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A Review of Pharmaceutical Compounds as an Emerging Aquatic Pollutant

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Abstract

Because of the negative effects on aquatic organisms, pharmaceutical compounds in the aquatic ecosystem are becoming a growing global concern. Pharmaceutical compounds from various drug classes and metabolites have been detected in various aquatic environments and are due to the improper disposal and sewage treatment. There is information available about the acute toxicity of some pharmaceutical compounds. However, chronic toxicity and its potential consequences in aquatic organisms are poorly understood. This review focuses on the environmental concentrations of major pharmaceutical classes, their mode of action in aquatic organisms, and their Eco toxicological effects based on current knowledge about pharmaceuticals in the environment. It is concluded that more targeted Eco toxicological studies are required in the future for better and more comprehensive risk assessments of pharmaceutical compounds.

Keywords: Aquatic Pollutant; Eco toxicity; Aquatic Ecosystem; Pollution

Abbreviations: STPs: Sewage Treatment Plants; NSAIDs: Nonsteroidal Anti Inflammatory Drugs; PPARs: Peroxisome Proliferator-activated Receptors; NOEC: No Observed Effect Concentration

Introduction

Pharmaceuticals are therapeutic drugs used in human and veterinary medicine to cure and prevent disease. The active pharmaceutical ingredients (APIs) in these medications are metabolites that are present in detectable concentrations and are released into the environment [1-4]. The presence of pharmaceutically active compounds in the aquatic environment became a concern only after the 1960s; prior to that, they were invisible pollutants. According to national reports, tonnes of medicines are prescribed and consumed globally [5,6]. Pharmaceutical discharge into the environment is excessively increasing due to rising consumption and demand [7,8]. A large amount of these pharmaceutical compounds, as well as their active and inactive metabolites, are released into the aquatic environment via a variety of means, including manufacturing waste, human or animal excretion, hospital effluents, domestic waste, and agricultural waste [9-19]. Municipal wastewater is the primary pathway through which these compounds enter the aquatic environment. Because active compounds released into sewage treatment plants (STPs) are not completely degraded, they become persistent and emerge as a group of

pollutants [20]. Drug residues have been found in the aquatic environment, according to monitoring studies [1,21-23].

Ternes and colleagues discovered up to one hundred pharmaceutical compounds from various drug classes, as well as their metabolites, in treated sewage, rivers, seawater, groundwater, and drinking water [1,24]. "Because pharmaceuticals are specifically designed to target specific metabolic and molecular pathways in humans and animals, one of the major concerns about their presence in the environment stems from the high likelihood of them being biologically active in wildlife, with the potential for unintended effects on non-target species" [25]. Unintended side effects include the feminization of male fish due to the oestrogen derivative ethinylestradiol in combination with other hormones and the death of millions of vultures in Asia due to diclofenac toxicity from bioaccumulation in the prey [26,27]. The fate of pharmaceuticals that enter the aquatic environment is unknown. They may be dispersed in the environment via aqueous transport and food chain dispersal. Adsorption to suspended solids and biodegradation are two important elimination processes in wastewater treatment. However, as evidenced by several monitoring studies, pharmaceutical levels in digested sludge and sediments are relatively low [28]. The removal of these compounds during treatment varies depending on the construction and technology, hydraulic retention time, season, and STP performance [29]. This review focuses on the effect of environmentally relevant pharmaceuticals, as reflected by consumption volumes, toxicity, and persistence in the environment, on the aquatic organisms.

Effect of Pharmaceuticals on Aquatic Organisms

Pharmaceuticals are specifically designed to target specific metabolic and molecular pathways in humans, which can result in some side effects of their actions [30]. When such compounds are released into the environment, it is more likely that they will affect similar pathways in other organisms, resulting in unexpected results [31]. Because pharmaceuticals are constantly introduced into the aquatic environment, they can cause toxic effects on living organisms even at ng L^{-1} concentrations [32]. Several drugs with different modes of action can cause different mechanisms in organisms [33].

Pharmaceutical eco toxicological effects on aquatic organisms are less well understood than environmental concentrations. Although some pharmaceuticals have standard acute eco toxicity data, such data cannot be used to make comprehensive hazard and risk assessments [29]. The environmental concentration, mode of action, and eco toxicity of major pharmaceuticals from various therapeutic classes, including analgesics and anti-inflammatory drugs, beta-blockers, blood lipid-lowering agents, and neuro active compounds, are summarized below.

Analgesics and Anti-Inflammatory Drugs

Environmental Concentration

Table 1 shows various concentrations of commonly found analgesics and anti-inflammatory drugs.

Compounds	Concentration	Source and location	Reference
Ibuprofen	1µg/L	Sewage and surface waters, USA.	[1,34]
	0.1-20 µg/L	Sewage samples and seawater, Norway	[35]
	674ng/L	Stormwater canals	[36]
Naproxen	1µg/L	Sewage and surface waters, USA	[1,34]
	145ng/L	Stormwater canals	[36]
	12.5µg/L	Canadian STP	[37]
Diclofenac	1µg/L	Sewage and surface waters, USA	[1,34]
Salicylic acid	4.1µg/L	wastewaters	[3]
Acetaminophen	10µg/L	Streams, US.	[3]
Codeine	0.01µg/L	Streams, US.	[3]

Table 1: Concentration of analgesics and anti-inflammatory drugs in aquatic ecosystem.

Modes of Actions

Nonsteroidal anti-inflammatory drugs (NSAIDs) either reversibly or irreversibly inhibit the two isoforms of the cyclooxygenase enzyme, which catalyses the synthesis of various prostaglandins from arachidonic acid [38]. Normal NSAIDs inhibit both COX-1 and COX-2 to varying degrees, whereas new NSAIDs inhibit only the inducible form of

COX-2, which is responsible for inflammatory reactions. The differences in the binding site determine the selectivity of these drugs [39,40]. An inducible COX-2 homolog has been found to be expressed in macrophages in rainbow trout (*Oncorhynchus mykiss*), and the translation product of the COX gene was found to have a high homology of 83-84 and 77 percent to its human counterpart COX-2 and COX-1. The COX enzyme is expressed in macrophages in goldfish, which is equivalent to mammalian COX-2 [41].

Eco Toxicological Effects

Mode of actions and Eco Toxicology

Pharmaceuticals' acute toxicity is evaluated using well-established laboratory organisms such as algae, zooplankton, and other invertebrates and fish. According to Kummerer K, et al. [23], algae were more sensitive to the listed pharmaceuticals than Daphnia magna. Fish have been discovered to be even less sensitive than these. The acute toxicity of diclofenac in algae and invertebrates was studied [42]. Phytoplankton was discovered to be more sensitive than zooplanktons [43]. Due to a lack of data, we only have a hazy understanding of pharmaceutical chronic toxicity. Ferrari B, et al. [44] reported diclofenac studies in invertebrates. Long-term exposure is most likely to cause renal and gill damage. Diclofenac affected the kidneys of vultures, resulting in acute renal failure [26]. Diclofenac does not affect embryonic development in zebra fish embryos, according to Hallare AV, et al. [45]; but it causes delayed hatching.

Beta-Blockers

Environmental concentration

Beta-blockers such as propranolol, bisoprolol, and metoprolol were found at the highest levels in the surface water, at 0.59, 2.9, and 2.2µg/L, respectively [1]. The surface water also contained low levels of nadolol and betaxolol (0.028µg/L) [1].

Mode of Action

Beta-blockers work by competitively inhibiting beta-adrenergic receptors. They are used to treat high blood pressure. Beta-adrenoreceptors were discovered in fish liver and red and white muscle, with a high degree of sequence conservation with other vertebrates. These are thought to play a similar role in humans. In rainbow trout, higher levels of β2-adrenoceptor expression were found in the liver, red and white muscles, and lower levels in the gills, heart, kidney, and spleen [46].

Eco Toxicological Effects

Except for propranolol, the acute toxicity of beta-blockers has received little attention. When compared to other beta-blockers, this compound has the highest acute toxicity. Metoprolol and verapamil increased heart rate in *D. magna* at low concentrations while decreasing heart rate at high concentrations [47]. Propranolol demonstrated chronic toxicity in fish in the cardiovascular system and reproduction, owing to the presence of 2 -receptors in the heart, liver, and most likely reproductive tissue [48]. Significant changes in plasma steroid levels were observed in the fish O. latipes after 14 days of exposure. The amount of eggs released by the fish was reduced [49]. It was discovered that changes in sex steroids cause decreased oxytocin excretion, resulting in a decrease in the number of eggs released.

Blood Lipid-Lowering Agents

Environmental Concentrations

Clofibric acid is a lipid regulator found in many pharmaceutical monitoring studies. These are present in high concentrations in groundwater and in low concentrations in wastewater and surface waters [50]. Up to µg/L levels of gemfibrozil, clofibric acid, and fenofibric acid have been detected in sewage and surface waters. Bezafibrate was found in wastewater and surface water at maximum concentrations ranging from 4.6 to 3.1 µg/L [1].

Mode of Action

Fibrates are more commonly found in the aquatic environment than statins, the two types of antilipidemic drugs. Their purpose is to lower the concentration of cholesterol and triglycerides in blood plasma. Debernard S, et al. [51] provides evidence for statin effects on juvenile hormone synthesis in insects, demonstrating that fluvastatin completely inhibited its biosynthesis in vitro. Fibriate binding to peroxisome proliferator-activated receptors (PPARs) activates nuclear receptors in various cellular pathways, increasing the expression of several lipid regulatory proteins. PPAR genes have been discovered in a variety of fish, including plaice, Atlantic salmon, and zebrafish [52-54]. In humans, PPARs found in fish have an amino acid sequence identity of 43-48 percent.

Eco toxicological Effects

Acute toxicity of lipid-lowering agents is not reported much. LC50 range values of clofibrate showed a range of 7.7-39.7mg/L, which can harm aquatic organisms. Nunes B, et al. [55] reported that the fish *Gambusia holbrooki* [LC50 (96 h) =7.7mg/L] is the most sensitive organism to acute clofibrate

concentrations studied so far.

This compound's chronic toxicity data is also scarce. The NOEC for clofibric acid was observed in C. dubia [NOEC (7 days)=640g/L], the rotifer B. calyciflorus [NOEC(2 days)=246g/L], and early life stages of zebra fish [NOEC (10 days)=70mg/L] [44]. The presence of gemfibrozil in goldfish blood plasma after 14 days of exposure was found to be 113 times higher than in water [56].

Neuroactive Compounds (Antileptics and Antidepressants)

Environmental Concentration

Table 2 shows the different concentrations of neuro active compounds found in different regions.

Compounds	Concentration µg/L	Source	Reference
Carba mazepine	2.3µg/L	STP effluent, Canada	[37]
	>1µg/L	German Surface waters	[1,50]
	20.9µg/L	STP effluents, U.S.	[57]
	0.04µg/L	STPs, Germany	[1]
Diazepam	0.012µg/L	STP effluents, Canada	[37]
Fluoxetine	0.012µg/L	U.S. streams	[3,58]
Primidone	0.6 µg/L	Sewage	[50]

Table 2: Concentration of Neuro active compounds Enrollment in local colleges, 2005.

Mode of Action

Antiepileptic drugs work on the central nervous system to reduce overall neuronal activity. This is accomplished by either blocking voltage-dependent sodium channels of excitatory neurons or increasing the inhibitory effects of the GABA neurotransmitter by binding on a specific site of the receptor [59-62], providing evidence of the occurrence of fluoxetine is a commonly used antidepressant which acts in the inhibition of serotonin reuptake. This hormone has hormonal and neuronal mechanisms that are important in functions like food intake and sexual behavior. Fluoxetine, sertraline, and SSRI metabolites have been found in fish from the United States, indicating the possibility of bioaccumulation [63].

Eco Toxicological Effect

The most severe acute toxicity for fluoxetine has been reported, with EC50 (48 h, alga) =0.024mg/L to LC50(48 h)=2mg/L [23]. Fluoxetine has a greater impact on phyto planktons than on other aquatic organisms. Diazepam and carbamazepine have acute toxicity levels below 100mg/L, indicating that they may be harmful to aquatic organisms. The majority of chronic toxicity data for antiepileptic carbamazepine and selective serotonin reuptake inhibitors were reported. Sub lethal effects were observed in Daphnia at 92µg/L, and the lethal concentration in zebra fish was determined to be 43µg/L [58]. At 10µg/L, diazepam inhibited polyp regeneration in cnidarian hydra. The majority of chronic studies focus on SSRIs. SSRIs such as fluoxetine, fluvoxamine, paroxetine, citalopram, and sertraline reduced the number of neonates or brood per female after 7-8 days of exposure [64].

Discussion

Acute and chronic toxicity of pharmaceuticals has been studied. Acute toxicity is primarily studied in a few species, including algae, zooplanktons, and fish. Only a few pharmaceuticals have been evaluated in the species using these tests. No one could predict the harmful effects of pharmaceuticals based on the data obtained from these tests, as in the case of vulture population decline due to diclofenac exposure. These tests are insufficient to determine the dangers and risks of specific pharmaceuticals. Current tests have only covered a small set of laboratory organisms, which is insufficient for understanding the adverse effects of pharmaceuticals. As a result, more tests with different species are required. Chronic toxicity tests are more useful for assessing the risk of pharmaceutical compounds in organisms.

Pharmaceuticals are compounds that are biologically active. Because the target receptors and biomolecules are identical, these compounds may have similar negative effects in lower vertebrates and invertebrates as they do in humans. Furthermore, due to biological differences, some pharmaceuticals may produce unexpected chronic effects in lower organisms. More emphasis on pharmaceutical in vitro studies is required for screening and understanding their mode of action in non-target organisms.

Pharmaceuticals are primarily studied as single compounds in eco toxicological studies rather than in mixtures with other pollutants. However, these compounds are present in the environment, along with other pollutants, which have an overall effect on the organisms. As a result, toxicity results from the sum of each compound's individual

concentration. As a result, the compounds detected as no-observed-effect-concentration (NOEC) can also affect the organism, albeit in a minor and subtle way. These minor effects can amplify over time as they bio accumulate and are passed on to higher trophic levels in the food chain. This was the case with the Indian vulture population decline caused by diclofenac bioaccumulation toxicity.

Conclusion

Improving STP processes is critical to reducing the amount of pharmaceutical residues in wastewater and surface water. To improve STP techniques, it is necessary to understand the fate of pharmaceuticals during sewage treatment. Improved STP technology will undoubtedly aid in reducing their release into the environment, reducing pollution and its consequences. According to available data, pharmaceutical residues in the aquatic system are unlikely to cause acute toxicity. In addition, data on chronic toxicity of pharmaceuticals is limited. An approach centered on the target molecule, tissues, and organs would be more beneficial than acute toxicity testing in understanding potential effects. Tests focusing on the impact on the organism's survival, growth, and reproduction would provide more relevant insights than traditional eco toxicity testing. In conclusion, more research into chronic toxicity testing is an important step forward.

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