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Adapting and applying common methods used in pharmacovigilance to the environment: A possible starting point for the implementation of eco-pharmacovigilance

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ABSTRACT

Now, the occurrence of pharmaceuticals in natural environment has been frequently reported around the world. As a kind of biologically active compounds specially designed to be effective even at very low concentration levels, pharmaceuticals in the environment could have adverse impacts to the health of human beings or other non-targeted organisms due to long-term exposures. To minimize the pharmaceutical pollution from the perspective of drug administration, a new concept called as eco-pharmacovigilance (EPV) has been proposed as a kind of pharmacovigilance(PV) for the environment. However, as a new and comprehensive science, EPV has not sophisticated methods in practice and formalized implementation model up to now. Since EPV is a special kind of PV, it could be feasible to draw on the experience of PV as a possible and reasonable starting point for EPV. In this paper, we discussed the common methods and activities used in PV including spontaneous reporting, intensive monitoring, database studies, and their potential applicability to the environment. And we concluded that these common methods in PV could be adapted and applied to EPV. But there is still the need for organizational, technical and financial supports of the EPV system.

1. Background

Due to the growing world population, the disease prevalence and the improved health-care, the production and consumption of pharmaceuticals have increased significantly. Accordingly, more and more pharmaceuticals enter into the natural environment through excretion after therapeutic use, manufacturing discharges, direct disposal of unwanted or expired drugs, etc. (Daughton, 2016; Holm et al., 2013) Up to now, the occurrence of common pharmaceuticals such as antibacterial, hormones, painkillers, analgesics, antiepileptics, antidepressants and lipid regulators in a variety of environmental matrices including surface water, groundwater, sediments, soil, even drinking water has been frequently reported around the world (Daughton, 2016; aus der Beek et al., 2016). As a kind of biologically active compounds specially designed to be effective even at very low concentration levels, pharmaceuticals in the environment could have adverse impacts to the health of human beings or other non-targeted organisms due to long-term exposures, such as chronic toxicity, antibacterial resistance, endocrine disruption, toxic effects on reproduction of terrestrial and aquatic organisms (Nödler et al., 2014; Gao et al., 2012). And along with the continuous development in modern pharmaceutical technology, more pharmaceutical chemicals are designated to be non-degradable in order to be long-lasting or resist the acid environment in the stomach, thus pose more persistent and accumulated environmental risks once they are released into the environment (Wang and Hu, 2014).

2. Eco-pharmacovigilance has been proposed as a pharmacovigilance for adverse effects of pharmaceuticals in the environment

To address the growing environmental issues caused by pharmaceutical pollutants, many environmental experts have made great efforts to gather monitoring data, as well as design management options such as upgrades of wastewater infrastructures and runoff control (Wang et al., 2015). Nevertheless, these methods and techniques in the environmental sciences could not effectively remove all the residues of existing and new pharmaceuticals, because of the chemical, structural, and biological diversities of pharmaceuticals. In view of the nature of pharmaceuticals, the pharmaceutical industry and the drug regulatory authorities should actively participate in the management of pharmaceutical contamination, which is the fundamental solution method for this environmental problem (Holm et al., 2013; Wang et al., 2015;

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Wang and Hu, 2014). Under such circumstances, a new concept called as eco-pharmacovigilance (EPV) has been proposed as a kind of pharmacovigilance(PV) for the environment (Holm et al., 2013), to minimize the pharmaceutical pollution from the perspective of drug administration.

PV is responsible for monitoring the safety of medical products after they have been licensed for marketing under the practical conditions of clinical usage in large communities. The overarching goal of PV is to minimize the risk and advance the safe use of marketed drugs, by detecting, identifying, discussing and clarifying drug adverse events that have previously been unrecognised in clinical trials (World Health Organization, 2002). No substance with pharmacological effects is absolutely safe (Norén and Edwards, 2009). And monitoring the Adverse Drug Reactions (ADRs) throughout the life period of a drug is one of concrete tasks of PV activities. World Health Organisation (WHO) has defined PV as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems". Generally, PV activities focus on the monitoring of pharmaceuticals' adverse effects in patients. However, as the scope of PV is broadened, it is considered that all kinds of drug-related problems should be captured (Olsson et al., 2010). In order to highlight the environmental aspects of the use of PV, EPV has been described as "the science and activities associated with the detection, evaluation, understanding and prevention of adverse effects of pharmaceuticals in the environment" (Holm et al., 2013).

3. Adapting and applying common methods used in pharmacovigilance to eco-pharmacovigilance

Although the urgency for EPV has been emphasized in several studies (Medhi and Sewal, 2012; Wang and Hu, 2014), compared to PV, EPV is a new and more comprehensive science that has not sophisticated methods in practice and formalized implementation model up to now (Holm et al., 2013). The existing approaches for EPV which are encouraged mainly target the contamination sources of pharmaceuticals in the environment, include green drug design and process development, rational use of drugs, the take-back and management of unused or expired drugs, minimization of emissions in manufacturing, etc. (Holm et al.,2013) And a dynamic update mechanism to allow the environmental risk assessments of pharmaceutical pollutants to be regularly revised was also suggested to maintain the effective EPV (Taylor and Senac, 2014; Silva et al., 2012). Nevertheless, these methods are not systematic or explicit. Additional work is needed to clarify the model and methods for implementation to ensure EPV to be effective in practice. Since EPV is a special kind of PV, it could be feasible to draw on the experience of PV as a possible and reasonable starting point for EPV. In this paper, we discussed the common methods and activities used in PV and their potential applicability to the environment (Table 1).

3.1. Spontaneous reporting

As the most commonly used method of PV, spontaneous reporting is a standardised and passive form used for the reporting of suspected ADRs of marketed drugs to the regulatory agencies, which predominantly relies on the voluntary reporting by healthcare professionals (including physicians, pharmacists, nurses), in some countries, by manufacturers, consumers, patients, even the public (Berrewaerts et al., 2016; Huang et al., 2014; Rachlis et al., 2016; Pal et al., 2013). Spontaneous reporting has been described as the backbone of data collection in PV, and the most important functions of which are the early identification of potential safety "signals" for medications, formulation of hypotheses, then further confirmatory investigations, sometimes regulatory warnings (Pal et al., 2013). The "suspected" adverse reactions based on clinical suspicion could be early detected and collected into standardized databases in the national or regional PV centers using telephone, paper, e-mail or directly online via the tablets, Internet, and smart-phones. The content of spontaneous reports consists of a description of the adverse event apparently caused by a drug, and the association between drug and adverse reaction is not required to be confirmed by the reporter (Ribeiro-Vaz et al., 2016). Then the reporting centers used some statistical or data mining measures for dis-proportionality analysis, which can form a safety "signal". The "signal" has been defined by WHO as "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously"(Wechwithan et al., 2014). A "signal" only suggests an adverse effect of interest and requires further evaluation and investigation to determine the drug–ADR pair (Shaw et al., 2012). Of all the common PV methods, this type of method could provide the highest volume of data at the lowest maintenance cost, is generally easy to run, and is the most efficient way to detect new, rare and severe ADRs (Rachlis et al., 2016).

This simple, practicable and inexpensive PV method could also be applied to EPV. But the spontaneous reporting in EPV is likely more dependent on manufacturers, hospitals, environmental researchers, consumers and the public, compared to that in PV. The content of spontaneous reports in EPV should mainly involve the report on the over-standard discharge of pharmaceuticals in wastewater, or the adverse environmental impacts apparently caused by pharmaceutical residues. For example, manufacturers and hospitals should have EPV obligations of minimizing the emissions of pharmaceutical-contaminated sewage under national directives and regulations, so as to further pollution management promoted by the government could be enforced. The roles of pharmaceutical manufacturers and hospitals as

Table 1
Summary of the possible application of commonly used methods of pharmacovigilance (PV) in the implement of eco-pharmacovigilance (EPV).

Methods		PV	EPV
Spontaneous reporting	Characteristics	The most commonly used, standardised, passive and voluntary	
	Content of reports	Suspected ADRs of marketed drugs	Over-standard discharge of pharmaceuticals in wastewater, or the adverse environmental impacts apparently caused by pharmaceutical residues
	Reporting entities	Healthcare professionals (including physicians, pharmacists, nurses), in some countries, by manufacturers, consumers, patients, even the public	More dependent on manufacturers, hospitals, environmental researchers, consumers and the public
Intensive monitoring	Characteristics	Active and targeted	
	Content	Intensive monitoring for the use of certain selected drugs on basis of clinical prescription data during a certain period of time	Intensive monitoring for the specific pharmaceutical products with higher volume of use and higher potential environmental risks
Database studies	Characteristics	Systematic and timely	
	Aim	To test hypotheses (i.e. the adverse event is suspected of being an ADR) developed after signals have been detected in spontaneous reports, in order to facilitate the more timely identification and quantitation of ADRs	To acquire more comprehensive real-time data on pharmaceutical residues