

Hazards of Pharmaceuticals in Water as New Area in Eco-Pharmacovigilance Research

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Abstract

Pharmaceuticals in water can have potential toxic effects on environment and human. It is becoming an emerging research area. Pharmaceuticals have received a growing attention from environmental and health agencies all over the world due to recent studies showing the occurrence of pharmaceutical compounds in environment, especially in water bodies and have become one of the emerging water pollutants. The aim of this review article is to study the hazards of pharmaceuticals in water reported in the literature in order to promote the safe use of medicines among the general public. The aim of this article is to increase the environmental knowledge of pharmaceuticals and to draw attention of pharmacovigilance researcher for more awareness of some of the emerged problems caused by medicines.

Detailed systematic review of the existing literature was carried out investigating the issue understudy. The review process included Pubmed database, Google Scholar, and other online resources available in the university library. The data obtained from the literature review were categorised before being analyzed by the researchers. Minor amount of medications in the water like in nanograms to low micrograms are already reported in per litre range including surface waters, wastewater, and groundwater and, to a lesser extent, drinking-water. Advances in analytical technology have been a key factor in the detection of the occurrence of these pharmaceuticals. Their presence in water, even at a very low concentration, has raised concerns among stakeholders, such as drinking water regulators, governments, water suppliers and the public regarding the potential risks to human health. The awareness about Ecopharmacovigilance as new science concern with the detection, assessment, understanding, and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, which affect human and other animal species and the environmental knowledge of pharmaceuticals must be increase. Ecopharmacovigilance issues must be urgently addressed

Key words: Ecopharmacovigilance, Pharmaceuticals, Pharmaceutical Analysis, Pharmacovigilance, Water.



INTRODUCTION

The advancement of medical technology and science had given rise to the growing number of pharmaceutical products which have helped in improving health and increasing life expectancy through successful treatment of diseases and illness. However, this achievement did come with tradeoffs. Active pharmaceutical ingredients (APIs) or their metabolites have been reported to impact the environment when these substances enter the aquatic environment through patient use or disposal.^[1] Stemming from this awareness, a new field of study known as *pharmacovigilance* has emerged. World Health Organization defined pharmacovigilance as ‘the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem’.^[2,3]

Ecopharmacovigilance can be defined as “science and activities concerning detection, assessment, understanding, and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, which affect human and other animal species”.^[4]

The aim of this article is to synthesize data from published studies and available literature to identify evidence of potential hazards of pharmaceuticals in water to increase the environmental knowledge of pharmaceuticals and to draw attention of pharmacovigilance researcher for more awareness of some of the emerged problems caused by medicines.

METHODOLOGY

Internet searching was used to identify Potential hazards of pharmaceuticals in water. Search terms were pharmaceuticals in water, pharmaceuticals in drink water. Detailed systematic review of the existing literature was carried out investigating the issue under study. The review process included Pubmed database, Google Scholar, and other online resources available in the university library. The data obtained from the literature review were categorised before being analyzed by the researchers. Abstracts of the identified studies were then assessed for relevance to the scope of the review. Studies were included if they included empirical data concerning the hazards of pharmaceuticals in water. The reference list of each paper was checked to identify any further relevant studies. No studies were excluded on grounds of quality.

Towards better Pharmacovigilance

A summary of the most common methods used in pharmacovigilance can be found in few research articles. Harmak and Grootheest (2008) reported that clinical trial

is the main method employed to gather information on a drug in the pre-marketing phase.^[5] This method divides pre-marketing trials into three phases namely phase I, phase II and phase III. Nevertheless, this method is deemed insufficient to monitor the safety of a drug hence it is insufficient to evaluate drug risks. The second method is spontaneous reporting which has become the primary method of collecting post-marketing information on the safety of drugs which aims to serve as early detection of signals new, rare and serious ADRs. The advantage of this method is it enables physicians and pharmacists and patients to report suspected ADRs to pharmacovigilance center. However, this method often flawed when underreporting of ADRs occurs. Another method being used is intensive monitoring.^[6,7] This method was introduced and implemented in New Zealand in the late 1970s and early 1980s. It mainly uses prescription data to identify users of a certain drug. Data about any adverse event occurring during the use of the drug was obtained from interviews with prescribers of the drugs. Generation of reports on event rates instead of incident rates has been identified as the limitation for this method. The fourth method is database studies which comprises of case-control studies and cohort studies. However, power considerations and study design need to be addressed better and data which have been collected in a reliable and routine fashion needs to be available to conduct retrospective cohort and case-control studies.

Towards better pharmacovigilance and medicine regulation, the way it is carried out needs to be modified. Previously, post authorization medicines regulations rely on spontaneous reporting of suspected adverse drug reactions. In addition, industry has very much responsibility to conduct studies to generate data which then used by regulators to make a judgment. However, this has often made the regulation process much more complicated and time consuming. Better pharmacovigilance can be attained if it is more patient focused approach, proactive, proportionate, multi-disciplinary, benefit risk balancing, transparent and science based approach.^[8] So, it must include all relevant data source including studies carried out by academia, industry and health authorities’ regulators. Ecopharmacovigilance as new science concern with the detection, assessment, understanding, and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, which affect human and other animal species must take its place and importance among health researchers.

Previous Studies on Pharmaceuticals in Water

Moving on to pharmaceutical studies, there have been many reports regarding pharmaceuticals in water. Kumar and

Xagorarakis (2010) who conducted a research on human health risk assessment of pharmaceuticals in water concluded that there is no potential risk of adverse effects due to individual exposures to meprobamate, carbamazepine and phenytoin because the observed concentration of the pharmaceuticals are lower than their calculated acceptable daily intake-equivalent drinking water levels. They further added that the hazard accompanying accidental ingestion of stream water and fish is lower compared to that through ingesting finished drinking water.^[9]

In another study conducted on pharmaceuticals and personal care products (PPCPs) in Illinois drinking water, the report stated that even though there are 16 PPCPs were identified in the untreated or potable water of five public supplies in the research field, the PPCPs were not found to pose any public health hazard when compared against conservative Screening Levels developed by Agency and Illinois Department of Public Health (IDPH) toxicologists.^[10] Besides that, quite similar result was reported in another research in Korea. The similar pattern reported in this research as compared to the former is, even though there are traces of pharmaceutical residues in body of waters being studied, the hazard quotient (HQ) found to be of ecologically low impact. In that research, Choi *et al.* (2008) reported that samples collected from sewage treatment plants and mainstream Han River in Seoul, Korea in three separate events of high, medium and low flow conditions showed high levels of acetaminophen (27,089 ng/L), caffeine (23,664 ng/L), cimetidine (8045 ng/L) and sulfamethoxazole (523 ng/L). The authors then suggested that further studies to be conducted to obtain a clearer picture of the situation.^[11]

Another research team who conducted a study on a densely populated area of Bangkok suggests that the canals in Bangkok area are at potential ecological risk which warrants appropriate management decision because the calculated HQs for pharmaceutical residues found in samples taken from five wastewater treatment plants, six canals, and from the mainstream of Chao Phraya River of Bangkok were very close to one which signifies high ecological hazards. Of the pharmaceutical residues observed, salicylic acid recorded the highest level (4700 ng/L) followed by caffeine (2250 ng/L), and ibuprofen (702 ng/L).^[12]

Mompelat *et al.* (2009) reported that there are about 4000 different pharmaceutical active compounds which are widely used as human and veterinary drugs in Europe have very high potential to reach every environmental compartment. In their article which reviewed the occurrence and fate of pharmaceutical products and by-products

based on data collected from previous studies summarizes some occurrences of these substances in water resources. Among pharmaceutical products (PPs) and by-products (BPs) commonly reported in previous studies include, paracetamol, ibuprofen, diclofenac, sulfamethoxazole carbamazepine, ranitidine, metformin and many more. The authors also presented a classification of pharmaceutical products. They reported there are about 160 PPs and 30 BPs have been recently studied. These PPs and BPs are divided into 24 classes according to their therapeutic nature. From all these there are 4 classes which are considered dominant in terms of references. These four are non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, anticonvulsants and lipid regulators. Most common NSAIDs found in body of water being studied were ibuprofen, diclofenac while for lipid regulator, the most common was gemfibrozil. Carbamazepine is an example of anticonvulsants.^[13]

Methodology for Pharmaceuticals Analysis

Since the beginning of scientific analysis of pharmaceuticals during 1960s, analyses of pharmaceuticals in water were often laborious which involved extraction of water in large quantities. This was followed by either Gas Chromatography technique or Gas Chromatography/Mass Spectrometry (GC/MS) technique. During this time, the data obtained was usually in the range of part per billion (ppb) but usually at the higher range hence this method was not very favorable due to its poor sensitivity. In addition, the rate of pharmaceutical detections was relatively low. By mid 1990s, a better method was employed which gave better detection rate. This method was known as solid phase extraction method. While it gave better results when used in tandem with GC/MS analysis, the range of pharmaceuticals detected was very limited. Soon, during late 1990s, GC/MS technique was replaced with a more viable technique known as Liquid Chromatography-Mass Spectrometry (LC-MS). This has opened a new horizon for pharmaceutical analysis because it has higher and improved sensitivity and was also able to achieve wider range of detection at sub ppb levels.^[14] An article published by World Health Organization (WHO) also detailed the analysis technique usually utilized by researchers all over the world in analyzing pharmaceuticals. The report outlines the suitability of certain techniques with the type of pharmaceuticals being analyzed. For instance, LC-MS/MS analysis is more suitable for measuring compounds that are of polar nature and highly soluble in water whilst for more volatile target compounds, GC-MS/MS technique is better.^[15]

Recently, a comprehensive method has been developed and validated by a research group when investigating

pharmaceuticals in Missouri natural and drinking water. For these different water matrices, analyses of 16 pharmaceutical compounds employed solid phase extraction method followed by liquid chromatography carried out in tandem with mass spectrometry technique.^[16] The target compounds for this study were acetaminophen, caffeine, carbamazepine, clofibric acid, codeine, estradiol, estriol, estrone, ethynylestradiol, ibuprofen, iopromide, lincomycin, sulfamethoxazole, triclosan, trimethoprim and tylosin. In this study, samples were collected treated and untreated water from water treatment facilities across Missouri and also municipal tap water. Results obtained indicates that the level of pharmaceuticals detection depend on the source of water. In this study, samples taken from river water and surface water exhibit higher level of detection compared to groundwater.

Pharmaceuticals analyses do not only deal with detection of pharmaceutical compounds. Studies conducted on these compounds were also helpful in providing vital information about the factors that lead to its occurrence in water bodies in general. Mompelat *et al.*, (2009), when conducting a review on previous works on pharmaceuticals analyses pointed out that pharmaceutical compounds were released mainly from hospitals compared to households due to the nature of the dosage of pharmaceuticals administered in hospitals being higher. Improper disposal of unused or expired drugs directly thrown in toilets or ended up in landfills as well as pharmaceutical residues from manufacturer spill accidents have been identified as the factors that lead to the occurrence of pharmaceuticals in water bodies.^[13] These pharmaceutical compounds are usually excreted via urine or faeces upon ingestion or metabolism which then enter sewer networks as urban wastewater route until reaching wastewater treatment plants (WWTP) or directly released into septic tanks (in countryside). Due to the nature of WWTP and septic systems which are not specifically designed to eliminate highly polar compound like these pharmaceutical compounds, the elimination rate of PPs could well be in the range between 0 and 100%, depending on the nature of PPs and process design of WWTP and septic systems. Direct release of veterinary pharmaceuticals to the environment occurs mainly in agricultural activities and application in aquaculture. Occurrence of PPs may be caused by indirect release by the animals, depending on how it is treated, via run-off and leaching through fields from manure spreading to agricultural fields and livestock wastes.

In contrast to pharmaceutical products, by-products (BPs) of pharmaceuticals usually include transformation products which can be formed in the environment which originated from PPs and metabolites released or the metabolites

itself when excreted via urine or faeces. Chemical and biological factors available in waste water treatment plants or water works also influence the occurrence of BPs. When pharmaceuticals are ingested, the parent molecule of pharmaceutical substances undergoes a set of biochemical reactions, leading to a different molecule than the parent compounds. Other metabolizations include enzyme reaction, and induction of the loss of pharmaceutical activity of the native pharmaceuticals. The concentration of PPs and BPs usually decreases from wastewater to the environment.

Brown *et al.*, (2006) reported that ofloxacin were detected to be 35.5 µg/L in Albuquerque (New Mexico, USA) hospital effluents while 410 ng/L were found in the Albuquerque WWTP influents, 110 ng/L in Albuquerque WWTP effluents and has not been detected in the Rio Grande river. The decrease in concentration of PPs is attributed to few factors known as attenuation factors. From its respective source of occurrences, namely discharge of WWTP effluents or animal farming or aquaculture, the first attenuation factor is dilution in surface water up to trace level (µg/L to ng/L).^[17] The second attenuation factor is the adsorption on suspended solids and sediments, colloids and natural organic matter. From its sources, PPs and BPs may also undergo biotic, chemical and physio-chemical changes when being dissolved in water. These transformations take place despite the fact that most of pharmaceuticals are designed to be chemically stable and has resistance to microbial degradations. Another factor that causes PPs and BPs level to decrease is photo degradation. As the name suggest, this process usually occur in the presence of sunlight. However, radicals may also facilitate the process of photo degradation. This process depends on solar irradiation, eutrophic conditions, depth of water course, composition of organic matter, latitude and also season.^[13,15]

Pharmaceuticals Potential Hazards

Based on reviews conducted on previous studies, it is found that potential hazards pose by pharmaceuticals can be classified into two categories namely hazard towards the environment and also hazard towards human being. In terms of environmental hazards, one of the important discoveries of pharmaceutical studies is the feminization of male fish by estrogens.^[15] This reflects that pharmaceuticals can impose hazard to aquatic life, particularly fish. The first report published which touched this matter was made by Sumpter and Johnson in 2008. They conducted a research on fish throughout several waterways and found that the water body received municipal wastewater discharged in the United Kingdom (U.K). Several fish were found to undergo feminization where the fish has altered their reproduction

strategies which in turn gave rise to hermaphroditism.^[18] This process started with endocrine disruption in the fish. Besides that, presence of ova within male testes and existence of egg yolk precursor protein, and vitellogenin even in the blood of males and the juvenile ones were also observed. This study was repeated by caging the fish and placing them in two different streams of water, namely upstream and downstream and it was observed that the one caged downstream of wastewater outfalls developed vitellogenin. The factor contributed to feminization of male fish was found to be estrogen. Sumpter and Johnson (2008) also reported that natural and synthetic steroids are predominantly responsible for the estrogenic activities observed in wastewater, particularly surface waters.^[18]

A year before Sumpter and Johnson reported their findings; a similarly unique study revealed that impact of pharmaceuticals on aquatic organism was also observed in population levels. There was a population collapse of an aquatic organism which cause was identified as exposure to pharmaceutical agents, in this case synthetic estrogen, EE2.^[19] The concern regarding this matter does not stop to the question of at what level of exposure does these pharmaceuticals causes the aforementioned impact, but it also lead to another question; do other pharmaceuticals capable of causing similarly devastating impact to the environment? With the number of pharmaceuticals, particularly compound derived from human usage is on the rise due to advances in analytical chemistry, the magnitude of concern regarding this question can only grow bigger. Due to lack of readily available toxicological data in the public domain, health risks from pharmaceuticals in water have been frequently assessed using the lowest concentration that evokes a desired therapeutic effect among population being studied. This value of lowest concentration amount is known as the minimum therapeutic dose (MTD). However, the application of MTD does has its own limitations, for example since the MTD is determined by controlled studies in specific populations which already selected before the research was conducted, it may not be based on the sensitivities of vulnerable subpopulations that would not normally given the drug.^[15]

Besides potential hazards on the environment, pharmaceuticals are also capable of affecting human. All these years, repeated analyses conducted in various pharmaceutical studies have revealed numerous residues of drugs to be present in drinking (tap) water samples. For adults who had already developed a functional immune system, this may not be fatal, but for newborn babies whose blood-brain barrier and body defense mechanism are yet to be fully developed and functional, administration of

milk substitute from very low age may be exposed to drug residues.^[20] This could potentially affect the life expectancy of human population in a whole if no serious considerations are given regarding this matter.

In a study conducted on Oriental white-backed vulture (OWBV; *Gyps bengalensis*) between 2000 to 2003 reported that there was a connection between population decline of the bird species with exposure to pharmaceutical compound. Kidney samples taken from OWBVs which died from renal failure were analyzed it was found that diclofenac residue concentrations in the sample showed proportionality with exposure dosage.^[21] The article revealed that the only drug identified in the survey which met the criteria was diclofenac, a non-steroidal anti-inflammatory drug (NSAID) used as analgesic, anti-inflammatory and antipyretic. They believed that the main source of diclofenac exposure is the consumption of treated livestock administered with diclofenac, or through water sources contaminated with diclofenac.

In recent study, another potential hazard of pharmaceuticals has been reported. Liu *et al.*, (2012) reported that six pharmaceuticals which are frequently detected in surface water worldwide namely erythromycin, sulfamethazine, sulfathiazole, chlortetracycline, oxytetracycline and diclofenac pose genotoxic potentials. Using isogenic chicken DT40 mutant cell lines to observe genotoxic effects of these pharmaceuticals which were determined based on the growth kinetics in at least one of several mutant cell lines, they were able to observe chromosome aberrations in both *wild-type* and susceptible mutants which indicates that these pharmaceuticals induce DNA damages that stall DNA replication, leading to chromosomal breaks as well as translation DNA synthesis.^[22]

CONCLUSION

Traces of pharmaceuticals, typically at levels of the nanograms to low micrograms per litre range, have been reported in the water cycle, including surface waters, wastewater, and groundwater and, to a lesser extent, drinking-water. Advances in analytical technology have been a key factor in the detection of the occurrence of these pharmaceuticals. Their presence in water, even at a very low concentration, has raised concerns among stakeholders, such as drinking water regulators, governments, water suppliers and the public regarding the potential risks to human health. Ecopharmacovigilance as new science concern with the detection, assessment, understanding, and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, which

affect human and other animal species. The environmental knowledge of pharmaceuticals must be increase and Ecopharmacovigilance issues must be urgently addressed.

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