high population density. Such analysis enables researches to further investigate in those local geographical areas where the potential for risk is higher. There are many potential reasons why the risk may be higher in some areas for example if there is inadequate waste water treatment and /or particularly high population density or low dilution capacity in the receiving environment.

5. Global EPV perspective:

Current ERA practices shows EU and US pharmaceutical use design and the potential risk associated with drugs in those regions. EPV should addresses, regional differences and provide protection in any region where drug is used. Disease prevalence and cultural practices are different in various parts of the world so the risk with different drugs may be different. This is highlighted with the unanticipated impact on didofenae on certain species of vulture population who were sensitive to this drug and the failure of risk assessment to identify the route of exposure. Another key Global challenges is that observation of ecological trends or adverse effect in the environment will at atleast initially be identified as being associated with any one particular one. It look several year to identify the cause of inter sex in fish and cause of vulture decline[68,69]. For this water all water resource should be monitored periodically. There ecological monitoring should be undertaken at a local level with data sharing on adverse effects of these pharmaceuticals within countries and globally. One additional challenge for EPV is that many older established drug do not have regulatory requirement for ERA.

Therefore for effective EPV practices relevant information should be shared between government academia, industry and interested stakeholders.

6. CONCLUSION:

Ecopharmacovigilance is the science and activities associated with the detection evaluation and understanding and prevention of adverse effects of pharmaceuticals in the environment. The main focus of EPV should be after launch of the drug which will help to identify any possible risk. It is a developing science and much work has to be done in our country and world over to device effective approach to EPV.

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