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Profile and behavior of antiviral drugs in aquatic environments of the Pearl River Delta, China

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HIGHLIGHTS

- Acyclovir was the only antiviral detected in the wastewater.
- Acyclovir was not completely removed in the wastewater in the STP.
- Acyclovir was widely detected in the recipient rivers and reservoirs.
- No antivirals were detected in the wells in the vicinity of the municipal landfills.

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ABSTRACT

Occurrence and behavior of six antiviral pharmaceuticals (acyclovir, ganciclovir, oseltamivir, ribavirin, stavudine and zidovudine) and one active metabolite oseltamivir carboxylate were investigated in wastewater, landfill leachate, river water, reservoir and well water in the vicinity of municipal landfills in the Pearl River Delta, China. Acyclovir was the only antiviral detected in the wastewater at 177–406 (mean = 238) and 114–205 (mean = 154) ng L^{-1} in the influent and final effluent, respectively. Aerobic biodegradation appeared to be the main process for the elimination of acyclovir in the wastewater. Acyclovir was also the only antiviral quantitatively detected in the Pearl River and its tributaries, with a maximum concentration up to 113 ng L^{-1}. Treated wastewater was a major source of acyclovir in the rivers. The highest concentration of acyclovir was observed in winter in the river water and the dilution effect by precipitation was suggested to be the dominant factor impacting the seasonal pattern of acyclovir in the rivers. No antivirals were quantitatively detected in the well water whereas acyclovir was frequently detected in the reservoirs at a maximal concentration of 33.6 ng L^{-1} in the vicinity of the municipal landfills. However, source identification and fate of acyclovir in the reservoirs pend on further research.

1. Introduction

Antiviral drugs are widely used in treatment and prophylaxis of various viral infections including influenza, hepatitis, herpes and HIV (De Clercq and Field, 2006; Kim et al., 2011; Kiso et al., 2004; Olsen et al., 2006; Singer et al., 2007). As many other pharmaceuticals, antiviral drugs may not be completely metabolized by treated human and animals and are subsequently excreted and discharged into wastewaters (Fick et al., 2007; Ghosh et al., 2010a,b; Renner, 2007; Soderstrom et al., 2009). As a result, antiviral pharmaceuticals may find their way to the environment if they are not effectively eliminated during wastewater treatment (Accinelli et al., 2010a,b; Fick et al., 2007; Ellis, 2010; Singer et al., 2007, 2008).

Studies about environmental toxicity of antiviral pharmaceuticals are so far mostly limited to oseltamivir and its active metabolite oseltamivir carboxylate (Singer et al., 2007, 2008, 2011). Research reported rather high chronic no-observed effect concentration for oseltamivir and oseltamivir carboxylate (≥1 mg/L) based on ecotoxic tests using traditional aquatic organisms (Hutchinson et al., 2009; Straub, 2009). Acute toxicity of oseltamivir and its carboxylate in traditional aquatic microorganisms was also shown to be less than predicted (Escher et al., 2010). On the other hand, antivirals were ranked as the eighth predicted most toxic drugs to typical aquatic organisms (Sanderson et al., 2004). Besides, antivirals may produce resistance strains of pathogens in human and animals, which are of particular concerns (Hauser et al., 2011; Kiso et al., 2004; Olsen et al., 2006). It has been reported that Japan has a high rate of emerging resistance to oseltamivir, probably because it is the country where oseltamivir is used most (Ghosh et al., 2009; Soderstrom et al., 2009). In addition, oseltamivir in the environment may also impact the bacterial community structure (Caracciolo et al., 2010).

There have been reports about occurrence of oseltamivir and oseltamivir carboxylate in wastewater and river water of Japan and

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Europe at tens of ng L^{-1} to low μg L^{-1} levels (Azuma et al., 2012; Ellis, 2010; Fick et al., 2007; Ghosh et al., 2009; Leknes et al., 2012; Prasse et al., 2010; Soderstrom et al., 2009; Takanami et al., 2010). Prasse et al. (2010, 2011) have also reported the presence of other antivirals, including acyclovir and its metabolite carboxy-acyclovir, zidovudine, lamivudine, abacavir, and penciclovir in wastewater, river water, and even groundwater in Germany. Zidovudine, lamivudine, and nevirapine were detected in rivers in Kenya at μg L^{-1} level (Koreje et al., 2012). Biodegradation, photodegradation, and ozonation of oseltamivir and its carboxylates have been studied via bench-scale experiments as well as investigations in sewage treatment plants (Accinelli et al., 2007, 2010a,b; Bartels and von Tumpling, 2008; Ghosh et al., 2010a,b; Goncalves et al., 2011; Mestankova et al., 2012; Sacca et al., 2009). Recently, Prasse et al. (2011) revealed rapid biotransformation of acyclovir and penciclovir in activated sludge, whereas the transformation product of acyclovir, carboxy-acyclovir was found to be persistent and was detected in drinking water, groundwater, and surface water from 40 ng L^{-1} to 3.2 μg L^{-1}. In addition, N-(4-carbamoyl-2-imino-5-oxoimidazolidin)-formamido-N-methoxyacetic acid, an ozonation product of acyclovir was detected in finished drinking water of a German waterworks (Prasse et al., 2012). After all, data about distribution and behavior of antivirals in the environment is still limited considering their wide and large amount of usage.

As the country of the biggest population in the world, China has a huge consumption of antivirals and the amount keeps increasing in recent years. The most frequently administered are nucleoside agents such as acyclovir, ganciclovir, ribavirin, and lamivudine (Wang, 2012). The Pearl River Delta (PRD), located in the south of China, is one of the most densely populated areas in the country. PRD may be one of the areas that consume the most antivirals in China due to the humid monsoon subtropical climate that may favor propagation and spread of viruses and germs. In addition, PRD was also one of the areas that have suffered pandemic outbreaks of avian influenza (e.g. H5N1) in China (Chinese Center for Disease Control and Prevention, 2013). Thus, the release of antivirals to the environment of this area is expected. However, there is so far no report about antivirals in the environment of the PRD and even throughout China.

The aims of this work are (1) to investigate occurrence of commonly prescribed antiviral drugs in municipal wastewater and landfill leachate in the PRD since they are important sources of pharmaceuticals, including antivirals in the environment, (2) to study the behavior of the antivirals in wastewater by sampling influent and effluents at the outlets of major treatment units in a typical sewage treatment plant, (3) to delineate distribution of the antivirals in the potentially impacted surface water and groundwater of the PRD, and (4) to reveal seasonal effects on the profile and fate of the antivirals in the aquatic environments. The targets of this work included acyclovir and ganciclovir that are most frequently used for treatment of herpes and viral infections of respiratory tract, ribavirin that is used to treat encephalitis B and hepatitis, and oseltamivir for treatment of avian influenza. In addition, stavudine, and zidovudine that are primarily used to treat HIV were also included.

2. Material and methods

2.1. Chemicals and reagents

Acyclovir (purity > 99%), ganciclovir (purity > 99%), ribavirin (purity > 97%), stavudine (purity > 98%), and zidovudine (purity = 98%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Oseltamivir (free base, purity = 96%) and oseltamivir carboxylate were bought from Dr. Ehrenstorfer GmbH (Augsburg, Germany) and Toronto Research Chemicals (Toronto, ON, Canada), respectively. Isotope-labeled standards ganciclovir-d_5, oseltamivir-d_3 phosphate, ribavirin-$^{13}C_5$, and zidovudine-d_3 were purchased from Toronto Research Chemicals (North York, Ontario. Canada) and acyclovir-d_4 was bought from Campro Scientific (Veenendaal, The Netherlands). All standards were obtained in solid form.

HPLC-grade methanol, *n*-hexane, formic acid, ammonium acetate, and ammonium hydroxide were purchased from Merck (Darmstadt, Germany). Ultra-pure water was generated by a Milli-Q ultra-pure water system (Millipore, Billerica, MA, USA). Analytical grade acetone was bought from Kaixin Chemical (Tianjin, China) and re-distilled prior to use. Sodium azide (NaN_3) was obtained from Fuchen Chemical (Tianjin, China) and washed with methanol for three times prior to use.

2.2. Study area and sampling

As the third largest river of China, the Pearl River flows through the PRD and finally merges into the South China Sea via the Pearl River Estuary (Fig. 1). The annual municipal and industrial wastewater productions of the PRD are around 6000 and 1800 million tons in which 78% and 100%, respectively of them are treated prior to discharge to the environment. The treated wastewater and the rest of untreated wastewater are all finally discharged into the Pearl River and its tributaries.

2.2.1. Wastewater samples

The STP is located in Guangzhou, the biggest city of the PRD (Fig. 1). Detailed description of the STP was provided previously (Yu et al., 2011). Briefly, it has three parallel treatment lines with a total capacity of 550 000 m^3 d^{-1}, serving a population of about 1.5 million. The first and second lines treat predominantly domestic wastewater (~90%) and use identical treatment composing of a screen, a grit chamber, a bioreactor consisting successively of anaerobic, anoxic, and oxic processes and a secondary clarifier. The third line has a bioreactor comprising successively anoxic, anaerobic, and oxic processes. Besides, the third line also receives a certain amount of industrial wastewater and municipal landfill leachate. The hydraulic retention time is 11.5 h for all the treatment lines and the solid retention time is about 10 days. The effluent is disinfected by chlorination prior to discharge into the Pearl River.

The influent and final effluent samples were collected along the first and third treatment lines of the STP in July 2010 (summer) to obtain a general profile of the antivirals in the wastewater. In order to gain an insight of fate of the antivirals in the wastewater, influent and effluents at the outlets of anaerobic tank, anoxic tank, secondary clarifier, and the final effluent were sampled along the first line in February 2011 (winter). Furthermore, daily variation was investigated through everyday sampling over a period of one week from February 15 to 21, 2011. Wastewater samples were collected hourly from 8:00 am to 12:00 pm (10 L/h) on a weekday to build a 40 L composite sample. Dewatered sludge was collected as grab samples during winter sampling.

2.2.2. Sampling in wells and reservoirs

Landfill leachates were collected from two municipal landfills in Guangzhou (Fig. 1). LF1 was put into operation in 1989 and closed in 2002, with a total filled waste of about 5 million tons. Adverse impact of its leachate on the groundwater was evidenced by increased levels of NH_3 and NH_4^+ in the well water (Guangzhou Environmental Protection Bureau, 2012). As for the largest landfill in Guangzhou, LF2 was operated in 2002 and is currently accepting municipal refuse of 7000–9000 tons/day. Raw leachates were sampled to get a profile of the antivirals in municipal landfill leachate. There are several villages in the vicinity of the landfills. Many villagers have wells at home that were used for water supplies. However, the well water is mostly used only for washing rather than drinking and cooking due to concerns of contamination by leakage of leachate from the landfills. Fourteen and 13 wells were sampled in the villages that are potentially impacted by the leachate from LF1 and LF2, respectively. The wells have depth of less than 10 m (shallow aquifers) and are with distance of 582–3178 m from the landfills. Most of the wells have covers and