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Review

Global scanning assessment of calcium channel blockers in the environment: Review and analysis of occurrence, ecotoxicology and hazards in aquatic systems

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HIGHLIGHTS

- Water quality hazards of calcium channel blockers (CCBs) remain poorly understood.
- CCB occurrence data is scarce in South America and unavailable for Africa.
- Diltiazem and verapamil are commonly reported CCBs; amlodipine requires much study.
- Limited ecotoxicology data and monitoring information for coastal and marine waters.
- Therapeutic hazard thresholds of CCBs exceeded in fish plasma, effluent and freshwaters.

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ABSTRACT

As an urban water cycle is increasingly realized, aquatic systems are influenced by sewage and wastewater effluent discharges of variable quality. Such urbanization results in exposures of non-target aquatic organisms to medicines and other contaminants. In the present study, we performed a unique global hazard assessment of calcium channel blockers (CCB) in multiple environmental matrices. Effluent and freshwater observations were primarily from North America (62% and 76%, respectively) and Europe (21% and 10%, respectively) with limited-to-no information from rapidly urbanizing regions of developing countries in Asia-Pacific, South America, and Africa. Only 9% and 18% of occurrence data were from influent sewage and marine systems, though developing countries routinely discharge poorly treated wastewater to heavily populated coastal regions. Probabilistic environmental exposure distribution (EED) 5th and 95th percentiles for all CCBs were 1.5 and 309.1 ng/L in influent, 5.0 and 448.7 ng/L for effluent, 1.3 and 202.3 ng/L in freshwater, and 0.17 and 12.9 ng/L in saltwater, respectively. Unfortunately, global hazards and risks of CCBs to non-target organisms remain poorly understood, particularly for sublethal exposures. Thus, therapeutic hazard values (THV) were calculated and employed during probabilistic hazard assessments with EEDs when sufficient data was available. Amlodipine and verapamil in effluents and freshwater systems exceeded THVs 28% of the time, highlighting the need to understand ecological consequences of these CCBs. This global scanning approach demonstrated the utility of global assessments to identify specific CCBs, chemical mixtures with common mechanisms of action, and geographic locations for which environmental assessment efforts appear warranted.

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1. Introduction

Whereas unprecedented growth and concentration of human populations is occurring in urban areas, resource consumption, including chemical use, is also concentrating (Brooks, 2014; Postel, 2010). Advancing sustainable water management is increasingly important as global access to chemical products is increasing faster than wastewater management systems and infrastructure are being implemented. For example, 80% of global sewage production remains untreated. Consumption of consumer goods, including human pharmaceuticals, varies worldwide, while the number of persons above age 60 is expected to double by 2050 (Gaw and Brooks, 2016; Kookana et al., 2014). Coincidentally, 70% of the human population reside in coastal cities where local water resources are stressed from insufficient waste management, climate change, and contaminant loadings (Hooper, 2013; Vorosmarty et al., 2010; Water, 2009). Herein, potential risks of pharmaceuticals in the aquatic environment are of increasing concern to water resources, wildlife, and public health (Arnold et al., 2014; Ashbolt et al., 2013), particularly in developing countries (Kookana et al., 2014).

Pharmaceuticals are often continuously released from wastewater treatment plants (WWTP) resulting in potential life cycle exposures to non-target aquatic organisms, especially in arid to semi-arid geographic regions where effluent-dominated or dependent systems are common (Ankley et al., 2007; Brooks et al., 2006). Around 98% of published literature on pharmaceuticals in the environment (PiE) has been published since 1995, and has increased by 5- and 10-fold in the past two decades (Daughton, 2016). This research growth has been spurred by an increasing ability to detect human and veterinary medicines in the environment, which has provided information to support exposure assessments and to consider their potential toxicological effects to non-target organisms (Halling-Soensen et al., 1998; Monteiro and Boxall, 2010; Ternes, 1998). However, various classes of pharmaceuticals have received differential attention. For example, initial studies emphasized endocrine disrupting compounds while more recent assessments have focused on antibiotics, antidepressants, antihistamines, and others (Brooks, 2014; Gaw and Brooks, 2016; Kookana et al., 2014; Kristofco and Brooks, 2017). Unfortunately, environmental hazards and risks of calcium channel blockers (CCB) to non-target aquatic organisms remain poorly examined.

CCBs represent a class of compounds previously identified to pose potential risks to ecosystems (Berninger and Brooks, 2010). These commonly prescribed substances are reported to accumulate in tissues of freshwater and terrestrial wildlife (Fick et al., 2010b; Lazarus et al., 2015; Scott et al., 2016). Calcium antagonists were discovered in the 1960s (Spedding and Paoletti, 1992) and then introduced to the market as medicines in the 1980s. These antagonists are intended to elicit therapeutic benefits through voltage dependent calcium channel inhibition for treatment of hypertension and angina (Law et al., 2013). Similar to other pharmaceuticals and down the drain compounds, CCBs are primarily introduced to the environment through reclaimed wastewater discharges following excretion as parent compounds or metabolites from patients. For example, approximately 30% of verapamil is excreted as the parent compound without metabolism while other CCBs can be almost entirely excreted as inactive metabolites (Law et al., 2013).

As urbanizing aquatic systems are increasingly influenced by WWTP effluent discharges and untreated sewage, understanding environmental hazards and risks of chronic low dose CCB exposures to non-target organisms is necessary for effective water management (Ankley et al., 2007; Brooks et al., 2006). For example, understanding differential hazards and risks of specific pharmaceuticals across geographic regions has recently been reported and emphasized as a critical research need (Boxall et al., 2012; Rudd et al., 2014). In the present study, we performed a novel global scanning assessment for CCBs in the environment. The objectives of this study were to critically review the current knowledge of CCB occurrence and to initially assess associated hazards in various environmental water matrices. We specifically examined the refereed literature for CCB occurrence and ecotoxicology data. When data availability was sufficient, environmental exposure distributions for specific CCBs were developed. These distributions were then used to predict the probability of exceeding individual CCB therapeutic hazard values (THV) in surface waters and effluents among geographic regions.

2. Materials and methods

2.1. Literature review of calcium channel blockers

A list of CCBs was compiled from the Mammalian Pharmacokinetic Prioritization For Aquatic Species Targeting (MaPPFAST) database (Berninger et al., 2016). Literature searches through March 12, 2017 returned approximately 143 relevant publications from almost 2800 hits. A similar search was conducted for CCB ecotoxicity data. In these publications, quantitative data on CCBs was collated based on standard study parameters, analytical instrumentation, and geographic region (e.g., Africa, Asia-Pacific, Europe, North America, and South America) as previously described (Corrales et al., 2015; Kristofco and Brooks, 2017).