Science of the Total Environment 645 (2018) 393–400

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Occurrence of antibiotic residues and antibiotic-resistant bacteria in effluents of pharmaceutical manufacturers and other sources around Hanoi, Vietnam

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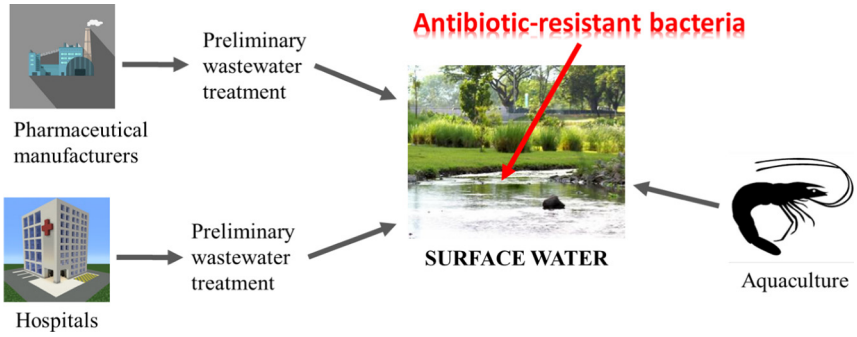
HIGHLIGHTS

- First study on antibiotics discharged from pharmaceutical manufacturer in Vietnam
- Results were higher compared with those from hospital and aquaculture effluents.
- Pharmaceutical manufacturing is an important source of antibiotics in open waters.
- Ubiquitous presence of bacteria resistant to popular antibiotics in the samples

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 29 April 2018
Received in revised form 10 July 2018
Accepted 10 July 2018
Available online xxxx

Keywords:
Antibiotic residues
Pharmaceutical manufacturing wastewater
Aquatic environment
Fishery industry
Hospital wastewater
Antibiotic resistance

ABSTRACT

Pharmaceutical manufacturers in Vietnam are producing a wide variety of antibiotics for human and veterinary use. Consequently, the water discharged from those facilities can contain residues of antibiotics, which could have adverse impact on the environment. However, studies on the occurrence of antibiotics in the wastewater from pharmaceutical manufacturers in Vietnam are almost non-existent. In this study, water samples were collected at around the outlets of four pharmaceutical manufacturing plants as well as from a hospital and an aquaculture farm around Hanoi in 2016 and 2017. Fifteen antibiotics from four major classes (β-lactam, quinolones, macrolides, sulfonamides) were monitored, using a validated LC-MS/MS method, based on their number of registrations at the Ministry of Health. Ten antibiotics, ampicillin, cefuroxime, cefotaxime, clarithromycin, azithromycin, sulfamethoxazole, trimethoprim, ofloxacin, norfloxacin, and ciprofloxacin were detected in the samples at different concentrations. Notably, sulfonamides and quinolones were occasionally detected at very high concentration, such as sulfamethoxazole (252 μg/L), trimethoprim (107 μg/L), ofloxacin (85 μg/L), and ciprofloxacin (41 μg/L). In this study, concentrations of antibiotic residues in effluent of pharmaceutical plants were higher than those from other sources. The antibiotic-resistance tests indicated the widespread resistance to

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https://doi.org/10.1016/j.scitotenv.2018.07.126

common antibiotics like quinolone and sulfonamides in the collected samples. This finding suggests that wastewater from pharmaceutical manufacturers could be an important source of antibiotics and antibiotic-resistant bacteria in the aquatic environment of Vietnam.

1. Introduction

Antibiotics have been used extensively to save millions of lives through prevention and treatment of infectious diseases. However, there is emerging concern about the impact of antibiotic residues in the environment (Kümmerer, 2003), especially in the aquatic environment (Kümmerer, 2009a; Kümmerer, 2009b). Many studies on the environmental impact of antibiotics have pointed out that these therapeutic substances can pose harmful effects on living organisms in the environment, and more importantly, can lead to the emergence of antimicrobial resistance (Andersson and Hughes, 2012; Baquero et al., 2008; Martínez, 2008).

Antibiotic-resistant bacteria are a global problem but it is even more serious in Vietnam where the use of antibiotics is usually uncontrolled (Mao et al., 2015). This problem is an increasing public health concern for the Government of Vietnam (Nguyen et al., 2013) because not only the first-generation antibiotics are losing their effect, the more expensive antibiotics of newer generations including some "last choice" antibiotics are also facing substantial resistance from bacteria. A Government report on antibiotic-resistance conducted in 19 hospitals in Hanoi, Ho Chi Minh City and Hai Phong in 2009–2010 reported four common bacteria strains resistant to most commonly used antibiotics such as penicillin, tetracycline, streptomycin, and third generation cephalosporins. Such a dire situation requires good understanding of all possible emerging pathways of antibiotic resistance, including the level of antibiotic residues in the aquatic environment.

Antibiotic residues in the aquatic environment can be from a number of sources: municipal (hospital, municipal sewage, and wastewater treatment plants), agriculture (aquaculture, husbandry) (Hirsch et al., 1999; Kümmerer, 2009a; Kümmerer, 2009b), and pharmaceutical industry (Cardoso et al., 2014). Among them, antibiotic residues in wastewater discharged from pharmaceutical plants have raised alarm in recent studies in some Asian countries, where the concentrations of antibiotics were reported up to level of mg/L (Cardoso et al., 2014; Larsson et al., 2007; Lin et al., 2008). Such finding indicated that a single pharmaceutical factory might contribute a significant amount of antibiotics to the aquatic environment and pose a serious risk to human and animal health. For example, a recent study in Pakistan reported a high level of antibiotics residues in wastewater close to the pharmaceutical factories and a positive correlation between the level of residues and antibiotic resistance in the samples (Khan et al., 2013). A similar study in India recently reported an association between antibiotic residues in sewage effluent and the presence of antibiotic resistant pathogens (Lübbert et al., 2017). It is probably because in India and Pakistan, the level of antibiotic residues in the effluent of pharmaceutical manufacturing plants is much higher than the level found in effluent of hospitals in those countries (Balakrishna et al., 2017).

The pharmaceutical industry in Vietnam is growing with >200 manufacturers (Angelino et al., 2017). Many of them are registered to produce antibiotic products. Specifically, in Vietnam, there were >3000 antibiotic formulations registered for production in the five-year period from 2008 to 2013. The majority of registered antibiotic products belong to groups of β-lactams (amoxicillin, cefuroxime, cefixim…), quinolones (ofloxacin, ciprofloxacin…), and macrolides (neomycin, clarythromycin, azithromycin…). However, according to our recent review, studies that monitored antibiotic residues in wastewater from pharmaceutical factories are very scarce in Vietnam (Binh et al., 2018). This source of antibiotic discharge to the environment was probably overlooked, whereas many monitoring studies have been conducted on the pollution of antibiotics due to aquaculture, as reviewed by (Thuy and Nguyen, 2013) or due to discharge from hospitals (Duong et al., 2008; Lien et al., 2016). In a recent review, Binh et al. (2018) has reported the occurrence of a variety of antibiotics in the water environment in Vietnam with high concentrations (ppm) of fluoroquinolones and sulfonamides from aquaculture and hospitals. Even antibiotics that were banned for animal use can be detected from aquaculture and husbandry sources. The residual antibiotics in water environment were the cause of the widespread emergence of antibiotic resistant bacteria in the country. (Suzuki, 2017) stated that due to the frequent detection of antibiotic resistant bacteria and gene in Vietnam and other Asian countries, waters in this region were a hot-spot of antibiotic resistant gene development.

Recently, a preliminary study by our research group has detected some residues of cephalosporins in wastewater from pharmaceutical factories ranging from 19.24 to 43.33 μg/L (Hue et al., 2014), much higher than the level found in the effluent of pharmaceutical plants in developed countries (Balakrishna et al., 2017). Such observation indicated a need for a more systemic monitoring of antibiotics around pharmaceutical factories in Vietnam (Binh et al., 2018).

This study hence aims to determine the level of antibiotic residues in wastewater effluent discharged from several pharmaceutical manufacturing plants around Hanoi and then compare them with the level of antibiotic residues from an aquaculture farm and a hospital. We also measured the prevalence of antibiotic-resistant bacteria in the same areas to evaluate the impact of the residues on the environment. The finding will be useful for policy makers in the urgent task of forming a strategy for the management of environmental pollution of antibiotics in Vietnam.

2. Materials and methods

2.1. Selection of target compounds

We targeted antibiotics with high numbers of registrations. Additionally, we aimed to cover more antibiotic classes that were not included in previous studies in Vietnam. Accordingly, 15 antibiotics from four major groups, β-lactam, macrolides, quinolones and sulfonamides were targeted. They are ampicillin (AMP), amoxicillin (AMO), cefaclor (CER), cefadroxil (CDX), cefixime (CFI), cefuroxime (CFU), cefotaxime (CFO), cephalexin (CEP), azithromycin (AZI), clarithromycin (CLA), ofloxacin (OFL), norfloxacin (NOR), ciprofloxacin (CIP), sulfamethoxazole (SMX) & trimethoprim (TRI). Information about the targeted antibiotics was presented in Table 1.

2.2. Study sites and sample collection

Four pharmaceutical manufacturers located around Hanoi were included in this study, considering their locations and the possibility of safe access for sampling. The selected manufacturers included one located within an industrial park (CP1) and three (CP2, CP3, CP4) located within residential areas (Fig. 1). All factories are located in outer suburbs of Hanoi but are not far away from densely populated villages. Some information about the product registration and actual production of those factories was presented in Table 2.

In order to compare the level of antibiotics in effluent of pharmaceutical factories with other sources, effluent samples from a general hospital (BV) and an aquaculture farm (TS) in Hanoi were also taken. Information about those sites was also presented in Table 2.