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The occurrence of antihistamines in sewage waters and in recipient rivers

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Abstract
Background, aim and scope Each year, large quantities of pharmaceuticals are consumed worldwide for the treatment and prevention of human and animal diseases. Although the drugs and the metabolites observed in the wastewaters and in the environment are present at concentrations several orders of magnitude lower than the concentrations required to exert their effects in humans or animals, their long-term impact on the environment is commonly not known. In this study, the occurrence of six antihistamines, which are used for the relief of allergic reactions such as hay fever, was determined in sewage treatment plants wastewaters and in recipient river waters.
Materials and methods The occurrence of the antihistamines cetirizine, acrivastine, fexofenadine, loratadine, desloratadine and ebastine in sewage treatment plants wastewaters and in recipient river waters was studied. The analytical procedure consisted of solid-phase extraction of the water samples followed by liquid chromatography separation and detection by a triple-quadrupole mass spectrometer in the multiple reaction mode.
Results Cetirizine, acrivastine and fexofenadine were detected in both influent and effluent wastewater samples at concentration levels ranging from about 80 to 220 ng/L, while loratadine, desloratadine and ebastine could not be detected in any samples. During sewage treatment, the concentration of the antihistamines dropped by an average of 16–36%. Furthermore, elevated concentrations of antihistamines were observed in samples collected during the season of most intensive plant pollen production, i.e. in May. In the river water samples, the relative pattern of occurrence of cetirizine, acrivastine and fexofenadine was similar to that in the wastewater samples; although the concentration of the compounds was substantially lower (4–11 ng/L). The highest concentrations of the studied drugs were observed near the discharging point of the sewage treatment plant.
Discussion The highest concentrations of antihistamines in STP wastewaters correlate with the outbreak of allergic reaction caused by high amounts of plant pollens in the air. The analysis results of the river water samples show that the antihistamines are carried far away from the effluent discharge points. They may account for a part of the mix of pharmaceuticals and of pharmaceutical metabolites that occur downstream of STPs.
Conclusions Antihistamines are poorly degraded/eliminated under the biological treatment processes applied in the wastewater treatment plants and, consequently, they are continuously being discharged along with other drugs to the aquatic environment.
Recommendations and perspectives As a huge quantity and variety of drugs and their metabolites are continuously discharged to rivers and the sea, the compounds should be considered as contaminants that may possess risks to the aquatic ecosystem. Further studies are urgently needed on the environmental fate of the antihistamines and other pharmaceuticals in the aquatic environment. These studies should be concerned with the stability of the compounds, their transformation reactions and the identity of the transformation products, the distribution of drugs and their uptake and effects in organisms. On the basis of these studies, the possible environmental hazards of pharmaceuticals may be assessed.

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1 Background, aim and scope

In recent years, the presence of medicinal drugs in the aquatic environment has been a topic of growing concern (Halling-Sørensen et al. 1997; Ternes 1998; Buser et al. 1999; Lindqvist et al. 2005). Human and veterinary drugs are continuously released into the environment mainly as a result of normal human consumption and excretion of parent compounds and metabolites. An additional input may be due to the disposal of unused pharmaceuticals into municipal wastewaters. The steady input of biologically active compounds to the aquatic environment may pose a serious threat to the integrity of the aquatic ecosystem, but also represents a hazard for the predators of aquatic organisms (Jones et al. 2004; Oaks et al. 2004; Oetken et al. 2005; Kidd et al. 2007).

Each year, large quantities of pharmaceuticals are consumed worldwide for the treatment and prevention of human and animal diseases. Most pharmaceuticals are designed to be non-bioaccumulative and eliminated from the human or animal body shortly after administration. Once administered, the metabolism of a drug generally introduces hydrophilic functionalities onto the drug to facilitate excretion with urine and/or faeces. Some drugs and the metabolites are not fully degraded under the typical biological treatment processes applied in the wastewater treatment plants and, consequently, the compounds are continuously discharged into the aquatic environment (Xia et al. 2005). Although the drugs and the metabolites observed in the wastewaters and in the environment are present at concentrations several orders of magnitude lower than the concentrations required to exert their effects in the target organisms, their long-term impact on the environment is not commonly known.

Recently, legislations for the pharmaceutical industry have been settled in order to reduce and prevent the possible environmental risks caused by new medicinal products. In accordance with an EU Directive, relating to medicinal products for human use, Article 8 3. (g), the evaluation of potential risk for the environment should be assessed (Directive 2001/83/EC 2001).

In large, the consumption of antihistamines is based on seasonal treatment of allergic reactions (hay fever) and this may be reflected in seasonal variations in concentrations of the drugs in wastewaters and in the discharges. Furthermore, the drugs possess a rather high biological activity as the defined daily dose (DDD) for cetirizine, loratadine and acrivastine is as low as 10–24 mg, whereas, in comparison, the DDD for ibuprofen is 1,200 mg (Parfitt 1999).

According to the Finnish National Agency for Medicines 2006, over 60% of the antihistamine preparations sold contain cetirizine. The other antihistamine preparations contain loratadine and desloratadine (20%), ebastine (10%), acrivastine (4%) and fexofenadine (4%) as the active compound. These antihistamines belong to the so called second generation antihistamines which cause less sedation and drowsiness than the previously used antihistamines (e.g. chlorphenirame, brompheniramine and diphenhydramine).

Cetirizine is excreted primarily with the urine and metabolised only to a limited extent (Parfitt 1999; Product monograph for Zyrtec (cetirizine) 2006). Loratadine is metabolised to descarboxyloratadine (desloratadine), which is the pharmacologically active compound. Most of loratadine (desloratadine) is excreted as desloratadine (Parfitt 1999). Ebastine is rapidly and almost completely oxidised to carebastine, which is the major detectable metabolite and is believed to be responsible for the pharmacological effects of the drug (Yamaguchi et al. 1994). Two inactive metabolites, hydroxyebastine and desalkylebastine, are also formed. Acrivastine and fexofenadine are excreted as parent compounds (Parfitt 1999).

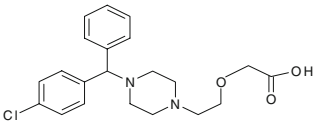
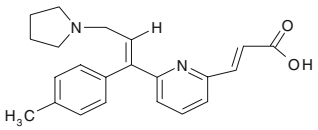
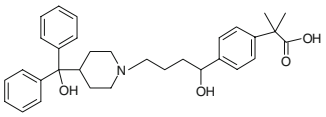
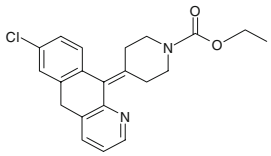
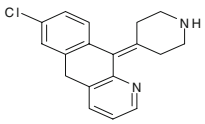
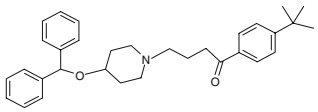
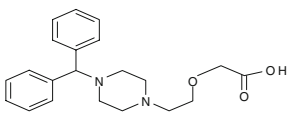
The objective of this work was to study the occurrence of antihistamine drugs in sewage waters of the city of Turku, Finland. In addition, river water that receives discharges from sewage treatment plants (STPs) was sampled and analysed for the antihistamines. The chemical structures of the compounds studied and data on their consumption based on sales statistics in Finland are presented in Table 1. As far as we know, the occurrence of the second generation antihistamines in wastewaters and in the environment has not previously been reported.

2 Materials and methods

2.1 Chemicals

Standards for cetirizine, fexofenadine, loratadine and desloratadine were purchased from Sigma-Aldrich (Schnelldorf, Germany). Acrivastine (Benadryl 8 mg tablet, Janssen-Cilag, Finland) and ebastine (Kestine 10 mg tablet, Leiras, Finland) were purchased as a commercially available pharmaceutical preparation and the active ingredients were extracted from the preparation using acetonitrile. Because the metabolite standards were not available at the time of the study, quantitative determinations of ebastine and its metabolites could not be performed. Only qualitative determinations of ebastine were performed, i.e. present or not present in the samples.

Table 1 Chemical structures and consumption data of the studied antihistamines

Compound	Systematic name (IUPAC) and CAS number	Structural formula, Molecular formula and Molecular weight (g/mol)	Defined dailydose [a] (DDD, mg)	Consumption [a] DDD/1000 inh/day
Cetirizine	(±) - [2- [4- [(4-chlorophenyl)phenylmethyl] -1- piperazinyl] ethoxy]acetic acid CAS: 83881-51-0	 $C_{21}H_{25}ClN_2O_3$ M_r 388.89	10	19.4
Acrivastine	(E)-3-{6-[(E)-1-(4-methylphenyl)-3-pyrrolidin-1-yl-prop-1-enyl]pyridin-2-yl}prop-2-enoic acid CAS: 87848-99-5	 $C_{22}H_{24}N_2O_2$ M_r 348.45	24	0.2
Fexofenadine	Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidine)-1-piperidinecarboxylate CAS: 83799-24-0	 $C_{32}H_{39}NO_4$ M_r 501.67	120	0.7
Loratadine	Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidine)-1-piperidinecarboxylate CAS: 79794-75-5	 $C_{22}H_{23}ClN_2O_2$ M_r 382.89	10	3.3
Desloratadine	8-Chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta-[1,2-b]-pyridine (Descarboethoxyloratadine) CAS: 100643-71-8	 $C_{19}H_{19}ClN_2$ M_r 310.83	5	3.3
Ebastine	4-(4-Benzhydryloxy-1-piperidyl)-1-(4-tert-butylphenyl)butan-1-one CAS: 90729-43-4	 $C_{32}H_{39}NO_2$ M_r 468.67	10	4.2
ISTD	[2-[4-(diphenylmethyl)piperazin-1-yl]ethoxy] acetic acid CAS: 83881-53-2	 $C_{21}H_{26}N_2O_3$ M_r 354.44	–	–

[a] Finnish National Agency of Medicines (2006). www.nam.fi

The internal standard was ([2-[4-(diphenylmethyl)piperazin-1-yl]ethoxy]acetic acid) that is structurally related to the analytes and kindly supplied by Matrix Laboratories (Secunderabad, India). The purity of all standards was >98%.

Individual standard stock solutions were prepared on a weight basis in acetonitrile and stored at about –20°C. A mixture of all pharmaceutical standards was prepared by appropriate dilution of individual stock solutions. Further

dilutions were made before the analyses of the samples and these solutions were used as working standard solutions.

HPLC grade acetonitrile and formic acid (98–100%) was supplied from Merck (Darmstadt, Germany). Milli-Q water was prepared at the laboratory (Millipore, Finland).

2.2 Sampling procedures

The influent and effluent water samples were collected from the Turku sewage treatment plant (STP), which serves about 170,000 people and the industry, mainly food and pharmaceutical industries. The amount of water processed in the Turku STP is about 60,000 m^3/day. The treatment process consists of a combination of biological and chemical processes including a denitrification–nitrification process for nitrogen removal (Lindqvist et al. 2005). The influent samples consisted of untreated wastewater, while the effluent samples consisted of water discharged to the recipient. The hydraulic retention time of the STP was 14 to 26 h.

The wastewater samples from the STP were collected in polyethylene bottles rinsed with Milli-Q water. The samples were collected as 64 h (3 days) composite samples from March to September 2007 (12 influent and 12 effluent samples). The samples were frozen at the treatment plant to –20°C.

The river water samples (grab samples) were collected in polyethylene bottles rinsed with Milli-Q water. Two samples were collected from the River Aura from two different locations. One point was located 1 km downstream of the STP of municipal Aura in June 2007. The average discharge volume of the STP was 650 m^3/day. The second sampling point was located about 32 km downstream of the Aura STP in July 2007. The sampling point is located close to the raw water intake of the drinking water treatment plant of the city of Turku. (Further details of the sampling points are given in Vieno et al. 2005). From the River Loimi, one sample was taken in June. At the sampling point, the water is mixed with discharges from three small STPs. The total discharge volume of the plants is about 4,000 m^3/day. The sampling point distance to the nearest STP was about 16 km. All the samples were frozen immediately after the sampling in the laboratory at a temperature of about –20°C.

2.3 Sample preparation and analytical methods

The same sample preparation procedure was used for influent and effluent wastewater as well as for the river water samples. The samples were filtrated through a 0.45 μm glass fibre filter (GF 6 from Schleicher & Schuell) prior to solid-phase extraction procedure (SPE). Solid-phase extraction was used in order to isolate and concentrate the pharmaceuticals from all water samples. The extraction volume of 100 ml was used in all samples. Oasis HLB 3 cc SPE cartridges (Waters, Finland) were used. The cartridges were pre-conditioned sequentially with 2 ml of methanol and 2 ml of Milli-Q water before sample loading. The water samples were allowed to pass the cartridges at a flow rate of about 4 ml/min. The internal standard was added to the 100-ml test portions immediately before the extraction procedure. After the sample had passed, the cartridges were washed sequentially with 1.5 ml 2% acetonitrile in acidified water (2% acetic acid) and then with 1.5 ml of 5% acetonitrile in water. The antihistamines were extracted from the cartridges with two 1-ml portions of acetonitrile. The extracts were evaporated to dryness under a gentle stream of nitrogen. The residues were dissolved in 100 μl of the mobile phase used for the LC separation (15% B, see below). Blank samples (Milli-Q water) were processed in the same way as water samples to ensure the purity of the system.

The determination of antihistamines in the extracts was based on separation by LC and subsequent detection by tandem mass spectrometry (MS/MS) using electrospray ionisation. The LC-MS/MS system consisted of Agilent 1100 Series Chromatographic system (binary pump, vacuum degasser, autosampler, column thermostat), which was connected to a Quattro Micro triple-quadrupole mass spectrometer (Micromass, Manchester, UK).

The analytes were separated on a reversed phase C-18 analytical column, XBridge 2.1×50 mm, 5 μm (Waters, Finland). The injection volume was 20 μl. The mobile phase consisted of (A) 0.5% (*v*/*v*) formic acid in water and (B) acetonitrile. The flow rate was 0.200 ml/min. The elution started at 15% B for 4 min and then the elution was linearly increased to 70% B in 3 min and lowered back 15% B in 1 min where the column was equilibrated for 7 min. The total run time was 15 min. The retention times for the studied pharmaceuticals and internal standard were between 7.0 to 10.4 min.

The mass spectrometer was operated in the multiple reaction monitoring mode (MRM) and negatively charged ions were recorded. Nitrogen was used as the desolvation and nebulising gas at a flow rate of 640 l/h and 30 l/h, respectively. Argon was used as the collision gas, at a collision cell pressure of 3×10^{-3} mbar. The source and desolvation temperature was 130°C and 325°C, respectively.

The cone voltages and collision energies were optimised for each compound in order to achieve sensitive and selective detection. The optimisation of the MS/MS parameters was performed by a continuous injection of pure compounds to the MS/MS compartment at a concentration of 5 mg/ml and a flow rate of 10 μL/min. A dwell time of 0.2 s/ion pair and inter channel delay of 0.2 s was used.

The sample preparation procedure and analytical method was validated for specificity, precision and accuracy. Linearity of the method was checked over the concentration range of 0.1 to 250 ng/L by spiking non-contaminated groundwater with each of the compounds and the internal standard and performing the SPE procedure. The limit of quantification (LOQ) and limit of detection (LOD) of the procedure were defined from the linearity curve.

To evaluate the magnitude of signal suppression caused by sample matrix effects, a set of experiments has been performed where the signal obtained with the compounds dissolved in pure water were compared to the signal obtained with the compounds dissolved in river water and wastewater.

3 Results

3.1 Validation of the analytical method

The method was validated for specificity, precision, linearity, accuracy and limit of quantification and detection. The optimised MS/MS parameters for each compound along with the validation data are presented in Table 2.

For specificity of the method, the gradient elution was used in order to separate the antihistamines from matrix and also from each other. The chromatographic (LC) retention times of the compounds were compared to the standards (±1%). The retention times of the studied pharmaceuticals and internal standard were between 7.0 to 10.4 min (Fig. 1).

Repeatability and intermediate precision of the method was evaluated from run-to-run experiments with standard solution at 50 ng/L (n=3 on two successive days) and with real samples (analyses on two successive days). The precision of the method has been expressed as the relative standard deviation (RSD %) of replicate measurements. The RSD values obtained from run-to-run experiments of three standard solutions at 50 ng/L ranged from 4.8% to 9.0% and RSD values for day-to-day experiments (two successive days) ranged from 11.0% to 13.3%. The variability of retention times compared to standard solutions was lower than 1% in all cases.

Linear dynamic range of the method was determined by injecting a standard mixture of pharmaceuticals in the range from 0.1 to 250 ng/L. Calibration curves were generated using linear regression analysis. All of the compounds had linear fit (R^2>0.985) in the range from 0.1 to 250 ng/L and the origins of the curves were covered by the 95% confidence limits.

Accuracy of the method expressed as recovery percentages of the spiked samples over the range of 5 to 200 ng/L was determined. The standard solutions for river samples were prepared using the River Aura water. The standard solutions for influent and effluent wastewater samples were prepared in effluent water. The studied antihistamines of cetirizine, acrivastine, loratadine, desloratadine and fexofenadine were relatively well recovered in the linear range of the method ranging from 78% to 115%.

Quantification limit and detection limit of the method has been calculated from the linearity curve data using a signal-to-noise ratio of 10 for LOQ and 3.3 for LOD. Instrumental quantification limit (IQL) was determined using pure standards dissolved in mobile phase. The IQL ranged from 0.9 to 4.5 ng/L. The limit of detection and

Table 2 LC-MS/MS parameters and method validation data

Test	Cetirizine	Acrivastine	Fexofenadine	Loratadine	Desloratadine	Ebastine*	ISTD
Specificity	8.49	8.15	8.46	8.91	8.34	10.42	8.03
Retention time (min)	389.2	349.4	502.5	383.2	244.2	470.5	355.4
Precursor ion (m/z)	201.4	278.4	466.5	337.4	180.3	167.3	167.4
Product ion (m/z)							
Precision		5.2	9.0	4.8	7.4	–	–
Repeatability (RSD %, n=3)	5.7	11.0	12.1	12.0	11.8	–	–
Intermediate precision (RSD %, n=2)	13.3						
Accuracy	105±6	78±4	104±9		115±9	–	–
Recovery % (n=3)				107±5			
Linearity	0.9994	0.9958	0.9985	0.9856	0.9988	0.9960	–
Linearity range 0.1–250 ng/L, R^2							
Sensitivity							
Instrumental limit of quantification (ng/L)	0.9	4.5	1.6	1.2	1.7	13	–
Limit of quantification (**LOQ**, ng/L)	4.7	22.5	9.7	27.3	9.1	–	–
Limit of detection (**LOD**, ng/L)	2.0	5.2	3.1	9.8	2.8	–	–

*Qualitative analysis

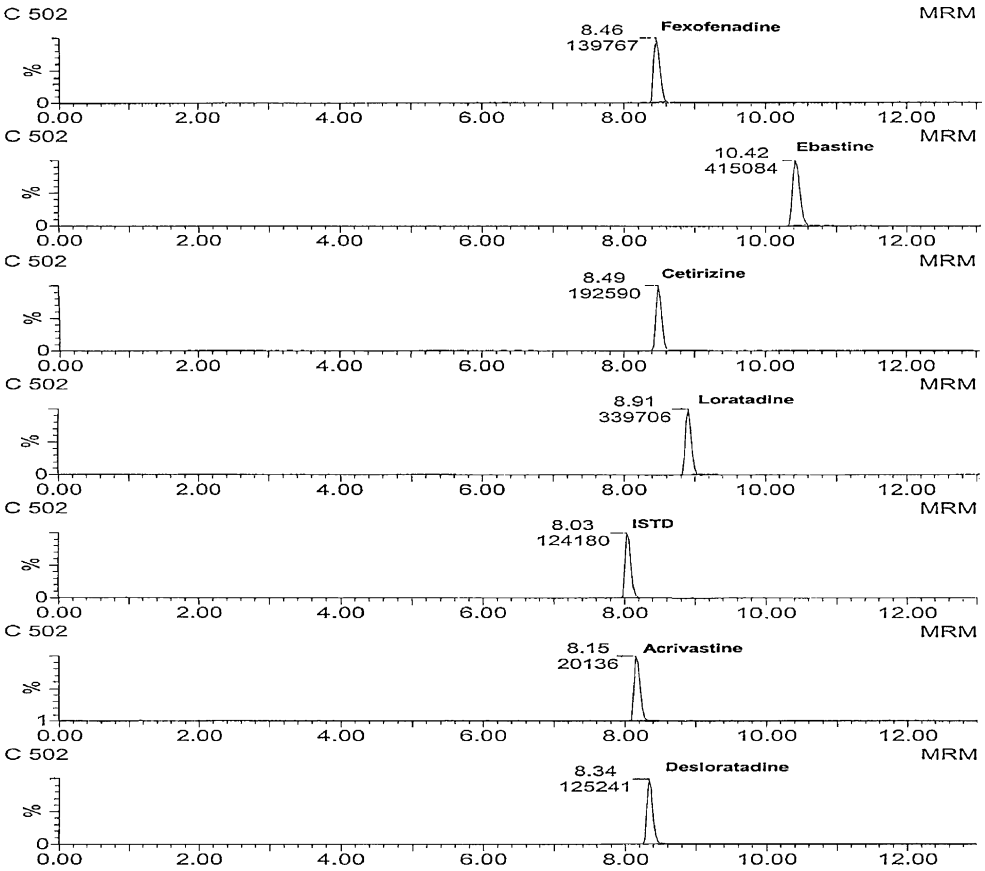


Fig. 1 LC-MS/MS chromatogram of a pure water sample spiked with antihistamines at a concentration of 50 ng/L *ordinate*; retention time (minutes). *Abscissa* abundance (%)

limit of quantification of method has been calculated from linearity curve with the following equation (EMEA 1995–2008):

$$\mathrm{LOD} = (3.3 \times \delta)/S \quad (1)$$

$$\mathrm{LOQ} = (10 \times \delta)/S \quad (2)$$

where δ is the standard deviation of the response and S is the slope of the standard calibration curve.

3.2 Matrix effect

One typical LC-MS/MS limitation concerning wastewater analyses is that the matrix components may suppress the analyte signal (Hernando et al. 2004). The evaluation of the extent of ion suppression/enhancement in the MS/MS system was conducted using spiked river water and wastewater effluent extracts (spike level of 50 ng/L). In the case of the wastewater matrix, the signal suppression/enhancement was calculated only for those compounds not present in the wastewater samples (loratadine, desloratadine and internal standard). The signal suppression was calculated as the percentage of signal intensity (area) in a sample matrix versus the signal intensity (area) of the same concentration in the pure solvent (pure water).

In river water for acrivastine, loratadine, desloratadine and the internal standard, the suppression of the signals was less than 30%, while suppression for cetirizine and fexofenadine was found to be 40–50%. In wastewater effluent, the suppression of the signals was 20% to 40%. The recovery data obtained with validation ensured that the matrix effects have been well compensated for by using standard solutions prepared in the river water. Therefore, cetirizine, acrivastine and fexofenadine determinations in wastewater samples as well as in river water samples are considered to be reliable.

3.3 Water samples

3.3.1 Wastewaters

The aim of this study was to determine the occurrence of the target antihistamines in wastewaters as well as in river waters in Finland. The wastewater samples were collected during March to September 2007 at the sewage treatment plant of the city of Turku, Finland. Cetirizine, acrivastine and fexofenadine antihistamines were found in all wastewater samples, whereas loratadine and desloratadine were not detected in any samples (Figs. 2 and 3).

Cetirizine was found to be the dominating antihistamine in all samples except for the March effluent and April

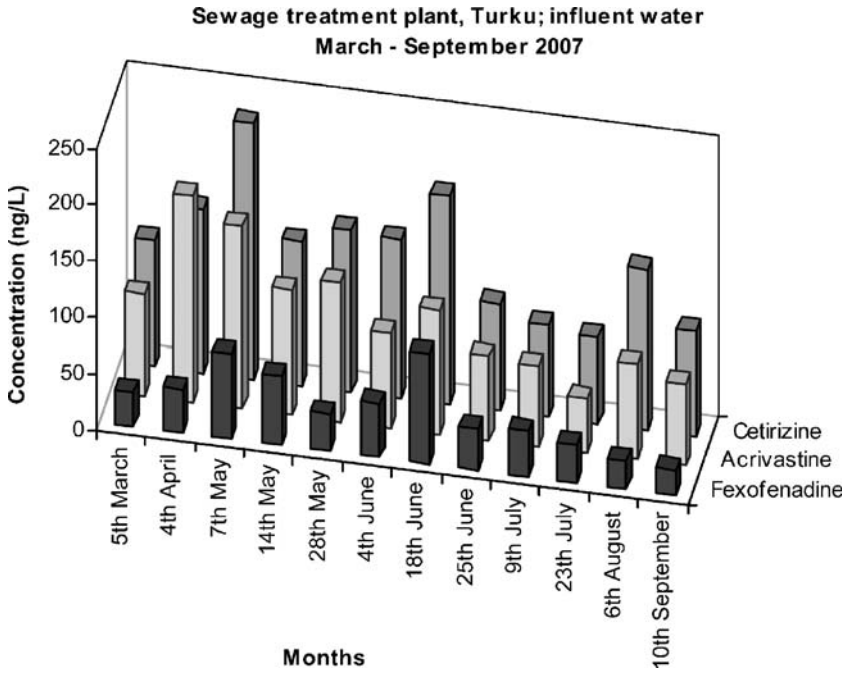


Fig. 2 Occurrence of antihistamines in influent wastewater

influent samples, where acrivastine was the dominating compound. The highest concentrations of cetirizine, acrivastine and fexofenadine recorded were about 220, 180 and 100 ng/L, respectively.

The elimination rate of cetirizine, acrivastine and fexofenadine in the sewage treatment process was estimated by comparison of the antihistamine concentrations determined in the influent and effluent wastewater (12 determinations, see Figs. 2 and 3). The concentrations of antihistamines present in wastewater determined from March to September are summarised and the effluent summary concentration can be compared to the influent summary concentration (Fig. 4). It was found that in the applied treatment process, about 36% of acrivastine was eliminated while the elimination rate for cetirizine and fexofenadine was significantly lower, being 16% and 18%, respectively. Due to the poor elimination of the antihistamines and the hydraulic retention of the STP, it was

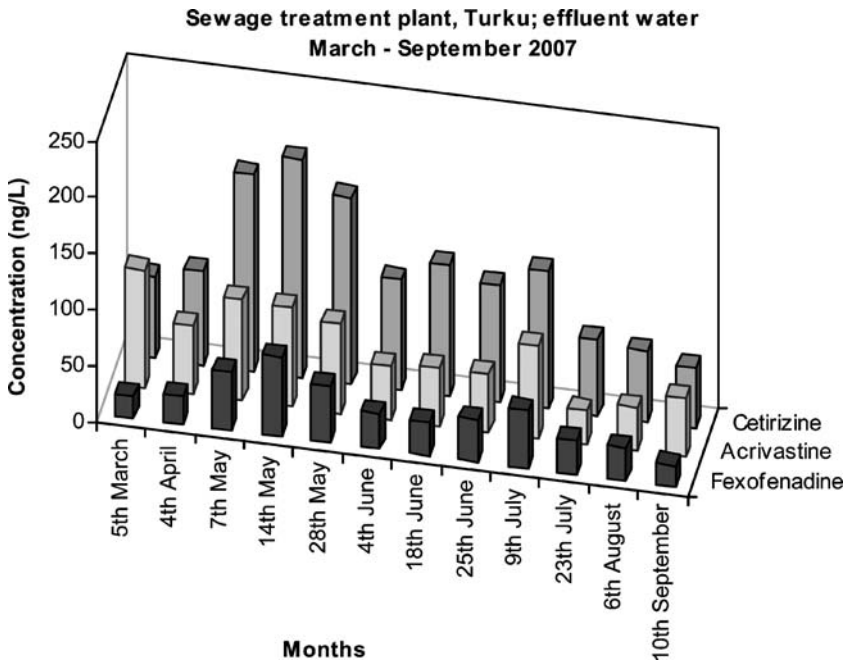


Fig. 3 Occurrence of antihistamines in effluent wastewater

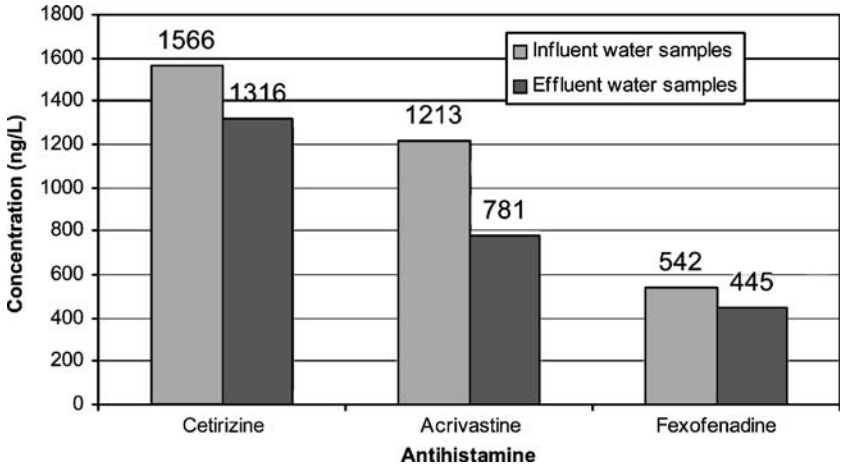


Fig. 4 The summary concentrations (sum of 12 determinations) of antihistamines in influent and effluent water

occasionally found that the concentration of antihistamines was higher in the effluent water than in the influent water.

3.3.2 River waters

In the river waters, the highest concentrations of the studied antihistamines were found at the sample collected close to the discharge point of the Aura STP (Fig. 5). The concentrations of cetirizine and fexofenadine were about 9 and 11 ng/L, respectively. Cetirizine was also detected nearby the intake of the drinking water treatment plant (32 km downstream from Aura STP) at a concentration level of about 4 ng/L and in the River Loimi at about 7 ng/L (16 km downstream from the nearest STP). Acrivastine was also detected in the samples taken from the River Aura and the River Loimi (at an estimated concentration of 5 ng/L, the concentrations were under LOQ of the method).

4 Discussion

In the effluent samples, a clear trend can be observed in concentration level of cetirizine, acrivastine and fexofenadine and date of sample collection (see Fig. 3). In these samples, an increase in concentration of the antihistamines took place during the period from March to the middle of May. The concentration dropped in June and stayed more or less stable till the beginning of July, and finally dropped to the lowest values in the late summer samples. In the influent samples, this trend is not as clear as in the effluent samples, probably due to the complex matrix of the samples, which may affect the reliability of the results (see Fig. 2).

On the basis of the consumption data of antihistamines in Finland (see Table 1), it would be expected that loratadine and desloratadine should occur in wastewater at concentrations over the LOQ of the analytical method. The

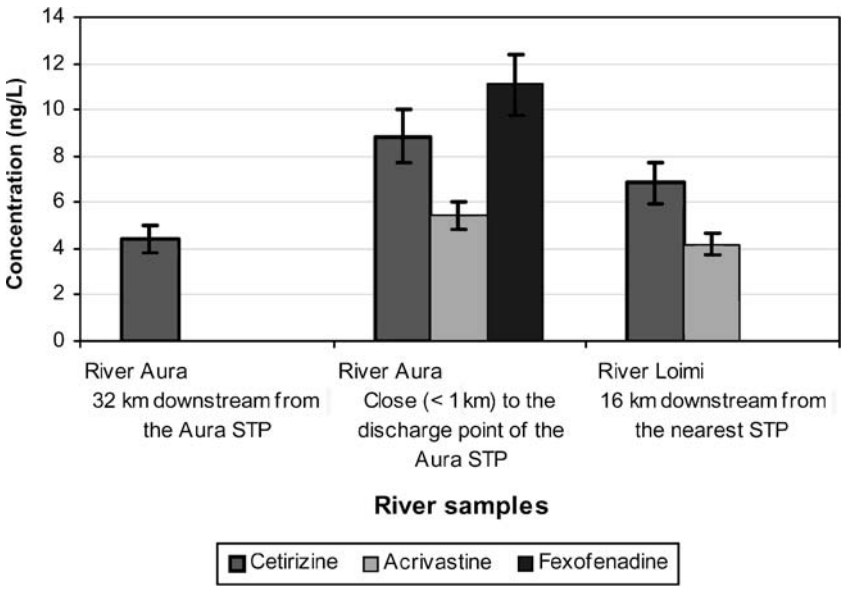


Fig. 5 Concentrations of antihistamines found in River Aura and in River Loimi (mean values of two LC-MS determinations)

reason for not being detected in the water is that these compounds are metabolically cleared from plasma (EMEA 2004) and not excreted as parent compounds via urine or faeces (Parfitt 1999). Also ebastine could not be found in wastewater probably due to a more or less complete metabolic transformation of the compound to carebastine (Yamaguchi et al. 1994).

Obviously, the reason for the concentration–time trend is due to the extent of use of the antihistamines, which in turn is due to the protection of hay fever and allergy outbreaks caused by plant pollens. Plant pollens are most abundant in the air during the spring time and earlier summer (April–June) and, consequently, the consumption of antihistamines is highest during this time. The allergenic reaction at this time of the year is caused by the pollen production primarily of Alnus and Betula (according to the aerobiology unit of the University of Turku, http://aerobiologia.utu.fi/en/index.html).

Not only the consumption but also the weather conditions have an impact on the concentrations of antihistamines in wastewater. Heavy rains will dilute the wastewaters, increase influent flow rate and the normal operation of the plant may be hampered. Heavy rains will also lower the amount of plant pollens in the air and decrease the use of antihistamines. In Turku city area a period of occasionally heavy rain took place at the end of May (27–31 of May, http://www.fmi.fi/saa/tilastot.html) and may be the reason for the decrease in antihistamine concentration observed in the effluent water samples collected in late May and the beginning of June.

In the river water samples, the relative pattern of occurrence of cetirizine, acrivastine and fexofenadine was similar to that in the wastewater samples, although the concentration of the compounds was drastically lower (4–11 ng/L) than in the effluents. It was found that the antihistamines cetirizine and acrivastine are relatively stable compounds in the aquatic environment and are carried far away from the discharge points. Thus, they may account for a part of the mix of pharmaceuticals and of pharmaceutical metabolites that occur downstream from STPs (Vieno et al. 2005, 2007). Consequently, antihistamines should be included in studies on the impact of pharmaceuticals on the aquatic environment.

5 Conclusions

The work shows that the level of antihistamines in wastewater is at the highest in the spring time and accordingly correlates with the outbreak of allergic reactions caused by high amounts of plant pollens in the air.

The antihistamines are not efficiently eliminated during wastewater treatment and a steady discharge to the aquatic environment takes place, which is reflected in the presence of the drugs in recipient river water. Since it was found that the drugs were rather stable in river water, further studies are needed on the environmental fate of the compounds and on their ecotoxicological properties. The results of such studies could form the basis of a risk assessment of antihistamines in the aquatic environment.

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