



Correspondence

Comments on “Chiral pharmaceuticals: Environment sources, potential human health impacts, remediation technologies and future perspective”


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1. Introduction

The presence of chiral pharmaceuticals in the environment is an issue of great concern since pharmaceuticals are biologically active compounds. Enantiomers of chiral pharmaceuticals often behave differently in chiral environments such as biological systems; hence, their toxicities, therapeutic properties, and environmental fate may exhibit stereoselectivity (Smith, 2009). The review “Chiral pharmaceuticals: Environment sources, potential human health impacts, remediation technologies, and future perspective” examined the toxicities, occurrences, and removal of pharmaceuticals and pesticides in built and natural environments (Zhou et al., 2018).

In this commentary, I argue that the review by Zhou et al. (2018) overlooked the implications of chirality on the environmental occurrence, removal technologies, and human toxicity of chiral pharmaceuticals. Zhou et al. (2018) identified wastewater treatment plants (WWTP) as the primary source of chiral pollutants but did not show the role of WWTPs in the enantiomeric enrichment as well as chiral inversion of some chiral pharmaceuticals. They discussed the potential human health risk of chiral pharmaceuticals by addressing their toxicities. However, they did not critically examine the human exposure pathways or stereoselective toxicity of the chiral pharmaceuticals. Zhou et al. (2018) misclassified pesticides as pharmaceuticals. Listed below are my main concerns regarding the review.

2. Pharmacological properties

Zhou et al. (2018) did not critically examine the complexities associated to enantioselective interactions and biotransformation of chiral pharmaceuticals in humans. Following the thalidomide tragedy, several studies were conducted on enantioselectivity in the pharmacokinetic properties (e.g. adsorption, distribution, metabolism, and elimination) of chiral pharmaceuticals (Albani et al., 1984; Ariëns, 1986; Bai et al., 1983; Walle et al., 1983). Plasma protein binding increase the half-life of the drugs while decreasing their volume of distribution and liver metabolism (Mehvar et al., 2002). However, the binding of chiral pharmaceuticals on plasma protein is usually enantioselective. For example, (*S*)-propranolol preferentially bound to α 1-acid glycoprotein and lipoproteins than (*R*)-propranolol and (*S*)-naproxen preferentially bound to human serum albumin (Shen et al., 2013). Chiral pharmaceuticals can undergo enantioselective biotransformation via enzymatic action resulting in the production of bioactive metabolites. Furthermore, interactions at the primary drug

target may favor one enantiomers resulting in differences in their therapeutic properties. In some cases, the antipode might be toxic; for example, (*S*)-naproxen and (*S*)-thalidomide have been shown to be teratogenic while (*R*)-naproxen is a painkiller and (*R*)-Thalidomide is a sedative. Hence, some researchers advocated for chiral switching (i.e. commercialization of single enantiomers) (Ariëns, 1986). For example, ibuprofen and ketoprofen were successfully switched to their *S*-enantiomers which are more potent inhibitors of the cyclooxygenase 1 (COX-1) enzyme (Calcaterra and D'Acquarica, 2018). However, accounting for chirality in human exposure is further complicated by the fact that some drugs such as ibuprofen and naproxen can undergo chiral inversion whereby one enantiomer is converted to its antipode (Zhou et al. (2018) inaccurately referred to this process as enantioselective transformation).

The US Food and Drug Agency recommended the evaluation of pharmacokinetics of individual enantiomers in racemic drugs (U.S. Food and Drug Administration, 1992). Zhou et al. (2018) suggested that the US FDA recommendation on stereoisomeric drugs accelerated development of single enantiomers drugs. However, surveys on new drugs that were approved by US FDA from 2002 to 2015 do not show a clear trend towards single enantiomer drugs (Agranat et al., 2012; Sanganyado et al., 2017). In fact, 50% of chiral drugs approved in 2009 were racemic while 8.3% and 0% were racemic in 2008 and 2010, respectively (Sanganyado et al., 2017).

3. Chiral separation and analysis

Previous reviews extensively discussed the current developments and challenges in chiral separation and analysis of chiral pharmaceuticals in environmental and biological matrices (e.g. Awad and El-aneed, 2013; Calcaterra and D'Acquarica, 2018; Sanganyado et al., 2017; Stalcup, 2010; Xie and Yuan, 2017). Chiral pharmaceuticals are commonly separated using chiral chromatography and capillary electrophoresis, and they are identified using mass spectrometry (Sanganyado et al., 2014). However, these techniques do not provide adequate information on the 3-D molecular structure of the analytes. In fact, previous studies often identified enantiomers according to their elution order, yet the elution order varied with mobile phase conditions (Sanganyado et al., 2017). Hence, techniques such as optical rotation, electronic circular dichroism, and vibrational circular dichroism are often used to determine the absolute configuration of the pharmaceuticals (Polavarapu and He, 2004). Stereoselective matrix effects may occur in the internal standard, particularly in electrospray ionization

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Table 1
Pharmacological and ecotoxicological behavior of selected chiral pharmaceuticals.

Drug	Pharmacology	Stereoselectivity	Ecotoxicity	References
Fluoxetine	Antidepressant	Activity mainly due to (S)-fluoxetine	(R)-fluoxetine was more toxic to <i>P. subcapitata</i> than the antipode.	De Andrés et al. (2009)
Venlafaxine	Antidepressant	(S)-venlafaxine inhibits serotonin reuptake, whereas (R)-venlafaxine inhibits the uptake of serotonin and noradrenaline.	(R)-fluoxetine was 30 × more toxic to a protozoa <i>T. thermophila</i> than its antipode.	Andrés-Costa et al. (2017)
Atenolol	Beta-blocker	Activity mainly due to (S)-atenolol	(R)-venlafaxine induced more oxygen radical in liver tissue of loach than its antipode.	Qu et al. (2018)
Metoprolol	Beta-blocker	Activity mainly due to (S)-metoprolol	(S)-atenolol was more toxic than the antipode to a microalga, but less to toxic than (R)-atenolol to a protozoan.	De Andrés et al. (2009)
Propranolol	Beta-blocker	Activity mainly due to (S)-propranolol	No stereoselectivity in observed changes in heart rate, hatching rate or mortality to zebrafish.	Sun et al. (2014)
Ephedrine	Sympathomimetic amine	Activity mainly due to IR,2S-(+)-ephedrine and IS,2S-(+)-pseudoephedrine	(S)-propranolol was more chronically toxic to <i>P. promelas</i> than (R)-propranolol.	Stanley et al. (2006)
			IR,2S-(+)-ephedrine and IS,2S-(+)-pseudoephedrine were more toxic than IR,2S-(+)-ephedrine and IS,2S-(+)-pseudoephedrine to <i>D. magna</i> .	Rice et al. (2018)

mass spectrometry may lead to inaccuracies in the determination of enantiomeric composition (Barclay et al., 2011; Evans et al., 2015). Such matrix effects can be corrected using isotope labelled analogues of the analytes. However, isotope labelled analogues were rarely used in previous studies probably due to their unavailability (Evans et al., 2015).

4. Sources and occurrence

More than 50% of pharmaceuticals in current use are chiral compounds which are predominantly sold as racemic mixtures and recently as single enantiomers. As noted by Zhou et al. (2018), chiral pharmaceuticals enter the environment through wastewater treatment plant and hospital discharge as well as improper disposal of unused pharmaceuticals in households. However, the authors failed to critically examine how each route of entry affect the enantiomeric composition of the pharmaceuticals. Between 20 and 90% of the pharmaceuticals ingested by humans are excreted unchanged; thus, enter the sewer system as the initial racemic mixture or single enantiomer. The fraction that is metabolized, and then excreted may experience a change in enantiomeric composition due to stereoselectivity in plasma adsorption and enzymatic action. For example, naproxen is sold as the single enantiomer (S)-naproxen. Although (S)-naproxen is known to undergo chiral inversion following administration to humans, no (R)-naproxen was detected in the influent of several wastewater treatment plants globally (Khan et al., 2013; Matamoros et al., 2009; Suzuki et al., 2014). However, (R)-naproxen was detected in the effluent suggesting chiral inversion took place in the wastewater treatment plant (Suzuki et al., 2014). Furthermore, EF values of pharmaceuticals arising from improper human disposal can be expected to be ~0.5 or 1.0 since they may not have undergone interactions in a chiral system.

5. Environmental fate and toxicity

Previous studies have demonstrated that understanding the enantiomeric composition of chiral pharmaceuticals in the environment is of great importance since enantiomers may have different fates and toxicities (Table 1). Zhou et al. (2018) did not discuss the enantiomeric composition of profens in the environment despite the numerous environmental monitoring and characterization studies that demonstrated their fate was stereoselective. Moreover, Zhou et al. (2018) stated the physicochemical properties of ketoprofen (i.e., its pKa value and solubility at various pHs) but did not examine how they may influence their fate, transport, and toxicity in the environment. Briefly, profens are the most widely consumed group of chiral pharmaceuticals; they may undergo unidirectional and bidirectional chiral inversion (Caballo et al., 2015; Hashim et al., 2011; Khan et al., 2013). Regarding β-blockers, Zhou et al. (2018) only focused at propranolol and atenolol leaving out metoprolol, pindolol, salbutamol, and many other well-studied β-blockers. For example, previous studies have shown that metoprolol is frequently detected in the environment since it is hydrolytically stable. However, results on its environmental fate have been mixed with some studies observing S-enrichment in wastewater (Souchier et al., 2016) while another found R-enrichment (Ribeiro et al., 2012). Zhou et al. (2018) included a brief discussion of a biodegradation microcosm study by Selke and Hühnerfuss (2011) that wrongly attributed the source of the experimental approach to Du et al. (2014) and Hühnerfuss and Shah (2009) and the results to a previous study by Selke and Hühnerfuss (2007) on icaridin.

Although understanding the toxicity of single enantiomers is critical for improving the accuracy of environmental risk assessments, data on enantiospecific bioaccumulation and toxicity of chiral pharmaceuticals remain scarce. Table 1 shows the current studies that have been conducted on enantiospecific toxicity of chiral pharmaceuticals. Exposing aquatic organisms such as microalga, protozoa, and fish to β-blockers has been shown to exhibit stereoselectivity. However, the

stereoselectivity demonstrated dependence on the type of organism as well as the β -blocker. For example, (S)-atenolol was found to be more toxic to a microalga (*Pseudokirchneriella subcapitata*) than its antipode, but it was less toxic than (R)-atenolol to a protozoan (*Tetrahymena thermophila*) (De Andrés et al., 2009).

6. Removal technologies

Removal of chiral pharmaceuticals in water and wastewater treatment systems can often lead to the enrichment of a single enantiomer, particularly in a chiral environment. To date, no studies have been conducted on the effects of chirality on the removal of chiral pharmaceuticals using sonolysis, photocatalysis, advanced oxidation processes, and ozonation. Such abiotic processes are often assumed to be achiral since they involve the interaction of the chiral pharmaceutical with an achiral reactive species in an achiral environment (Kasprzyk-Hordern, 2010).

Bioremediation processes involve the enzymatic breakdown of chiral pharmaceuticals by microbes. Enzymes are chiral sensitive and enantiomeric enrichment may result. Hence, the review should have discussed how aerobic granular sludge-sequencing batch reactor and constructed wetlands can result in enantiomeric enrichment. For example, Matamoros et al. (2009) did not observe stereoselectivity in the removal of ibuprofen enantiomers using horizontal subsurface-flow constructed wetlands (an anaerobic system) whereas the (S)-ibuprofen degraded faster than (R)-ibuprofen in the vertical-flow constructed wetland (an aerobic system) (Matamoros et al., 2009). In contrast, (S)-naproxen degraded faster than (R)-naproxen in both types of constructed wetlands. Amorim et al. (2016) found that the removal of norfluoxetine using an aerobic granular sludge-sequencing batch reactor was stereoselective. However, the removal of alprenolol, bisoprolol, metoprolol, propranolol, venlafaxine, salbutamol, and fluoxetine were not stereoselective (Amorim et al., 2016). Amorim et al. (2016) suggested the lack of stereoselectivity was because adsorption was the predominant removal mechanism. In this review, Zhou et al. (2018) make the same assumption that adsorption is a non-stereoselective. However, a previous demonstrated that adsorption of β -blockers on to sludge was stereoselective when ionic interactions dominate the sorption process (Sanganyado et al., 2016). Hence, the need for more systematic studies on factors influencing the stereoselective removal of chiral pharmaceuticals using aerobic granular sludge-sequencing batch reactor.

Incorporating chirality when assessing the occurrence, fate, and toxicity of pharmaceuticals is essential for improving the accuracy of human risk assessments. The review did not critically engage relevant literature on environmental behaviors of chiral pharmaceuticals, focusing on the impact of chirality. As a result, the significance and sometimes validity of the discussions and conclusions drawn in the review are inadequate.

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