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Review

Targeted eco-pharmacovigilance for ketoprofen in the environment: Need, strategy and challenge

Jun Wang [a, c], Shu-qi Zhao [a, c], Meng-ya Zhang [a, c], Bing-shu He [b, *]

[a] Department of Pharmacy, College of Medicine, Wuhan University of Science and Technology, Wuhan 430065, China
[b] Hubei Woman and Child Hospital, Wuhan 430070, China
[c] Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Science and Technology, Wuhan 430065, China

HIGHLIGHTS

- High potential environmental risks and wide usage of ketoprofen.
- Ketoprofen frequently present in environmental compartments around the world.
- Some recommendations for the targeted EPV strategies for ketoprofen were proposed.

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ABSTRACT

Implementing "targeted" eco-pharmacovigilance(EPV) which focuses on individual or specific pharmaceuticals on a prioritised basis is a feasible, economical and customized approach to reduce the environmental concentrations and risks of pharmaceuticals. Non-steroidal anti-inflammatory drugs(NSAIDs) remaining in environment are a kind of priority hazard substances, due to a notable case that diclofenac residues caused the loss of more than 99% of vultures across the Indian sub-continent. Ketoprofen, as another widely used NSAID with comparable or even higher global consumption than diclofenac, in the environment has been shown to present a potential risk to non-target terrestrial and aquatic species. Based on the review of 85 articles reporting the analyses of ketoprofen residues in environment since 2010, we found that this NSAID frequently present in various environmental compartments around the world. Therefore, it is urgent to implement EPV targeting ketoprofen pollution. Here, we provide some recommendations for implementing the targeted EPV for ketoprofen, including: Closely monitoring ketoprofen in the natural environment; Reducing the residues of ketoprofen through source control; Encouraging urine source separation and treatment; Limiting the application of veterinary ketoprofen; Designing and constituting a framework system of targeted EPV. But some challenges, such as ambiguity in the accountability of the main bodies responsible for continued monitoring of ketoprofen residues, the lack of optimized urine source separation scenarios and procedure, the need for detailed design and application schemes of the framework system of targeted EPV, *etc.* should be addressed.

Contents

* Corresponding author.
E-mail address: hbs102626@163.com (B.-s. He).

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1. Introduction

In line with tremendous growth in the development and application of pharmaceuticals to treat human or veterinary diseases, the topic of pharmaceuticals as emerging pollutants of concern in the environment has become increasingly popular in recent years (Noguera-Oviedo and Aga, 2016; Madikizela et al., 2017; Holm et al., 2013). The pathways for environmental contamination of pharmaceuticals include the excretion in urine and faeces after human or veterinary consumption, inappropriate household disposal of unused medicines (out-of-date or unwanted) through the sink/toilet or *via* waste collection, the effluents of hospitals or pharmaceutical production facilities, and other anthropogenic mechanisms such as aquaculture, pharmaceutical-contaminated wastewater treatment plant (WWTP) sludge or urine/faeces of pharmaceutical-treated animals for land application, and manufacture spill accidents (Santos et al., 2010; Sousa et al., 2011). Pharmaceuticals are designed to have biologic activity at very low concentration levels, therefore, these compounds could cause undesired effects on non-target organisms even at trace levels once in the environment (Nödler et al., 2014; Gao et al., 2012). Moreover, along with the pursuit of long-acting biodegradable medicines, together with their continuous use and release, pharmaceuticals can persist in the natural environment, thus are considered as pseudo-persistent contaminants (Vulava et al., 2016). As pharmaceutical residues are a kind of new emerging contaminants, no systematic legal control over their discharge and/or environmental levels has been set up yet (Mendoza et al., 2015).

Under such circumstances, eco-pharmacovigilance (EPV) has been proposed as a kind of pharmacovigilance (PV) for possible drug-related adverse effects in the environment (Holm et al., 2013; Wang and Hu, 2014), under which many approaches are designed and advocated from the perspective of drug administration to reduce the environmental concentrations and risks of pharmaceuticals. So far, approaches to EPV mainly comply with sustainable pharmacy and green chemistry principles, such as green chemistry in process development, green drug design, minimization of manufacturing emissions, rational drug use and the safe management of unused medicines (Holm et al., 2013). However, since EPV as a new and comprehensive science is still in the initial stage of moving from concept to implementation, there are not formalized implementation model and sophisticated methods in practice up to now (Holm et al., 2013).

Remarkably, various obstacles need to be overcome before EPV and its management practice can be put in place. Among them, "*extensive and expanding spectrum of contaminants*" has been suggested as one of important issues constraining the management strategies for pharmaceutical pollution (Naidu et al., 2016). Pharmaceuticals cover a large group of substances that display complex biological or toxicological properties, and belong to different chemical families (Vulava et al., 2016). It is impracticable to practise rigorous EPV for all the pharmaceuticals. Continuing to treat the pollution of all pharmaceuticals as a group of contaminants will lead to a significant waste of resources (Taylor and Senac, 2014). Therefore, at the present stage of EPV development, it is more effective to implement "targeted" EPV which focuses on individual or specific pharmaceuticals on a prioritised basis.

In this paper, we will focus on the current knowledge about ketoprofen (2,3-benzoyl phenyl-propionic acid), a first-line drug from the non-steroidal anti-inflammatory drugs (NSAIDs) class, as an environmental contaminant, and discuss the necessity, challenge and possible strategies for the implementation of targeted EPV for ketoprofen.

2. The necessity for the implementation of targeted EPV for ketoprofen

2.1. High potential environmental risks and wide usage

Some pharmaceutical products with serious residue problems in environment and potential environmental risks have been considered as high priority hazard substances, which should be closely monitored in environment, in the European Union (EU). For example, analgesics, antibiotics and antidepressants were identified as the highest priority in surface water, sediment and terrestrial environment and included in the watch lists (EC, 2011; EMEA, 2006). Especially for NSAID analgesics, their high environmental risks have placed themselves in the spotlight. The most notable case of global concern is the loss of more than 99% of vultures across the Indian sub-continent in 15 years (1992–2007) mainly caused by the dose-dependent acute kidney failure because of veterinary use of diclofenac, a common NSAID (Shore et al., 2014). Therefore, diclofenac has been regarded as one of most devastating environmental toxicants, and proposed as first priority hazard substances in the EU Water Framework Directive (EC, 2011). Accordingly, the legislative target for consent of diclofenac in water environment was recommended for 100 ng/L in Europe (Petrie et al., 2013), and other related measures under EPV (*e.g.* closer monitoring on the environmental levels, the ban on the manufacture of veterinary diclofenac, application of vulture safe alternative NSAID meloxicam for the treatment of livestock diseases) have been adopted (Wang and Hu, 2014; Velo and Moretti, 2010). Then later, the rapid decline of vulture populations slowed down (Shore et al., 2014; Prakash et al., 2012), suggesting this targeted EPV for diclofenac achieved a certain effect.