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Ecopharmacovigilance

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Abstract
In this article we have presented some ideas on what Ecopharmacovigilance (EPV) might mean in practice, together with what challenges and opportunities it poses in today's scenario implementing EPV procedures.

Introduction

Unlike many chemicals that enter the environment from various origins, human drugs target specific tissues in the body with specific biochemical and patho-physiological effects in the intended target species[1]. At the same time, if such pharmaceuticals are freely disposed in the environment by any means, these specific effects might have significant impact on accounts of its interaction with aquatic life, higher predators and humans[2]. There have been many studies suggesting presence of pharmaceuticals in the environment. Yet, very few adverse environmental impacts in the field have been exclusively credited to a pharmaceutical. Diclofenac, a non-steroidal anti-inflammatory drug, has been known to have adverse impact on non- target populations in the wild[3].

Another example is the case of ethinylestradiol (EE2), presence of which in the environment has shown to affect the sexual development of male fish in very low concentrations in the laboratory studies[4-6]. British rivers survey have displayed widespread presence of intersex fish[7,8]. This enlightens us with the intricacy in proving the cause and effect linking of the pharmaceuticals with changes in the nature if ever detected.

Recently, alarm has been expressed over the probable impact of pharmaceuticals in the environment (PIE) and consequently a comprehensive Environmental Risk Assessment (ERA) is now a regulatory requirement in before a drug comes into market for use. However, there is no specific protocol to review the ERA, or to scrutinize for potential adverse effects in the environment, after a drug gets launched.

Ecopharmacovigilance (EPV) is a branch of pharamacovigilance that deals with effects of the pharmaceuticals disposed in environment. Pharmacovigilance is defined by the World Health Organisation (WHO) as ''the science and activities relating to the detection, assessment

understanding and prevention of adverse effects or any other possible drug related problems''[9,10]. Thus, Ecopharmacovigilance (EPV) may be defined as the process of detecting, evaluating, finding cause & effect, and preventing adverse effects of pharmaceuticals in the environment.

Recently, human pharmaceuticals from many therapeutic classes have been detected to a large extent in the environment[11-26]. The possible routes of environmental entry have been widely studied. These are (i) Excretion of parent compound or metabolites via the sewer system, (ii) Direct release into the waste water system from various sources like manufacturing companies, hospitals and (iii) Terrestrial depositions, for example landfills, irrigation with treated waters, sludge application to land, or irrigation with treated or untreated wastewaters [13,22, 25, 27, 28].

In North America and Europe, regulatory requirements govern the ERA of human pharmaceuticals[29,30]. ERA is assessed by calculating a risk quotient, which is the ratio of the predicted environmental concentration (PEC) to the predicted no-effect concentration (PNEC) ratio (PEC:PNEC). The PEC provides is the maximum predicted concentration to occur in the environment, resulting from disposal into the wastewater system. The PNEC is estimated from eco-toxicological tests, routinely on algae, daphnids and fish (which represent three trophic levels), along with an assessment factor that takes into account interspecies differences in toxicity. Initially, worst-case assumptions made for estimating the PEC (e.g., 100 % excretion by patients, no removal during sewage treatment), and generally if the PEC: PNEC is <1 no further information is required. However, if PEC:PNEC is >1 then additional testing is usually required to refine the PEC or PNEC. If the problem persisits, appropriate risk management measures may need to be put in place to refine the risk quotient to >1. The ERA is a must before a new drug is approved in European Union. If an environmental risk is known, specific measures to limit it should be in place[30]. But, there is no further need for an ERA updation or review, after the new drug is been approved.

AstraZeneca has developed a framework for capturing environmental risks for its products from early development to the launch and all over product life. It includes information such as physico-chemistry, pharmacokinetics, human metabolism, preclinical toxicology and environmental data (when available) of the Active Pharmaceutical Ingredient (API). All the available data related to environment is taken into account at key steps during drug development, thus giving early warning of drugs that could be a potential threat to the environment. Also, any new information that is obtained subsequently is taken into account after launch of the drug[31].

Many targets of a drug, e.g., metabolic pathways and receptors that are aimed in humans, are also found in environmental species. It is of interest to know whether upon knowing the preclinical and clinical data that the potential threat can be predicted[2]. A study reviewed the challenges faced during use of such preclinical data, mechanism of action, from drug discovery and development to an aid for designing a more useful ERA[32]. Such use of data can help in identifying sensitive species and its sensitive life stages, so that an appropriate testing strategy is developed[2]. Also, the pharmacokinetics properties of the drug can help to identify relevant environmental domains where it is may be present, giving a clue for further analysis.

The complexity of effects of various pharmaceuticals acting together or alone and their effect on various species makes it a challenge to both identify the culprit/s and to look for probable sequence of events that has lead to environmental harm. It is not possible to monitor all species exposed. It took decades after the fall in vulture population to identify the cause as diclofenac poisoning. It might take years to know the causes and consequences of intersex in fish.

In the European Union, monitoring of effects of pharmaceuticals is a part of Water Framework

Directive (WFD), which monitors every watercourse within the EU27 periodically to determine its ecological status. If good ecological status is complied by any of the watercourse, further investigation is done to determine the reason for the non-compliance. As the reason of the non-compliance is known, remedial measures are identified through systematic planning.[31]

On taking into account the status in India, the country has entered into implementing Pharmacovigilance Program of India in 2013. A lot more of polices and stringent laws are needed to make this program fruitful. Thus, it seems highly improbable that Ecopharmacovigilance will be implemented in India in near future.

Discussion

Most of the pro-active measures that shall help in preventing environmental toxicity are already a part of research activities undertaken by pharmaceutical companies, academics and governments. Of about 4,000 APIs on the market today only about 10 % have sufficient data to enable a PEC:PNEC value to be calculated [33]. The information that is available is of occurrence of these drugs in environment. The significance of trace levels of these drugs in the environment is often not known. It is important to identify which of these APIs should be further evaluation on priority basis.

Roos et al. have used nine prioritization schemes to rank 582 APIs, on the basis of environmental hazard and risk, for prioritization of these drugs[34]. On account of insufficient data, all drugs could not be assessed. The authors suggest to use hazard-based approaches only for human drugs when insufficient data exists. Using the traditional PEC:PNEC prioritization approach on 196 human drugs, for which robust data were available, they identified seven with a PEC:PNEC <1, indicating that, where sufficient data exist for analysis, the majority of pharmaceuticals pose no significant risk to the environment.

Conclusions

It should be emphasized that EPV is a developing science, still very much in its infancy, and there is therefore room for further debate and research before any formalized approach to EPV is established. In particular, to determine a causal relationship between a drug and an ADR is not straightforward in terms of a patient, but nowhere near as difficult as attributing adverse impacts in environmental species to a single drug. Ecopharmacovigilance shall require proactive involvement on the part of pharmaceutical companies, governmental authorities and pharmacologist for its growth into an important of Pharmacovigilance.

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