

Occurrence and distribution of selected pharmaceuticals and personal care products in aquatic environments: a comparative study of regions in China with different urbanization levels

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Abstract

Purpose We analyzed and compared the distributions of 13 target pharmaceuticals in different water samples from the Hangzhou metropolitan area and Linan County, Southeast China.

Methods Sampling was conducted in five hospitals, two wastewater treatment plants (WWTPs), and Qiantang River. Samples were concentrated by solid-phase extraction and PPCP concentrations were determined by UPLC-MS/MS.

Results and discussion Trimethoprim, erythromycin A dihydrate, norfloxacin, ofloxacin, diclofenac sodium, and atenolol were the most frequently detected pharmaceuticals in hospital effluents. Most of the pharmaceutical concentrations in hospital effluents were higher than those in the WWTP influents. Although both WWTPs adopt the anaerobic–aerobic–anoxic treatment process, the removal rates for pharmaceuticals, such as trimethoprim and diclofenac sodium, were completely different. Meanwhile, erythromycin A dihydrate, ofloxacin, penicillin-G, cephalexin, cefazolin, ibuprofen, and diclofenac sodium were detected in Qiantang River.

Conclusions These results indicate that hospitals are more concentrated sources of pharmaceuticals than WWTPs, and the WWTPs are not the only route of entry of pharmaceuticals into aquatic environments in these two regions.

Keywords PPCPs · UPLC-MS/MS · Urbanization · Hospitals · WWTPs · Qiantang River

1 Introduction

Pharmaceuticals and personal care products (PPCPs) have become emerging chemicals of environmental concern. Despite their broad application range, they are regarded as contaminants that threaten drinking water safety and aquatic ecosystem health. PPCPs are considered potentially hazardous compounds because some are ubiquitous, persistent, and biologically active compounds with recognized endocrine-disrupting functions (Fent et al. 2006). Thus, increasing interest has been accorded to the occurrence and fate of PPCPs in aquatic environments. These compounds have been widely detected in various waters throughout Europe (Ashton et al. 2004; Bendza et al. 2005; Kasprzyk-Hordern et al. 2008; Zuccato et al. 2008), North America (Glassmeyer et al. 2005; Yu and Chu 2009; Yu et al. 2006), Japan (Nakada et al. 2008), and Korea (Yoon et al. 2010), often at concentrations that range from the nanogram per liter to microgram per liter levels. A few studies on the occurrence and distribution of pharmaceuticals in China have already been published. The concentrations of several most frequently detected drugs in the Pearl River Delta varied from 10^2 to 10^3 ng L⁻¹ (Peng et al. 2008). Jiang et al. (2011) investigated the occurrence and distribution of antibiotics in Hangpu River and found that the detection frequencies for 18 antibiotics were in the range of 5.3–100%.

PPCPs have also been found in the fillet and liver tissues of fishes from five US rivers, which receive direct discharge from wastewater treatment facilities, with the effluents

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having concentrations that range from the nanogram per gram to microgram per gram levels (Ramirez et al. 2009). Mohamed et al. (2010) found that triclosan, diclofenac, and carbamazepine significantly affected the behavior of Japanese medaka fish via different mechanisms.

The concentrations and fate of pharmaceuticals considerably vary in different waters and depend on several parameters such as geographic location, physicochemical properties of pharmaceuticals, sewage treatment technology, and climatic conditions (e.g., rainfall, temperature, and sunlight), among others (Andreozzi et al. 2003; Hijosa-Valsero et al. 2010; Kasprzyk-Hordern et al. 2008). Given the pathways by which PPCPs enter water environments, effluents from wastewater treatment plants (WWTPs) are considered important sources. Many studies have reported that the concentrations of the pharmaceutical substances found in WWTP effluents occur at low parts-per-billion concentrations (Andreozzi et al. 2003; Carballa et al. 2004; Loganathan et al. 2009; Radjenović et al. 2009; Ternes et al. 2004). Hospital wastewater has also become a known source of pharmaceuticals discharged into water environments (Kosma et al. 2010; Sim et al. 2011).

Some researchers have recently investigated different sources of wastewater that contain PPCPs; these include hospitals, residences, dairy farms and nurseries, and slaughterhouses (Brown et al. 2006; Chang et al. 2010). However, few of these studies focused on the spatial relevance of different sources of PPCP-containing wastewater, and no attempts have been made to compare the distributions of PPCPs in the aquatic environments of different regions with varied urbanization levels. Given that the population densities, living habits of residents, and levels of economic and infrastructure development in these regions differ, these factors may influence the distribution of PPCPs in these areas.

In this work, we investigated the occurrence of 13 pharmaceuticals in different water samples from two regions with different urbanization levels (i.e., the Hangzhou metropolitan area and Linan County, Southeast China). The differences in PPCP distribution between the different water environments in the two regions were compared. Samplings were conducted in five hospitals, two wastewater treatment plants, and Qiantang River within the two regions. The target PPCPs were divided into three categories: (1) antibiotics: trimethoprim (TRI), erythromycin A dihydrate (ERY-A), penicillin-G (PEN-G), penicillin V potassium salt (PEN-V), norfloxacin (NOR), ofloxacin (OFL), cefazolin (CFZ), and cephalexin (CPL); (2) nonsteroidal anti-inflammatory drugs: ibuprofen (IBU), naproxen (NAP), and diclofenac sodium (DIC); (3) other pharmaceuticals (liquid-regulating agents and β -blocking drugs): clofibrac acid (CLO) and atenolol (ATEN).

2 Material and methods

2.1 Chemicals

ERY-A, DIC, CPL, and NAP of analytical grade with a purity of 98% or higher were purchased from Sigma-Aldrich (St. Louis, MO, USA). TRI (99.5%), NOR (99.5%), OFL (99.0%), ATEN (98.5%), CLO (99.5%), IBU (99.0%), PEN-G (99.0%), and PEN-V (98.8%) were purchased from Dr. Ehrenstorfer GmbH, Germany. CFZ (99.4%) was purchased from European Pharmacopoeia. Detailed information about target drugs is listed in Table 1. High-performance liquid chromatography-grade formic acid (96%) and methanol were purchased from Tedia Company, Inc. All reagent water used in this study was Milli-Q water.

Stock solutions of pharmaceuticals were prepared at 1 mg mL⁻¹ in methanol and stored at -20°C. New stock solutions were made every 6 months. Mixed working solutions were prepared fresh daily by diluting the stock solution with methanol.

2.2 Sampling

All field samplings were conducted from September to October in 2010 in Hangzhou metropolitan area and Linan County. Hangzhou, the capital of Zhejiang Province, is the provincial center of economy, culture, science, and education. The Hangzhou region or prefecture-level city comprises the Hangzhou metropolitan area (eight districts) and five county-level cities. Linan County is one of the five counties. Sample locations included five hospitals, two WWTPs, and Qiantang River basin. Hospitals 1, 2, 3, 4, and 5 have capacities of 1,000, 1,900, 1,700, 950, and 700 beds, respectively. Hospitals 1, 2, and 3 are all third-grade class-A comprehensive hospitals, while hospital 4 is a maternal and child care service center and hospital 5 is a second-grade class-A comprehensive hospital. Hospitals 1, 2, 3, and 4 were located within the city of Hangzhou with a population of six million and hospital 5 was located within Linan County with a population of 560 thousand. WWTP 1 with a daily treatment volume of 60,000 tons mainly receives domestic sewage from the suburbs of Hangzhou including hospital 5, while WWTP 2 with a daily treatment volume of 200,000 tons receives both industrial and domestic sewage from Hangzhou city including hospitals 1, 2, 3, and 4. Both WWTPs use the anaerobic-aerobic-anoxic technology. The hydraulic retention times of WWTP 1 and WWTP 2 are 14 and 15 h, respectively. In the region of Qiantang River basin, mean annual temperatures varied from 16.1 to 17.7°C, while mean annual rainfall capacities varied from 1,200 to 2,200 mm. Detailed information on locations of hospitals, WWTPs, and two sampling sites of Qiantang River are shown in Fig. 1.

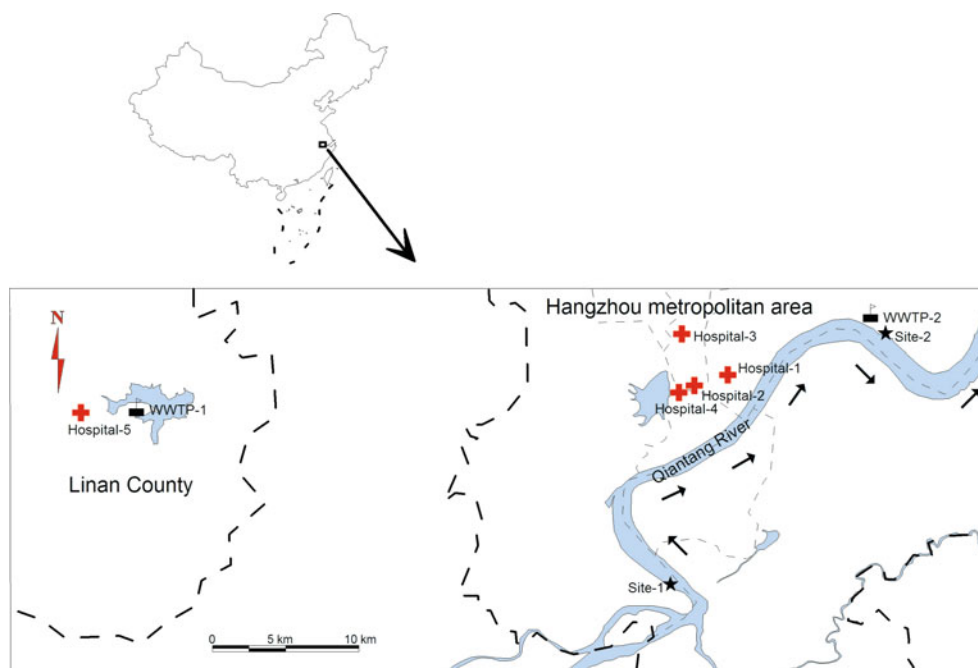
Table 1 Optimized MRM conditions for analysis of the selected pharmaceutical by UPLC-MS/MS

Group	Compound	Abbreviations	CAS	ESI	Retention time (min)	Precursor ion (m/z)	Product ion (m/z)	Cone voltage (V)	Collision energy (eV)
Antibiotics	Trimethoprim	TRI	738-70-5	+	0.81	290.8	122.8	25	28
	Erythromycin A dihydrate	ERY-A	59319-72-1	+	1.05	734.0	157.8	28	25
	Penicillin-G	PEN-G	61-33-6	+	1.01	334.9	159.8	20	12
	Penicillin V potassium salt	PEN-V	132-98-9	+	1.11	350.8	159.8	20	12
	Norfloxacin	NOR	70458-96-7	+	0.83	319.8	301.8	18	20
	Ofloxacin	OFL	82419-36-1	+	0.85	361.8	317.8	18	20
	Cefazolin	CFZ	25953-19-9	+	0.86	454.6	322.7	15	12
	Cephalexin	CPL	15686-71-2	+	0.83	347.8	157.6	20	10
NSAIDS	Ibuprofen	IBU	15687-27-1	−	1.92	204.9	160.9	15	7
	Naproxen	NAP	22204-53-1	−	1.32	228.8	184.7	18	9
	Diclofenac sodium	DIC	15307-79-6	−	1.79	293.8	249.7	18	12
Liquid-regulating agents	Clofibrac acid	CLO	882-09-7	−	1.37	212.8	126.8	18	12
Beta-adrenoceptor blocker	Atenolol	ATEN	29122-68-7	+	0.81	266.9	189.8	18	20

Grab samples were conducted in amber glass bottles from effluents of hospitals. Both influent and effluent of two WWTPs were sampled. All samples from WWTPs were collected on an equal proportion in each hour with 24-h composite samplers. Grab samples were conducted at two sites of Qiantang River basin in the region of Hangzhou, which is the main region for effluent drainage of WWTP 2. Samples of the river

were obtained from the riverbank or from bridges at a depth below 1 m. No heavy rains were observed before or during the sampling period. All samples were later vacuum filtered through 1.0- μ m glass fiber filters (Whatman GF/B, Maidstone, UK). Collected samples were stored below 4°C before sample pretreatment. Two replicate grab samples were collected during each sampling.

Fig. 1 The geographic locations of sampling sites



2.3 Solid-phase extraction

The samples were extracted using solid-phase extraction (SPE) within 48 h after sampling. Cleanert PEP extraction columns (6 mL/500 mg, Agela) used for SPE were activated with 5.0 mL of methanol and 5.0 mL of Milli-Q water. Then, samples were passed through the SPE columns at a flow rate of approximately 4 mL min⁻¹ which was driven by a vacuum pump. The volume load for the sewage from hospitals and WWTPs was 500 mL and that for samples from surface water was 1 L. After the passage of samples, the PEP columns were rinsed with 5 mL of Milli-Q water and were then dried under gentle nitrogen gas for 30 min. After drying, each cartridge was eluted with 3 mL of methanol at a speed of one drop per second. The methanol elution was repeated two times. Then, the three elute volumes were combined and concentrated to a volume of about 0.5 mL under a gentle stream of nitrogen gas, and the final volume of elutes was adjusted to 1.0 mL with methanol. After, the homogeneously mixed, pretreated samples were respectively transferred into amber autosampler vials and were stored under -10°C till analysis.

2.4 Analytical methods

The determination of pharmaceuticals in samples was conducted by the ultra-high-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) system equipped with an Acquity™ UPLC and a Quattro Premier Micromass® MS (Waters/Micromass, Milford, MA). A 10-μL aliquot of the extract was injected into a BEH C18 column (Waters Corp, 50×2.1-mm length, 1.7 μm). The column temperature was maintained at 45°C. Different drugs in sample extracts were separated by UPLC with a gradient mobile phase with 0.1% formic acid/water and methanol used as mobile phases, which firstly started at 70% methanol. With a flow rate of 200 μL min⁻¹, the component of mobile phases altered to 90% methanol at 2.5 min, reverted to 70% methanol at 4 min, and remain unchanged till 5.5 min. IBU, NAP, DIC, and CLO were detected under the negative ion electrospray ionization mode (ESI-) with multiple reaction monitoring (MRM) by the mass spectrometer (MS), while the other nine pharmaceuticals, i.e., TRI, ERY-A, PEN-G, PEN-V, NOR, OFL, CFZ, CPL, and ATEN, were detected under the positive ion electrospray ionization mode (ESI+). Systematic operating parameters were thoroughly optimized, which were listed as follows: temperatures of electrospray source and desolvation were respectively 110°C and 350°C; argon collision cell pressure was 4.10 mbar; flow rates of cone nitrogen gas and desolvation gas were respectively 50 and 500 L h⁻¹; and capillary voltage was 3.10 kV. Detailed information

concerning optimized MRM conditions for target pharmaceuticals are listed in Table 1.

2.5 Quality control

Calibration curves were made through eight concentrations (2, 10, 20, 50, 100, 200, 500 ng mL⁻¹) of mixed standard samples in methanol. As shown in Table 2, mean correlation coefficients (R^2) of all calibration curves were higher than 0.99, indicating excellent linear correlation of curves. Method detection limits (MDLs) and method quantification limits (MQLs) of target compounds in water samples were shown in Table 2. Seven replicates of standard samples were conducted by UPLC-MS/MS. Relative standard deviations (RSDs) of target compounds ranged from 1.7% to 10.6%, indicating a good instrumental precision.

Method reliability could be quantitatively expressed by recoveries and corresponding RSDs. Spiked recoveries were conducted at three concentrations (100, 200, and 500 ng L⁻¹ in Milli-Q water). As shown in Table 2, recoveries of target compounds of three concentrations ranged from 40.2% to 113.8%, and RSDs ranged from 1.7% to 14.4%, which indicated that the method is reliable.

The internal standard method was employed to determine the target compounds in water samples. Briefly, a pretreated sample was firstly analyzed by the UPLC-MS/MS, which produced a batch of peak area response values. Then, certain amounts of target compounds were spiked to the pretreated sample. The spiked sample was later analyzed by the UPLC-MS/MS, which got another batch of peak area response values. Finally, target compounds in the sample were determined by comparing the two batches of response values and the practical spiked amount. During the treatment of each batch sample, two blank samples in Milli-Q water and two water samples spiked with a certain amount of target compounds were set. All the four samples were uniformly pretreated through the SPE process mentioned above and later analyzed by a UPLC-MS/MS. Thus, the spiked recoveries of practical samples were calculated.

3 Results and discussion

3.1 Concentrations of pharmaceuticals in the Hangzhou metropolitan area

3.1.1 Concentrations of antibiotics

The concentrations of eight target antibiotics (TRI, NOR, ERY, OFL, CPL, CFZ, PEN-G, and PEN-V) from hospitals 1, 2, 3, and 4 and WWTP 2 are shown in Fig. 2. The removals for pharmaceuticals in the WWTPs are shown in Table 3. Figure 2 shows that TRI, ERY-A, NOR, and OFL

Table 2 Linear equation, correlation coefficients, MDLs, MQLs, instrumental precision, and spiked recoveries of 13 pharmaceuticals

PPCPs	Work curve	Correlation coefficient (R^2)	MDLs (ng L ⁻¹)	MQLs (ng L ⁻¹)	Instrumental precision RSD (%)	Method precision					
						Spiked concentration(ng L ⁻¹)					
						100 (n=3)		200 (n=3)		500 (n=3)	
Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)						
Trimethoprim	$Y=-33.1127+1.37\times 10^{-3}X$	0.9924	0.12	0.4	9.3	94.2	11.4	102.7	10.5	79.0	2.8
Erythromycin A dihydrate	$Y=-14.5315+6.714\times 10^{-4}X$	0.9980	0.12	0.4	10.0	74.3	9.8	93.5	7.4	55.2	4.1
Penicillin-G	$Y=2.31139+9.84\times 10^{-3}X$	0.9966	0.6	2	3.0	66.1	6.5	59.2	11.5	48.6	6.4
Penicillin-V	$Y=-16.55852+8.7\times 10^{-3}X$	0.9940	0.6	2	2.3	65.7	4.0	68.4	4.6	64.1	5.3
Norfloracin	$Y=13.0315+2.83\times 10^{-3}X$	0.9991	1.2	4	4.4	44.5	6.4	43.3	5	40.2	3.3
Ofloxacin	$Y=-7.95731+1.42\times 10^{-3}X$	0.9904	0.6	2	9.9	41.4	4.2	41.0	6.4	41.1	1.9
Cephalexin	$Y=11.0728+4.94\times 10^{-3}X$	0.9983	0.6	2	10.6	49.3	5.1	46.9	8.4	45.8	5.8
Atenolol	$Y=-14.545+2.40\times 10^{-3}X$	0.9961	0.3	1	1.7	106.3	11.5	106.3	1.7	90.3	3.3
Cefazolin	$Y=15.6765+1.844\times 10^{-2}X$	0.9923	1.2	4	8.2	46.1	2.2	44.1	2.4	46.3	2.6
Ibuprofen	$Y=14.9333+0.2835X$	0.9919	60	200	4.5	93.1	6.3	85.3	6.1	79.5	2.7
Naproxen	$Y=16.9519+0.16579X$	0.9969	30	100	3.2	106.2	12.9	98.3	13.9	95.8	4.2
Diclofenac sodium	$Y=4.0805+3.05\times 10^{-2}X$	0.9993	6	20	2.7	113.8	3.3	97.5	2.1	94.2	4.3
Clofibrac acid	$Y=-2.54816+1.719\times 10^{-2}X$	0.9989	1.2	4	5.9	54.2	4.6	51.9	1.9	51.3	4.8

Y concentration, X peak area

were the most frequently detected antibiotics in samples from hospitals 1, 2, 3, and 4, with concentrations ranging from 220.8 to 744.2 ng L⁻¹, 33.0 to 1325.5 ng L⁻¹, 763.0 to 1,155.6 ng L⁻¹, and 90.6 to 1,998.8 ng L⁻¹, respectively. These concentrations are similar to the results for the Chongqing region (Chang et al. 2010), where the ERY-A concentration in Chongqing hospital samples ranged from 448 to 827 ng L⁻¹. Brown et al. (2006), however, found that the TRI concentrations in hospital samples from New Mexico varied from 2,900 to 5,000 ng L⁻¹, which are much higher than the results obtained in the current work. Except for NOR, concentrations of the eight drugs from the four hospitals considerably fluctuated. The TRI, ERY-A, NOR, and OFL concentrations in the WWTP 2 influent were generally much lower than those in the hospital effluents. The TRI concentrations in both the WWTP 2 influent and effluent were below 30 ng L⁻¹, whereas the ERY-A concentrations remained comparatively high at about 75 ng L⁻¹. Table 3 shows that TRI and ERY-A were hardly removed, whereas NOR and OFL were efficiently removed from the WWTP 2 wastewater. The concentrations of TRI, ERY-A, and OFL in the samples from Qiantang River were comparatively low, with average concentrations below 70 ng L⁻¹. Although the concentration of NOR in the WWTP 2 effluent was extremely low, that at site 2 of Qiantang River was high, with an average of 508.7 ng L⁻¹. These results indicate that aside from WWTP 2 (the main wastewater source for Qiantang River), other wastewater sources discharge NOR into Qiantang River.

The PEN-G concentrations in the effluents from hospitals 1, 2, 3, and 4 and PEN-V concentrations in the effluents from hospitals 3 and 4 were below the MDL. The PEN-V concentrations in hospitals 3 and 4 effluents ranged from 277.3 to 338.6 ng L⁻¹, indicating that the PEN series is not a commonly used drug in Hangzhou. Because of the side effects of PEN, it cannot be mixed with other antibiotics such as sulfanilamide, tetracycline, and aminoglycosides. Furthermore, a skin test is absolutely necessary before PEN is used because it will cause serious allergic reactions in certain groups of patients (Macy et al. 2003). These properties limit the wide use of PEN in most hospitals in Hangzhou. The PEN-G and PEN-V concentrations in the WWTP 2 influent were 179.7 and 152.0 ng L⁻¹, respectively. WWTP 2 receives industrial and domestic sewage from the Hangzhou metropolitan area; therefore, PEN-G and PEN-V may originate from related industrial use. High removal rates for PEN drugs in WWTP 2 were achieved (Table 3) because PEN, as a kind of β-lactam antibiotic, may exhibit molecular rearrangement and may be easily hydrolyzed in neutral water given its chemically unstable β-lactam rings (Cha et al. 2006). The PEN-G and PEN-V concentrations in the WWTP 2 effluent were below MDL, while the samples from site 2 in Qiantang River exhibited concentrations above 100 ng L⁻¹, indicating that PEN sources other than WWTP 2 exist in this region.

The concentrations of CPL in the effluents from all the hospitals, as well as in both the influent and effluent of

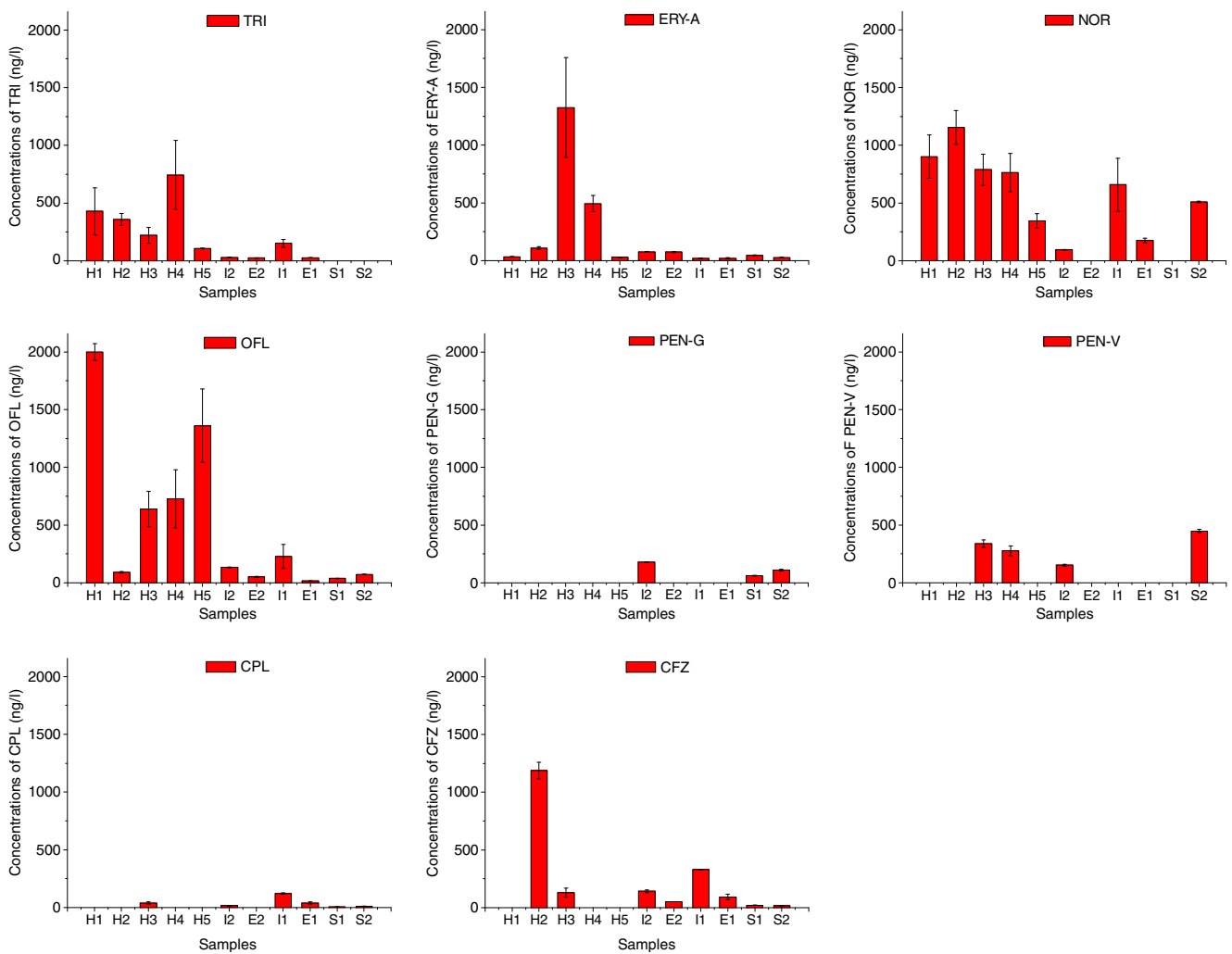


Fig. 2 Concentrations of target antibiotics in each sample (*H1*, *H2*, *H3*, *H4*, and *H5*, respectively, represent hospitals 1, 2, 3, 4, and 5; *I1*, *E1*, *I2*, and *E2*, respectively, represent influents and effluents of

WWTP 1 and WWTP 2; *S1* and *S2*, respectively, represent sites 1 and 2 of sampling sites in Qiantang River)

WWTP 2, were extremely low. The CFZ concentrations in hospital 2 and 3 effluents were 1,186.3 and 130.6 ng L⁻¹, respectively, while those in the effluents of hospitals 1 and 4 were below MDL. Thus, CFZ is a commonly used drug in hospital 2. The 63% removal rate for CFZ was lower than that for PEN in the wastewater from WWTP 2, which corresponds to the fact that cephalosporin, as a kind of β -lactam antibiotic, appears to be more stable than PEN in

water environments (Jiang et al. 2010). Both the CPL and CFZ concentrations in Qiantang River were extremely low. As shown in Fig. 2, the environmental concentrations of cephalosporin antibiotics, such as CPL and CFZ, in the samples from Hangzhou exhibited lower concentrations than did NOR, OFL, or PEN. The specific effects of these different antibiotics on aquatic organisms are attributed to the comprehensive effect of dosage, toxicity, and exposure

Table 3 Removal rates of pharmaceuticals in WWTP 1 and WWTP 2

	Removal rate (%)												
	TRI	ERY-A	NOR	OFL	PEN-G	PEN-V	CPL	CFZ	IBU	NAP	DIC	CLO	ATEN
WWTP 1	82	2	73	93	na	na	67	72	na	na	1	na	76
WWTP 2	11	1	100	62	100	100	100	63	1	100	59	7	69

na not available

time. The varied effects of these drugs on the environment require further research.

3.1.2 Concentrations of nonsteroidal anti-inflammatory drugs

The concentrations of the nonsteroidal anti-inflammatory drugs (NSAIDs) IBU, NAP, and DIC in the samples from Hangzhou are shown in Fig. 3. The average IBU concentrations in the samples from hospitals 2 and 3 were 442.4 and 1,702.1 ng L⁻¹, respectively, while those in the samples from hospitals 1 and 4 were below MDL. Table 3 shows that IBU was hardly removed from WWTP 2. The IBU concentration in Qiantang River ranged from 54.4 to 62.3 ng L⁻¹, which is approximately half of the IBU concentrations in the Llobregat River Basin, investigated by Kuster et al. (2008). The NAP concentrations in most of the hospital samples from Hangzhou were below MDL. However, a NAP concentration of 46.2 ng L⁻¹ was detected in the WWTP 2 influent, suggesting that the hospital is not the main NAP source. NAP was efficiently removed in WWTP 2. The DIC concentrations in the samples from hospitals 1, 2, and 3 were 33.1, 79.4, and 103.7 ng L⁻¹, respectively, while that in the sample from hospital 4 was below MDL. DIC was removed in WWTP 2 at a rate of 59%, higher than the removal rate reported for DIC in another WWTP (Yu et al. 2006). Both the NAP and DIC concentrations in Qiantang River were below 15 ng L⁻¹.

3.1.3 Concentrations of other pharmaceuticals

Aside from the 11 drugs discussed above, CLO (liquid-regulating agents) and ATEN (β -adrenoceptor-blocking drugs) were also investigated. The CLO concentration in the hospital 1 effluent was 22.8 ng L⁻¹, while those in the other hospital effluents were below MDL. The ATEN concentrations in the hospital effluents ranged from 46.0 to 300.8 ng L⁻¹, and its removal rate in WWTP 2 was

approximately 70%. The ATEN concentrations in Qiantang River were below 20 ng L⁻¹.

3.2 Concentrations of pharmaceuticals in the samples from Linan County

3.2.1 Concentrations of antibiotics

The concentrations of antibiotics in the samples from Linan County are shown in Fig. 2. The concentrations of OFL and NOR in the hospital 5 effluent were high at average levels of 1,361.1 and 346.7 ng L⁻¹, respectively, while the PEN-G, PEN-V, CPL, and CFZ concentrations in the samples from hospital 5 were all below MDL. The TRI, NOR, CPL, and CFZ concentrations in the WWTP 1 influent were higher than that in the hospital 5 effluent. Given that WWTP 1 primarily receives domestic sewage from the county, household wastewater that enters into WWTP 1 through the urban sewage pipe network may contain these drugs. The removal rates for TRI, NOR, OFL, CPL, and CFZ in WWTP 1 were 82%, 73%, 93%, 67%, and 72%, respectively, demonstrating that these drugs were efficiently removed from the WWTP of Linan County. The concentrations of PEN-G and PEN-V in the samples from hospital 5, as well as those in both the influent and effluent from WWTP 1, were all below MDL, which further confirmed that PEN was not a favored drug in most hospitals.

3.2.2 Concentrations of NSAIDs

The concentrations of NSAIDs in the samples from Linan County are shown in Fig. 3. The CID concentration in the hospital 5 effluent was high at an average concentration of 1,284.1 ng L⁻¹, while the IBU and NAP concentrations in the samples from the same hospital were below MDL. This finding indicates that hospital 5 prefers DIC as an anti-inflammatory drug over IBU and NAP. DIC could not be

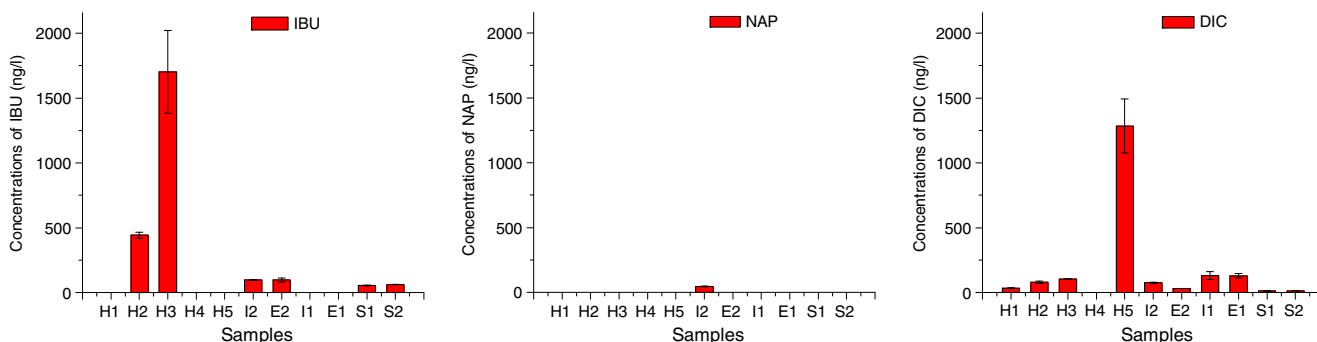


Fig. 3 Concentrations of target NSAIDs in each sample (H1, H2, H3, H4, and H5, respectively, represent hospital 1, 2, 3, 4, and 5; I1, E1, I2, and E2, respectively, represent influents and effluents of WWTP 1 and

WWTP 2; S1 and S2, respectively, represent sites 1 and 2 of sampling sites in Qiantang River)

removed in WWTP 1, and IBU and NAP were not detected in both WWTP 1 influent and effluent.

3.2.3 Concentrations of other pharmaceuticals

The CLO and ATEN concentrations in the samples from Linan County are shown in Fig. 4. The average ATEN concentration in the hospital 5 effluent was 28.7 ng L^{-1} , which is considerably lower than that in the WWTP 1 influent. ATEN was efficiently removed in WWTP 1, with a removal rate of 76%. CLO in the samples from hospital 5 and WWTP 1 was not detected. Therefore, we can conclude that CLO is not commonly used in Linan County.

3.3 Comparison of target pharmaceutical distributions in the two regions

As shown in Figs. 2, 3, and 4, the TRI, ERY-A, OFL, PEN-V, CFZ, IBU, DIC, and ATEN concentrations in all the hospital effluents in the two regions considerably varied, reflecting the different prescription practices of these hospitals. TRI, ERY-A, NOR, OFL, DIC, and ATEN were the most frequently detected drugs in the hospitals in Linan County and the Hangzhou metropolitan area. The detection frequencies for PEN-G, CPL, CLO, and NAP were low for all the hospital effluents, indicating the uncommon use of these drugs in the two regions. The average TRI, NOR, OFL, and ATEN concentrations in the hospital 1, 2, 3, and 4 effluents were higher than those in the WWTP 2 influent, indicating that the hospitals are the main sources of these pharmaceuticals to rivers in the Hangzhou metropolitan area. The average concentrations of these four drugs in the hospital 5 effluent were lower than that in the influent of WWTP 1 in Linan County, where domestic sewage may be the main source of these drugs. PEN-G and NAP were not detected in the hospital 1, 2, 3, and 4 effluents, but detected in the WWTP 2 influent. Given that PEN-G and NAP are rarely used in the Hangzhou metropolitan area, we conclude that other wastewater sources (such as pharmaceutical factories) that contain these drugs exist.

As shown in Table 3, NOR, OFL, CPL, CFZ, and ATEN were efficiently removed from WWTP 1 and WWTP 2 with removal rates higher than 60%, whereas ERY-A in both

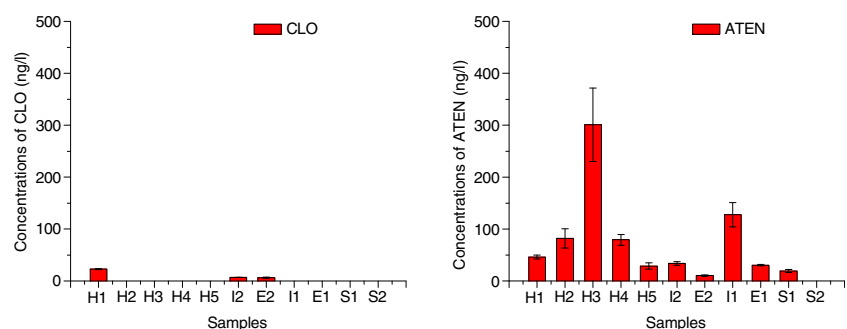
WWTPs was difficult to remove. TRI was efficiently removed from the WWTP 1 wastewater, but the removal rate for TRI from WWTP 2 was low. Although DIC was essentially removed from WWTP 2, its removal from WWTP 1 was difficult. The removal rate for drugs in wastewater treatment is related to the dissolved oxygen level and aerobic conditions (Xue et al. 2010). In the two regions, although the WWTPs adopt the anaerobic–aerobic–anoxic treatment process, their operating parameters are different, resulting in varied removal rates for the same drugs in these facilities.

ERY-A, OFL, PEN-G, CPL, CFZ, IBU, and DIC were detected in both the sampling sites of Qiantang River, whereas TRI, NAP, and CLO were below MDL. The average OFL, PEN-G, and IBU concentrations in Qiantang River were comparatively high, with values above 50 ng L^{-1} . The NOR and PEN-V concentrations at site 2 of Qiantang River were high at 508.7 and 447 ng L^{-1} , respectively. Those at site 1 were below MDL. Site 2 is located downstream of the river, and concentrations of those two in the effluent of WWTP 2 were below MDL; thus, sources of these two drugs other than WWTP 2 exist near the river.

4 Conclusion

- TRI, ERY-A, NOR, and OFL were the most frequently detected antibiotics in hospital effluents in Linan County and the Hangzhou metropolitan area; so were DIC (NSAIDs) and ATEN (other pharmaceutical). The concentrations of these drugs were comparatively high in hospital effluents. The occurrence of IBU (NSAIDs), CFZ, and PEN-V (antibiotics) in hospital effluents were different between Linan County and Hangzhou metropolitan area.
- Antibiotics, like NOR, OFL, CPL, and CFZ, and other pharmaceuticals like ATEN could be efficiently removed in the WWTPs of both Linan County and Hangzhou metropolitan area, while ERY-A could not. The removals of TRI (antibiotics) and DIC (NSAIDs) in WWTPs of Linan County and Hangzhou metropolitan area presented an opposite state.

Fig. 4 Concentration levels of CLO and ATEN in each sample (H1, H2, H3, H4, and H5, respectively, represent hospital 1, 2, 3, 4, and 5; I1, E1, I2, and E2, respectively, represent influents and effluents of WWTP 1 and WWTP 2; S1 and S2, respectively, represent sites 1 and 2 of sampling sites in Qiantang River)



- Antibiotics, like ERY-A, OFL, PEN-G, CPL, and CFZ; NSAIDs like IBU; and other pharmaceutical DIC were detected in Qiantang River. In particular, the average concentrations of OFL, PEN-G, and IBU in Qiantang River were comparatively high.

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