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Occurrence and removal of frequently prescribed pharmaceuticals and corresponding metabolites in wastewater of a sewage treatment plant

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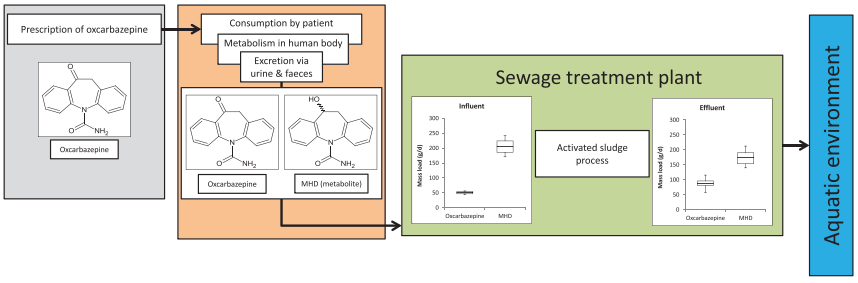
HIGHLIGHTS

- Ten days of monitoring for 49 pharmaceuticals and 7 metabolites in urban sewage
- 41 (influent) and 42 (effluent) analytes were detectable in all sewage samples.
- Only five compounds were removed with a rate higher than 50% during treatment.
- Five compounds had a significantly higher mass load in effluent than in influent.
- Metabolites are an important class of pharmaceutical residues.

GRAPHICAL ABSTRACT



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ABSTRACT

The present study determines removal rates (RR) of 56 pharmaceuticals and metabolites, respectively, in an urban sewage treatment plant using mass flow analysis by comparing influent and effluent loads over a consecutive ten-day monitoring period. Besides well investigated compounds like carbamazepine and metoprolol, less researched targets, such as topiramate, pregabalin, telmisartan, and human metabolites of pharmaceuticals were included. Another aim was to determine the ratio of pharmaceuticals and corresponding metabolites in raw wastewater.

Valsartan and gabapentin were detected at the highest average concentrations in influent (c_{val} = 29.7 (±8.1) μg/L, c_{gab} = 13.2 (±3.3) μg/L) and effluent (c_{val} = 22.1 (±5.1) μg/L, c_{gab} = 12.1 (±2.6) μg/L) samples. The comparison of mass loads in influent and effluent showed a significant removal ($p < 0.1$) for 20 compounds but only enalapril, eprosartan, losartan, pregabalin, and quetiapine were removed from the aqueous phase by more than 50%. Another 20 compounds were determined without significant difference and for five compounds (clindamycin, lamotrigine, oxcarbazepine, O-desmethyl venlafaxine, triamterene), a significant higher mass load in the effluent than in the influent was observed.

It has to be noticed that metabolites like 10,11-dihydro-10-hydroxy carbamazepine (MHD) are found in higher mass loads than the corresponding parent compound in the sewage samples. Furthermore, metabolites and parent compound behave differently in the sewage treatment process. While MHD (RR = 15.1%) was detected with lower mass load in the effluent than in the influent, oxcarbazepine (RR = −73.2%) showed the contrary pattern.

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When comparing expected and measured ratios of parent compound and metabolite in raw sewage, citalopram/N-desmethyl citalopram for example, showed good results. However, a major problem exists due to insufficient data regarding metabolism and excretion of many pharmaceuticals. This complicates the prediction of relevant metabolites and further efforts are needed to overcome this problem.

1. Introduction

In recent years many studies have focused on the quantification of pharmaceuticals in surface, ground, and drinking water (Huerta-Fontela et al., 2011; Mompelat et al., 2009; Valcárcel et al., 2011), and municipal sewage (Martínez Bueno et al., 2012; Metcalfe et al., 2010, 2003; Santos et al., 2010; Vieno et al., 2007) or evaluated toxicological effects of pharmaceuticals in the aquatic environment (Brausch et al., 2012; Fent et al., 2006; Kostich and Lazorchak, 2008). These studies focused primarily on compounds such as carbamazepine, sulfamethoxazole, trimethoprim, metoprolol or bezafibrate. Several pharmaceuticals like telmisartan (angiotensin receptor antagonist), quetiapine (antipsychotic), pregabalin, and topiramate (both anticonvulsants) or corresponding metabolites of pharmaceuticals were not investigated intensively enough, if at all, (Petrovic, 2014) and at this time it is not possible to properly evaluate their environmental relevance (Besse et al., 2008; López-Serna et al., 2012; Petrie et al., 2014). Nevertheless, the fate of many pharmaceuticals post-ingestion, excretion and release into the sewer network has been extensively examined, especially concentrations in sewage treatment plant (STP) influent and effluent. Based on these studies, removal rates were calculated for many pharmaceuticals. The results indicate a compound specific removal rate. While some pollutants are removed completely from the aqueous phase, several of them are insufficiently or not removed while passing through the STP (Majewsky et al., 2011; Verlicchi et al., 2012). However, the removal rates were often determined by comparing results of grab or 24 h-composite samples of single days resulting in values with high uncertainty and variation (Petrie et al., 2014; Verlicchi et al., 2012). Majewsky et al. (2011) demonstrated that even considering the mean hydraulic retention time (HRT) of the wastewater in a STP and shifting the sampling period of the composite sample for influent and effluent sampling by this HRT is not an appropriate way to calculate the removal rates correctly. Ort et al. (2010) published a *Sampling Guide* indicating clearly that it is necessary to take flow-proportional composite samples of consecutive days especially when the aim of the study is to compare the loads at different locations (Ort et al., 2010).

The aim of this study was to calculate the removal rates of pharmaceuticals of different therapeutic classes and corresponding metabolites for the treatment in a STP. To ensure the determination of accurate removal rates, samples were taken on ten consecutive days and daily mass loads for influent and effluent were calculated and a mass flow analysis was applied over the whole monitoring period. The pharmaceuticals were selected based on regional prescription amounts. The prescription data were analyzed for the period from 2008 until 2012 for the city Dresden, Germany (Gurke et al., 2015). Due to technical limitations compounds not analyzable with reversed phase chromatography or positive electrospray ionization were excluded. Furthermore, relevant metabolites of the selected pharmaceuticals like O-desmethyl venlafaxine, N-desmethyl citalopram, 10,11-dihydro-10-hydroxy carbamazepine, and clindamycin sulfoxide were examined throughout the monitoring period. Based on a literature analysis and excretion rates expected ratios of pharmaceutical and corresponding metabolite were calculated and compared with the ratio determined in this study as well as in previous studies.

2. Materials and methods

2.1. Study area and sampling

The STP Dresden Kaditz, Germany (740,000 inhabitant equivalent, sewage water of 55 million m^3/year, hydraulic retention time of 24 h) was selected for the monitoring program. The wastewater is mechanically treated by four coarse screens of 65 mm, three fine screens of 15 mm, a grit chamber with integrated fat trap and primary clarifiers with a total volume of 4800 m^3. The plant was designed for biological nitrogen removal and chemical precipitation of phosphorus with a total tank volume of 112,000 m^3. The secondary settling tanks have a total surface area of 10,920 m^3 and are equipped with submerged effluent pipes. For further information on the catchment area see Marx et al. (2015).

Samples were taken on ten consecutive days in January/February 2015 as flow-proportional 24-h composite samples from the influent, after the primary clarifier and from the effluent (Table S1). The automatic sampler (Endress + Hauser ASP Station 2000) took a sample volume of 25 mL per 480 m^3 inflow and was equipped with 12 and 24 bottles, respectively. The total sample volume during dry weather is about 250–300 mL/h. The samples were retrieved from the automatic sampler at 8:00 AM, 50 mL was transferred into sterile 50 mL polypropylene centrifuge tubes (Greiner Bio-One, Frickenhausen, Germany) and stored at 4 °C in the dark until they were analyzed. Samples from Days 1, 2 and 3 were analyzed on Day 4, samples from Days 4, 5, 6 and 7 were analyzed on Day 8 and samples from Days 8, 9 and 10 were analyzed on Day 11 (February 5th, 2015).

2.2. Analytical method

Fifty-six pharmaceuticals and metabolites (Table 1) were analyzed in the different sewage samples using a method described elsewhere in detail (Gurke et al., 2015). Briefly, all samples were extracted by solid phase extraction (SPE) in duplicate using an Abimed ASPEC XL (Gilson, Middleton, WI, USA) with Oasis HLB 10 mg Extraction Cartridges (Waters, Milford, MA, USA). Samples (1 mL) were adjusted to a pH of 3 by adding formic acid and spiked with an internal standard (IS) solution (Table S2). The elution was done using a mixture of methanol, deionized water and formic acid (90/9/1, v/v/v). The treatment of the eluates was slightly changed. Instead of evaporating the eluates to dryness, 25 μL DMSO (Sigma, St. Louis, MO, USA) was added before the evaporation. After the evaporation, the remaining DMSO was filled up with 225 μL solvent A (97/3/0.05; v/v/v; 2 mM ammonium acetate solution/acetonitrile/formic acid). This change leads to a significant improvement especially for the polar analytes like pregabalin and gabapentin.

For the HPLC–MS/MS measurements a system, consisting of a Dionex-HPLC composed of an UltiMate3000 Pump and Autosampler (Thermo Fischer Scientific, Dreieich, Germany) with a Chromeleon Chromatography Data System (Dionex Softron, Idstein, Germany) and coupled to an API 4000 tandem mass spectrometer (AB Sciex, Framingham MA, USA) equipped with an electrospray ionization source (ESI), was used. All analytes were analyzed using positive ESI and an injection volume of 20 μL was selected. The chromatographic separation was performed with a Synergi 2.5u HydroRP 100A, 100 × 2.0 mm and a C18 security guard 4 mm × 2 mm (both Phenomenex, Aschaffenburg, Germany). The column temperature was held at 40 °C with a column oven (Shimadzu, Kyoto, Japan). The Analyst data system 1.6.2 (AB Sciex, Framingham MA, USA) was applied for MS control and MultiQuant 3.1 (AB Sciex, Framingham MA, USA) was used for the peak area evaluation, regression analysis of calibration curves and calculation of concentrations.

The LC–MS parameters of the metabolite clindamycin sulfoxide (Clearsynth, Mumbai, India) and the internal standard candesartan-d5