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Review

Occurrence, ecotoxicological effects and risk assessment of antihypertensive pharmaceutical residues in the aquatic environment - A review

Aline A. Godoy [a], Fábio Kummrow [b,*], Paulo Augusto Z. Pamplin [a]

[a] Science and Technology Institute, Federal University of Alfenas (Unifal-MG), Rodovia José Aurélio Vilela, 11,999, Poços de Caldas, MG 37715-400, Brazil
[b] Institute of Environmental, Chemical and Pharmaceutical Sciences, Federal University of São Paulo (Unifesp), Rua São Nicolau, 210, 09972-270 Diadema, SP, Brazil

HIGHLIGHTS

- Antihypertensives are frequently detected in aquatic environments.
- There is a notable lack of reports on ecotoxicity data for some antihypertensives.
- Scientific community has mainly concerned their attention on beta-blockers.
- Acute ecotoxicity studies still predominate relatively to the chronic ones.
- An aquatic environmental risk is suspected to atenolol, metoprolol and propranolol.

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ABSTRACT

This study presents a review of the investigated antihypertensives in different aquatic compartments. It aims to compare these data with those regarding ecotoxicity effects in order to find out ecotoxicological data gaps for these pharmaceuticals and to point out the need for future studies. In addition, part of this article is dedicated to the risk assessment of the parent compounds atenolol, metoprolol, propranolol and verapamil, which are of great environmental concern in terms of contamination levels and for which there are sufficient ecotoxicological data available. 79 articles were retrieved presenting quantization data for 34 different antihypertensives and/or their metabolites. Only 43 articles were found regarding acute and chronic ecotoxicological effects of antihypertensive drugs. The results indicated that the beta-blockers atenolol, metoprolol and propranolol are the antihypertensives most frequently detected in the aquatic environment. They are also the drugs which reached the highest maximum concentrations in surface waters in the data reported in the literature. The highest percentages of ecotoxicity data regarding antihypertensives were also related to these beta-blockers. On the other hand, there is clearly a lack of ecotoxicity data, especially the chronic ones, regarding other antihypertensives. The environmental risk assessment (ERA) showed that all three of the evaluated beta-blockers can pose a potential long-term risk for non-target organisms of both fresh and marine water species. However, more meaningful ecotoxicity data for antihypertensives, including saltwater species, are required to refine and enlarge these results. Additional studies focusing on potential interactions between pharmaceutical mixtures, including antihypertensives, are also an urgent need.

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* Corresponding author.
E-mail addresses: agodoy.aline@gmail.com (A.A. Godoy), fkummrow@unifesp.br (F. Kummrow), paulo.pamplin@unifal-mg.edu.br (P.A.Z. Pamplin).

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1. Introduction

Contaminants of emerging concern can be defined as naturally occurring, anthropogenic chemicals or materials which have now been discovered or are suspected to be present in the environmental compartments and whose toxicity or persistence are likely to adversely affect the biota in a significant way (Sauvé and Desrosiers, 2014). These chemicals have been released into the environment over a long period of time. However, concerns with their harmful effects on the environment and human health have been raised only recently (Sauvé and Desrosiers, 2014). Pharmaceuticals are a class of environmental contaminants that emerged at the end of the twentieth century due to the rapid development of sensitive and automated analytical instrumentation (Taylor and Senac, 2014). Improvements in analytical science have made it possible to understand the distribution patterns of pharmaceutical residues in several environmental samples and highlighted the most important therapeutic classes among these contaminants (Santos et al., 2010).

Within this context, Santos et al. (2010) reported that the antihypertensives, including the beta-blockers, are one of the most frequent therapeutic classes detected in the environment, representing 12% of total retrieved data. These conclusions are based in a review study comprising data collected from 134 articles published between 1997 and 2009. Besides the beta-blockers, the antihypertensive therapeutic class includes the angiotensin-converting-enzyme (ACE) inhibitors, the angiotensin II receptor antagonists (sartans) and the calcium channel blockers.

The frequent detection of antihypertensive pharmaceuticals in the aquatic environment reflects a rapidly growing pharmaceutical industry (Maszkowska et al., 2014a) and a high consumption of these drugs all over the world (Gu et al., 2012; Bayer et al., 2014). Other reasons for the high frequency of detection of these contaminants in aquatic environments are the incomplete removal during passage through sewage treatment plants (STP) (Ternes, 1998; Bayer et al., 2014) and the relatively high persistence in water matrices presented by some of them (Piram et al., 2008; Maszkowska et al., 2014a).

The presence of antihypertensives in the environment can lead to toxicological effects on non-target organisms. For example, Maszkowska et al. (2014b) pointed out that the beta-blockers belong to the class of Endocrine Disruptive Compounds, since they can disrupt testosterone levels in male organisms. Therefore, it is important to assess the environmental risk posed by these contaminants. A first approach of the risk assessment for the aquatic environment can be calculated comparing the measured environmental concentration (MEC) to the toxicologically relevant predicted no-effect concentrations (PNEC) (Bayen et al., 2013). It is worthy to emphasize that the MEC provides an important estimate of external exposure concentration or dose (Bayen et al., 2013).

This paper presents a review of the investigated antihypertensives in several aquatic matrices. These data were correlated to the ecotoxicological ones available in the literature in order to identify ecotoxicological data gaps for these drugs and to point out the need for future studies. It is also presented a first approach to the environmental risk posed by the antihypertensive pharmaceuticals (considering only parent compounds) of higher aquatic environmental concern in terms of contamination and/or by those for which there are sufficient ecotoxicological data available in the literature.

2. Retrieved data published in the international literature on the occurrence and ecotoxicity of antihypertensives

As a first step, data from 79 international articles on MEC of antihypertensives and their metabolites/transformation products (TP) in aquatic matrices all over the world were retrieved from several databases including ScienceDirect and SciELO. These articles date from 1998 to 2015. These 79 scientific publications are reported in Table A.1 (Appendix A of Supplementary material). The total number of molecules covered in these studies reaches 34.

A total of 397 antihypertensives concentration data were retrieved from the literature. The concentration data concern freshwater (161) and marine/estuarine surface waters (23); effluents from wastewater/sewage treatment plants (WWTP)/(STP) (147), hospitals (28) and drug production facilities (3); drinking waters (14) and groundwater (21). The frequency of detection of each antihypertensive pharmaceutical in the aquatic environment was calculated from the collected data. In addition, the pharmaceutical residues that reached the highest maximum concentrations in each aquatic environment were identified, especially those in surface waters.

Next, validated data reported in the literature on antihypertensives ecotoxicological effects were collected from 43 articles, including both acute and chronic studies. These ecotoxicological data are reported in Table B.1 (Appendix B of Supplementary material). From these papers, effective/lethal concentration at a 50% level ($E(L)C_{50}$) and/or no-observed effect concentration (NOEC) values obtained from algae, macrophyte, crustacean, fish, as well as representative mollusk and microorganisms were recorded. Then, the PNEC values were calculated for antihypertensive pharmaceuticals with sufficient ecotoxicological data. The PNEC values were calculated based on both NOEC and $E(L)C_{50}$. NOEC is the most frequently used measure for toxicity in the low effect region (Isidori et al., 2005). $E(L)C_{50}$ is independent of the concentrations and spacing that each researcher selects (Isidori et al., 2005). The PNEC values were obtained by dividing the worst NOEC and/or $E(L)C_{50}$ obtained from tests on different aquatic organisms by adequate assessment factors (AF), according to European Commission (2003).

In the following step, the antihypertensives of higher environmental concern in terms of contamination and with a sufficient amount of ecotoxicological data available were identified in order to calculate for them a first approach of risk for fresh and marine/estuarine surface waters. The risk quotient (RQ) was calculated considering the ratio of the highest MEC to the PNEC calculated for both NOEC and $E(L)C_{50}$ values. In the cases where the MEC/PNEC ratio was $\geqslant 1$, an ecological risk was suspected (Isidori et al., 2005).